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24 Cardiometabolic Risk and its Antecedents among Law Enforcement Officers in Trinidad and Tobago

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M Saygin, O Ozturk, H Asci, D Bayram, İA Candan

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42 Histopathological Examination of the Effects of Butane Gas on Nasal Mucosa in Rats

S Yaslikaya, I Topaloglu, G Hafiz

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K Kilic, MS Sakat, O Araz, MS Gozeler

The study investigated the serum levels of magnesium and red blood cell distribution width (RDW) values and their relationship with polysomnographic parameters in patients with Obstructive sleep apnoea syndrome (OSAS). Serum RDW values were significantly elevated and magnesium levels were significantly decreased in OSAS. Also, RDW was positively and magnesium was negatively correlated with polysomnographic parameters. To our knowledge, this was the first study investigating the association between RDW and Mg levels in the same patient population.

EDITORIAL

Acknowledging and Addressing Bias Towards Research from Lower and Middle-income Countries

A. Ali, Departments of Medicine, Kingston Public Hospital and Faculty of Medical Sciences, UWI

Bias against research and indeed researchers from lower and middle-income countries (LMICs) does exist (1). A fair amount has been written about the subject, including by the author of this editorial, prompted by a painful rejection. Painful mainly because of the dismissive tone used by two of the three reviewers of a paper (2). This paper remains unpublished primarily because it has been so hard to revisit it.

It appears both conscious and unconscious forms of bias exist against research from low-income countries. Major journals attempt to mitigate this source of bias by choosing diverse members for their editorial boards and reviewers from developing countries to review manuscripts from other LMICs (3). In the specialty of Neurology, a recent review of the current status found that none of the 144 editorial board members of 5 leading Neurology journals had any representation from the developing world (4). While doing this proactively is a step in the right direction, it does not fully eliminate the risk of bias which does also exist in LMIC researchers against research and researchers from other countries in this greatly inhomogeneous designation bloc (5). Thus, reviewers of manuscripts from LMICs should be aware of these forms of bias and consciously attempt to mitigate it, perhaps by blind reviewing (5). Indeed the very term 'LMIC' itself reinforces the High Income Country (HIC):LMIC dichotomy (6). This has been examined further, identifying that lower income does not necessarily mean low-resourced and conversely high-income countries can sometimes be less adequately resourced (7). Also, challenging the very fundamental core pretexts of bias is the recent debate in the literature about the validity of existing constructs of race, ethnicity or geographic origin, implying greater shared genetic ancestry, as valid ways of subdividing the human race in biomedical research (8, 9).

Over the years of publishing from my research, I have often felt that names like mine or other "ethnic" sounding names can lead reviewers to spuriously comment on the English and grammar in the article, perhaps assuming that English is not my native language. While this may indeed be driven by bias, it also has been my own observation that American English grammatical styles are subtly different from the way English is used in the UK and the English-speaking Caribbean. The differences can be enough to prompt the request for more attention to be paid to grammar and punctuation, or suggest the article be proof-read by a native English-speaker! While there is no specific published evidence for this hopefully unconscious bias, there is, on the other hand, evidence that names of prestigious authors can significantly impact the acceptance rate of articles submitted for publication. Reviewers were more likely to recommend acceptance when the prestigious authors' names and institutions were visible (single-blind review) than when they were redacted (double-blind review) (87% vs 68%). They also gave higher ratings for other details including methods (10). This would appear strongly confirmatory of the profound impact of conscious bias. While studying this prospectively would, in theory, provide the best quality evidence, it is likely that the Hawthorne Effect - better performance when under observation- could come into play as a confounding factor (11).

It is undoubtedly true that LMICs are underrepresented in making good quality data available through good research. For example, Africa hosts 15% of the world's population but contributes 1.3% of global health research publications. Research output is closely correlated with Gross National Product (GNP) and as this continent grows its economic base, research output has been rising (12).

However, bias alone does not always explain these discrepancies and we must also accept that sometimes, the quality of research submitted for publication is not as good as it needs to be in order to attain peer approval. It is difficult to receive a rejection especially as the more time we spend on a research paper the more we become attached to the way we did the work. A rejection if unanimous among 3-4 reviewers is likely to be sending an important message (13). We must understand the value of the evidence we are providing, not only in terms of statistical accuracy but also in terms of the strength of the conclusions drawn (14). As a researcher from a LMIC, I have gained several insights over the years: developing

core competencies to improve research capabilities is essential (15); formal training in research methodologies helps; publishing collaboratively with recognized researchers, local and foreign, also helps to get experience in addressing reviewer comments; collaborating with intellectual honesty, not just to get your name on a publication but to be a meaningful contributor to the generation of new knowledge; avoid taking personal offence to reviewer comments, while not being afraid to write to the editors if you feel the reviewer comments are unfair and/or inappropriate.

Of course, many logistical hurdles do impede research in LMICs. A paucity of digital data from the lack of electronic health record systems (EHRs) make doing clinical research difficult, although paradoxically, the use of paper files can be an advantage in places where electricity supply is erratic (16). Despite this, collaborators from developed countries may still find it difficult to transcend the frustrations we have to live with in many LMIC settings. But building relationships will pay off. To this end, using the growing plethora of electronic communication platforms such as Teams® and Zoom® helps to sustain contact and build friendships. Technologies bridge gaps and appropriately used, can advance research and clinical care at an often surprisingly quicker pace and less expensively than you might anticipate (16).

In principle, in LMICs, like HICs, we need to recognize the importance of research quality instead of quantity. Good quality research generates good quality data which is the basis for making important contributions to health policy and clinical care. Ultimately, the principal driver for good research is that we are all the beneficiaries of good quality research. It is attention to detail that will raise the quality of our research and help to dispel the stigma and biases against research from LMICs. Most of us who have worked or collaborated overseas with major academic institutions have eventually felt accepted, valued and comfortable working with these external agencies. We have a lot to contribute, especially with the growing interest in North America and Europe in understanding diseases of "minority" populations given the growing diversity of their own populations through migration. Medical research whether basic science, clinical or epidemiological, utilizing quantitative methodologies or the less used but valuable qualitative or mixed methods, serves critically important roles in advancing healthcare in the setting where the research is done and may be generalizable to other similar LMICs and relevant minority populations living in HICs. It must be emphasized too that not prioritizing ethical issues in research undermines everyone's work and leads to the perpetuation of suspicion and skepticism. These issues continue to be relevant(17, 18).

Finally, organs like the West Indian Medical Journal (WIMJ) serve a very important role in disseminating our research throughout the region and beyond. An increasingly competitive forum for submissions that have regional relevance raises the standing of our beloved Journal, which is in and of itself an important aspiration. Enjoy your research journey and the excitement and satisfaction that publishing meaningful research can bring.

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ORIGINAL ARTICLE

Oesophageal Carcinoma in Jamaica, 1978–2007: Histological Distribution and Trends in Incidence

KCS Mills, TN Gibson, DP McNaughton, B Hanchard

ABSTRACT

Objective: *To investigate trends in incidence and histological distribution of oesophageal carcinoma in Kingston and St Andrew (KSA), Jamaica, over the 30-year period 1978–2007.*

Methods: *All oesophageal carcinomas registered in residents of KSA during the study period were extracted from the Jamaica Cancer Registry, and the following were collected for each case: gender, age, basis of diagnosis, year of diagnosis, histological subtype and subsite. The data were used to calculate age-specific incidence rates and age-standardized incidence rates (ASRs). The results were compared to those from other countries.*

Results: *Oesophageal carcinoma was more common among males than females, and both genders showed decreasing incidence over the 30-year period. The highest ASRs (males, 4.0 per 100 000; females 2.6 per 100 000 per year) were recorded in the 1978–1982 reporting period and the lowest (males, 1.7 per 100 000 per year; females 0.6 per 100 000 per year) in the 2003–07 period. The leading histological subtype among both genders was squamous cell carcinoma (SCC), and this subtype showed a decrease in incidence in both genders over the period of review. Adenocarcinomas, the second commonest histological subtype, showed a decrease in ASR over time in females and a rise in males.*

Conclusion: *Incidence rates of oesophageal carcinomas overall have decreased in KSA, Jamaica, and this trend is mirrored by the SCC subtype. However, while adenocarcinoma ASR is decreasing in females, it is increasing in males. These data support the need for investigation into the risk factors for oesophageal adenocarcinoma in Jamaica.*

Keywords: Cancer, Jamaica, oesophagus.

INTRODUCTION

According to the 2014 World Cancer Report, low-to-middle income countries, such as Jamaica, accounted for 73% of all new cases of oesophageal cancer, with 49% of these cases occurring in China (1). Squamous cell carcinoma (SCC) and adenocarcinoma represent the two leading histological subtypes of oesophageal cancer worldwide, and each of these subtypes has its own epidemiological profile (1).

Squamous cell carcinoma has a high incidence in Central Asia, Eastern Asia and Eastern Africa, and the lowest incidence rates occur in Western Africa and Latin America (1). Adenocarcinoma is commonest in Caucasian populations than in any other racial groups. It exhibits high incidence rates in the United Kingdom, Australia, the Netherlands and the United States of America and the lowest rates in Latin America, Asia and Africa (1). Historically, SCC has accounted for the majority of oesophageal cancers worldwide, but there has been a shift in epidemiology over the last several generations and adenocarcinoma now accounts for more than 50% of oesophageal cancer in Western countries (2).

Trends in incidence rates for oesophageal cancers in the Jamaican population for the period 1973–1997 were previously analysed (3) and showed decreasing incidence in both genders, however, analysis according

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to histological type was not undertaken. There has been no published data on the trends of oesophageal cancer incidence in the Jamaican population since 1997, and the histological distribution of oesophageal cancer in the Jamaican population has not been previously defined. These factors formed the basis of this study.

SUBJECTS AND METHODS

Data was obtained from the Jamaica Cancer Registry (JCR), a population-based registry, which collects all cases of cancer diagnosed in the resident population of the parishes of Kingston and St. Andrew, Jamaica. Data is collected from private and public hospitals, pathology departments, radiotherapy facilities and palliative care institutions in these parishes.

From the archives of the JCR, we abstracted all cases of oesophageal cancer diagnosed over the 30-year period 1978–2007 and documented the following for each case: gender, age, year of diagnosis, basis of diagnosis code (International Agency for Research on Cancer-International Association of Cancer Registries), subsite (International Classification of Diseases for Oncology, 3rd edition) and histology (World Health Organization Histological Classification for Oesophageal Tumours, 2010).

Data was used to calculate frequencies, age-specific incidence rates (ASIRs) and age standardized incidence rates (ASRs) for each 5-year stratum of the period 1978–2007.

Calculation of rates

Age-specific incidence rate (ASIR)

The ASIR was calculated by dividing the total number of cases of each five year period by five times the population estimate for that stratum and multiplying the result by 100 000. The rate is therefore expressed as per 100 000 per year.

Age standardized incidence rate (ASR)

The ASR was calculated in a two-step procedure. For each site, the product of each ASIR and its corresponding world standard population were obtained, and then all were summed to produce the ASR.

Statistical analysis

Linear regression analysis was used to determine the significance of trends in ASRs over time. This was calculated using the GraphPad Quickcalcs Linear Regression Calculator (GraphPad Software, Inc.) accessed at http://www.graphpad.com/quickcalcs/linear1. Significance was defined as a p-value of < 0.05.

RESULTS

A total of 415 cases of oesophageal cancer were diagnosed over the period 1978–2007. Two hundred and eighty-three cases (68.2 %) were ascertained via histology, 122 cases (29.4 %) via clinical investigation, 6 cases (1.4 %) via clinical history and examination only and 2 cases (0.5 %) via cytology. Of the 415 cases, 259 were males and 156 were females (male:female ratio 1.7:1), and the ages of these patients ranged from 26 to 93 years. Peak incidence in males occurred in the 75–79 year age group, and in females, in the 70–74 year group (Fig. 1).

Fig. 1: Age-specific incidence of oesophageal cancer, Kingston and St. Andrew, Jamaica, 1978–2007.

Of the 283 cases ascertained via histology, SCCs were the commonest (251; 88.7%), followed by adenocarcinoma (20; 7.1%). The remaining 12 cases included 4 cases of anaplastic carcinoma, 4 cases of poorly differentiated carcinoma, 3 cases of undifferentiated carcinoma and 1 case of mucoepidermoid carcinoma.

Figure 2 shows the distribution of subsites for cases of oesophageal adenocarcinoma and SCC. The majority of adenocarcinomas (18 out of 20; 90%) were located in the lower third of the oesophagus; in the remaining 2 cases, no location had been recorded. For the 126 cases of SCC in which the subsite had been recorded, there was a spread of distribution, with the middle third of the oesophagus being the commonest subsite (55; 44%), followed by the lower third (44; 35%) and then the upper third (15; 12%).

The ASR for SCC was higher in males than in females in every 5-year period of the 30-year range (Fig. 3). The 1978–1982 period showed the highest ASRs of SCC for both genders, and this was followed by a progressive

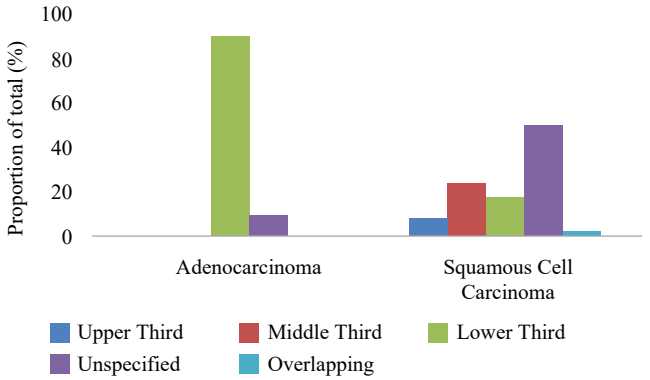

Fig. 2: Oesophageal adenocarcinoma and squamous cell carcinoma subsites, Kingston and St. Andrew, Jamaica, 1978– 2007.

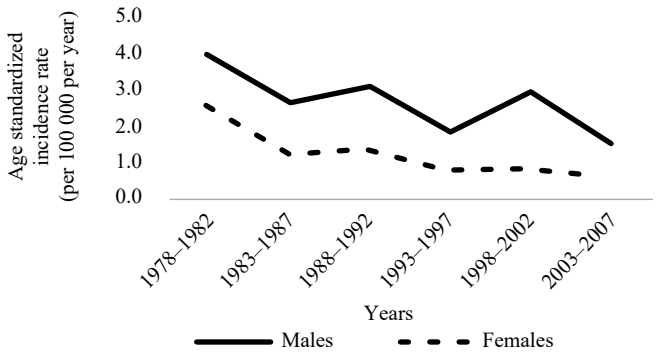

Fig. 3: Age standardized incidence rates, oesophageal squamous cell carcinoma, Kingston and St. Andrew, Jamaica, 1978–2007.

decline in rate in both genders, with the lowest figures in both being seen in the final 5-year period of the study (2003–2007). The decreasing trend was statistically significant only in females ($p = 0.028$).

Fig. 4 shows that no cases of adenocarcinoma were recorded in the 1978–1982 reporting period. In the first two periods of the study in which this histological type was documented (1983–1987 and 1988–1992), it demonstrated higher ASRs in females than in males. However, subsequent to 1992, ASRs in males progressively increased, surpassing the rates in females, and the ASRs in females showed progressive decline. The increasing trend of ASRs in males was statistically significant ($p = 0.001$). The trend observed in females was not significant.

DISCUSSION

In this study, the majority of cases of oesophageal carcinoma occurred in males. In addition, ASRs for SCC of the oesophagus were consistently higher in males than in females, while those for adenocarcinoma were initially higher in females, but in the later periods of the study,

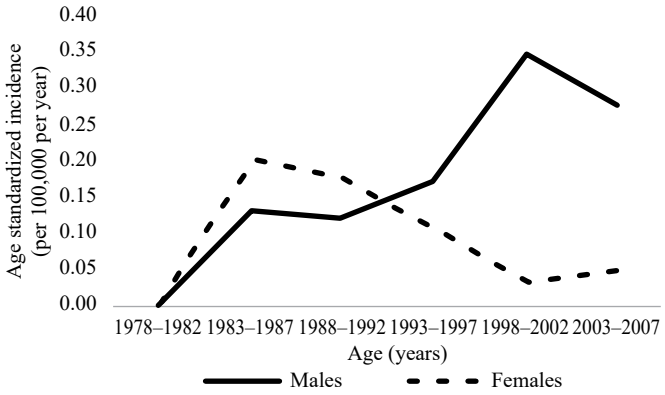

Fig. 4: Age standardized incidence rates, oesophageal adenocarcinoma, Kingston and St. Andrew, Jamaica, 1978–2007.

they were consistently greater in males. These findings are in keeping with international studies, which report both SCC and adenocarcinoma of the oesophagus as being more common among men than women (4–6).

The higher SCC ASRs in males documented globally has been explained by the higher consumption of alcohol and tobacco—the two main risk factors for the disease—among men, compared to women (4). The reasons for the gender disparity in oesophageal adenocarcinoma are less clear. Gastroesophageal reflux, a strong risk factor for Barrett's oesophagus (2, 4), and subsequent development of oesophageal adenocarcinoma, is reportedly more common in men than women (6–8), and this may contribute to the higher incidence rates of oesophageal adenocarcinoma in men. In addition, some studies have suggested a protective role of oestrogen in the development of oesophageal adenocarcinoma (8, 9), showing that strong male preponderance is seen in the pre- and peri-menopausal age groups, but that this is followed by a decline in the male to female ratio in the post-menopausal years (8). In our data, the initial higher rates in females for adenocarcinoma may perhaps be partially explained by the small numbers of cases overall.

Data from this study showed that oesophageal carcinoma was commoner after the age of 54 years, with peak frequencies occurring in the 75–79 year and 70–74 year age groups for men and women, respectively. These findings are similar to those reported internationally, where both SCC and adenocarcinoma of the oesophagus occur in older age groups. Squamous cell carcinoma of the oesophagus is uncommon before the age of 30 years (5, 10), exhibiting peak incidence in the seventh decade (10–12), and the peak incidence of oesophageal adenocarcinoma is seen in the 50–60 year age group (11, 13).

Our data showed that SCC accounted for the majority of oesophageal carcinomas, and most of these involved

the middle third of the oesophagus. This is similar to data reported globally, where SCC is the predominant histological subtype of oesophageal carcinoma, and it most often affects the middle third of the oesophagus, though it may occur throughout the oesophagus (6, 10). Our data additionally showed that the incidence of oesophageal SCC decreased in both genders over the 30-year period under review, and this is in keeping with reports from other geographical regions (6, 10, 14), where the decrease has been attributed to decreasing smoking prevalence (10). Decreases in males but stable rates in females have been documented elsewhere (15). It is unclear whether changes in smoking patterns may have contributed to the decreases observed in our population, as national tobacco control programmes have only been recently implemented in Jamaica (16).

The trends in this study of increasing incidence in males and decreasing incidence in females for oesophageal adenocarcinoma differ somewhat from international data, which show an increasing incidence in both genders (2, 6, 15). Adenocarcinoma now accounts for more than 50% of cases of oesophageal cancer in some Western countries (2, 4, 6). This increase has been less dramatic in Black populations, and there has been no increase among Asians (14, 17). Oesophageal adenocarcinoma most commonly arises on the background of Barrett's oesophagus, caused by chronic gastro-oesophageal reflux and therefore most commonly occurs in the lower third of the oesophagus (6, 10), which was the commonest topographical location for oesophageal adenocarcinoma in this study. It would therefore appear that gastro-oesophageal reflux, which is reportedly more common in males (7, 8, 14), may be a significant contributor to the development of oesophageal adenocarcinoma in our population. The decreasing incidence in females, though not statistically significant, warrants further study, including an investigation into the risk factors for oesophageal adenocarcinoma in the Jamaican population.

In summary, in Jamaica, oesophageal carcinoma is commoner in males than in females, and SCC is the commonest histological type, though its incidence has been decreasing in both genders. The incidence of oesophageal adenocarcinoma has been decreasing among females but increasing among males, suggesting that gastro-oesophageal reflux may be more common in males than in females in the Jamaican population. Further study is warranted to investigate the risk factors for oesophageal adenocarcinoma in our population.

AUTHORS' NOTE

TN Gibson and B Hanchard conceived the paper, supervised database creation, performed data analyses, reviewed and corrected drafts of the paper and approved the final draft. KCS Mills abstracted collected data into an electronic database, performed data analyses and wrote drafts of the paper. DP McNaughton collected data and reviewed drafts of the paper. All authors approved the final draft. There are no financial interests or other dual commitments that represent potential conflicts of interest for any of the authors.

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ORIGINAL ARTICLE

Analysis of Axillary Lymph Nodes in Breast Cancer Patients with Positive Sentinel Lymph Node Biopsy

D Grebić[1], H Grbas[1], PV Zujić[2], M Mavrić[3], AM Tomašić[4]

ABSTRACT

Objective: *To determine the prevalence of positive non-sentinel nodes (non-SLN) after axillary dissection for positive sentinel lymph node (SLN) and the relationship between occurrence of positive non-SLNs and penetration of the sentinel's capsule by malignant cells, as well as grade and molecular subtype of the breast cancer.*

Methods: *An analysis was performed of a total of 77 patients with a positive SLN from a five-year period. Patients were categorized according to the following criteria: positivity of non-SLN, invasion of SLN capsule, tumour grade, T stage and molecular subtype.*

Results: *In over 65% of patients, non-SLN were negative for metastases despite a positive SLN. A statistically significant correlation was observed between SLN capsule penetration and positive non-SLN metastases (*$p < 0.001$*). It was also observed that non-SLN metastases are more commonly positive in patients with a high tumour grade, high T stage, and HER2-positive and triple-negative tumours.*

Conclusion: *Non-SLN metastases are generally found in patients with SLN capsule penetration by malignant cells, in those with poorly differentiated tumours (high grade), and in those with high T stage, as well as in triple-negative and HER2-positive tumours. Based on these findings, such patients should undergo axillary dissection due to an increased risk of non-SLN metastases.*

Keywords: Axillary dissection, breast cancer, positive sentinel lymph node, radiotherapy, surgery

INTRODUCTION

A sentinel lymph node (SLN) or lymph node guardian is defined as the first lymph node that drains lymph from a given area. A sentinel lymph node biopsy (SLNB) implies focused excision and pathological examination of axillary lymph nodes most likely to receive tumour metastases while avoiding morbidities associated with complete axillary nodal dissection (1).

Today, there are a number of controversial opinions on the indications and contraindications for a SLNB.

According to guidelines set forth by the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI), a SLNB is indicated for patients with early-stage (T1 and T2) breast cancer proven by cytology or biopsy, and in whom axillary metastases are not suspected clinically or already proven by histology or cytology. Former standard practice of axillary lymph node dissection (ALND) in order to stage the disease has been replaced with SLNB in early-stage breast cancer patients. Therefore, ALND is performed if the dissemination of disease to axillary lymph nodes is shown preoperatively, or in the case of a positive SLN (metastasis shown in

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pathohistological analysis) and in cases when a SLN was not identified by lymphoscintigraphy (2).

Based on the St. Gallen and the American Society of Clinical Oncology (ASCO) guidelines, ALND is not recommended prior to pathohistological analysis in the case of isolated positive, cytologically proven, tumour cells in a SLN. The American Society of Clinical Oncology (ASCO) does not recommend a SLNB for inflammatory carcinoma, advanced tumours (T3 and T4) or ductal carcinoma *in situ* (DCIS), when breast sparing surgery is anticipated. A sentinel lymph node biopsy (SLNB) can be done for multicentric tumours, although a high percentage of false negatives and axillary metastasis is found in these patients (3, 4). A sentinel lymph node biopsy (SLNB) for DCIS is indicated when mastectomy is planned (5). The indications for SLNB are controversial in pregnancy, although according to the ASCO guidelines SLNB is not recommended in pregnancy (3, 6). If a patient receives neoadjuvant chemotherapy prior to surgery, SLNB may be taken, but axillary dissection is obligatory in the case of a positive finding (7). Of SLN marking techniques, the dual-marking technique (lymphoscintigraphy and dye marking) is recommended in order to reduce the possibility of false-negative results. The reasons for lack of SLN presentation may include obstruction of lymph flow or SLN infiltration with tumour or malignant cells, for which axillary dissection is required (8). In the case of SLN micrometastases, ALND is unnecessary (9). There are still studies that show a longer period without disease recurrence in cases where axillary dissection is performed along with systemic therapy and axillary radiotherapy when one or two positive SLNs are found (studies MA.20 i EORTC 22922/10925) (10).

Newer studies suggest the use of systemic therapy and radiotherapy as an alternative to axillary dissection when one or two positive SLNs are found (AMAROS study i ACOSOG Z0011). This research compared two groups of patients with early stages of breast cancer and positive SLNs. One group of patients underwent tumour removal and axillary dissection, although the second group underwent tumour removal and postoperative radiotherapy (without axillary dissection). It was concluded that there is no difference in the recurrence-free period or a period of survival in these two groups of patients. For this reason, updated guidelines suggest that for patients with one or two positive SLNs, breast sparing surgery and subsequent radiotherapy, axillary dissection is unnecessary (11).

The aim of this study was to determine the prevalence of a positive non-SLN after axillary dissection was done due to a positive SLN and also to determine how the prevalence of positive non-SLNs relates to penetration of the sentinel's capsule by malignant cells, T stage, grade and molecular subtype of the breast cancer.

SUBJECTS AND METHODS

The proposed study was undertaken at the Department of General and Oncological Surgery, Rijeka Clinical Hospital Center. Consent was obtained from the Ethics Committee. Data were collected on patients with invasive breast cancer with a positive SLN. The study included data from a total of seventy-seven (77) patients from a five-year period (2009–2014), meaning that the study was retrospective, descriptive and analytical. Data on the total number of positive non-SLN metastases after axillary dissection were key. Additional data processed included: SLN penetration by malignant cells, tumour grade, T stage and molecular subtype.

Patients were divided into several groups. The first group included patients with positive non-SLN metastases after axillary dissection was done due to a positive SLN, as opposed to those in which after axillary dissection due to a positive SLN, non-SLN were negative. The second group included patients with SLN capsule penetration by malignant cells, compared to those in which the SLN capsule was intact. Based on this division, the following two subgroups were created: patients with SLN capsule penetration and positive non-SLN after axillary dissection versus patients with SLN capsule penetration, but negative non-SLN. The next group consisted of patients in which the SLN capsule was intact and after axillary dissection, non-SLN were negative, compared to patients with an intact capsule, but positive non-SLN after axillary dissection. Additional groups included patients with a positive non-SLN after axillary dissection due to a positive SLN, and patients with a negative non-SLN after axillary dissection according to the tumour grade, tumour T stage, and molecular subtype.

Statistical analyses

Data were collected and sorted on Microsoft Windows using the Microsoft Excel application. Statistical analysis was done using the Statistica 12 program, with the Fisher's exact test, p-values less than 0.05 were considered statistically significant.

RESULTS

A total of 26 patients (33.77%) had non-SLN metastases after axillary dissection for positive SLN, the remaining 51 patients (66.23%) having a positive SLN with negative non-SLNs (Figure).

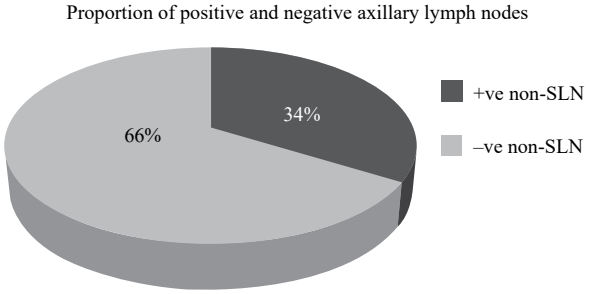

Figure: This figure shows the proportion of patients with positive non-SLN after axillary dissection was done due to a positive SLN compared to patients with a negative non-SLN after dissection due to a positive SLNB.

Analysis of the sentinel lymph node capsule

Based on the pathohistological analysis, 29 patients (37.66%) had a positive SLN where cancer cells penetrated the SLN capsule (Table 1). Among these 29 patients with capsular penetration, 19 patients (65.52%) had positive non-SLN (Table 2).

Table 1: Proportion of positive SLN with an intact capsule compared to SLN with a penetrated capsule

Positive SLN
Intact capsule-penetrated capsule
Patients 48 (62%); 29 (38%)

The table shows the percentage of cases in which malignant cells penetrated the sentinel's capsule (29, 38%) compared to the percentage with an intact sentinel's capsule (48, 62%).

Table 2: Proportion of positive and negative non-SLNs in cases with penetrated sentinel's capsule

Penetrated sentinel's capsule	
Positive non-SLN patients	Negative non-SLN patients
19 (66%)	10 (34%)

Among the remaining 48 patients with an intact SLN capsule, seven patients (14.58%) also had positive non-SLN after axillary dissection (Table 3). The Fisher's exact test calculated a statistically significance difference between these two groups ($p < 0.001$) for the likelihood of non-SLN metastases in cases of SLN capsular penetration compared to cases without capsular penetration.

Table 3: Percentage of positive and negative non-SLNs in the axilla in cases of an intact sentinel's capsule

Intact capsule of SLN	
Positive non-SLN patients	Negative non-SLN patients
7 (15%)	41 (85%)

Grade of tumour and positive axillary lymph nodes

Of the total of 26 patients with a positive non-SLN, six patients (23.07%) had tumour grade 1, 17 patients (65.39%) had grade 2 and three patients (11.54%) had grade 3 (Table 4). In the 51 patients who had negative non-SLN, 39 patients (76.48%) had tumour grade 1, 11 patients (21.56%) had grade 2 and one patient (1.96%) had grade 3. The Fisher's exact test calculated a statistically significant difference ($p < 0.001$) for the likelihood of non-SLN metastases between low- and high-differentiated tumours (Table 5).

Table 4: Proportion of each histological grade of tumours in the 26 patients with a positive non-SLN

Grade	Number (percentage) of patients
Grade 1	6 (23%)
Grade 2	17 (65%)
Grade 3	3 (12%)

Table 5: Proportion of each histological grade of tumours in the 51 patients with a negative non-SLN

Grade	Number (percentage) of patients
Grade 1	39 (76%)
Grade 2	11 (22%)
Grade 3	1 (2%)

Tumour T stage and positive axillary lymph nodes

Of the total of 77 patients, 35 patients (45.45%) had stage T1 carcinoma, and 42 patients (54.55%) had stage T2. Positive non-SLN were found in two (5.71%) patients with stage TI disease, but in 24 (57.14%) with stage T2. Fisher's exact test once again calculated a statistically significant difference ($p < 0.001$).

Tumour molecular subtype

According to molecular findings, patients were classified into four main groups: luminal A, luminal B, HER2-positive and triple-negative tumours. The luminal A group included 25 patients of which only four cases (16.00%) had positive non-SLN. The luminal B group had 40 patients of which 16 patients (40.00%) had positive non-SLN. The HER2-positive group had 10 patients

of which four patients (40.00%) had positive non-SLN. The final triple-negative group had only two patients with positive non-SLN in both cases (100%) (Table 6). The Fisher's exact test calculated a statistically significant difference ($p < 0.001$) for the likelihood of non-SLN metastases between triple-negative and HER2-positive tumours compared to luminal A and luminal B tumours.

Table 6: Molecular subtypes of the breast cancer. The table shows the number (percentage) of positive non-SLN according to the molecular subtype of the tumour

Molecular subtypes	Luminal A	Luminal B	HER-2 positive	Triple negative
Number of patients	25	40	10	2
Positive non-SLN	4 (16%)	16 (40%)	4 (40%)	2 (100%)

DISCUSSION

Of a total of 77 patients who underwent breast cancer surgery and had a positive SLN, 26 patients had positive non-SLN. This is a frequency of 33.77%, which is in line with other studies (9). Between the patients with an intact SLN capsule and those with SLN capsular penetration, a statistically significant difference was shown in terms of the occurence of positive non-SLN ($p < 0.001$).

A majority of patients had cancer classified as grade 1 (58.44%), followed by grade 2 (36.37%) and grade 3 (5.19%). The lowest prevalence of positive non-SLN was observed in patients with grade 1, then grade 2 and the highest with grade 3, as expected, considering that an increase in tumour grade means more malignant, less differentiated tumors (12–14). The study shows a statistically significant correlation between higher grade tumours and non-SLN metastases ($p < 0.001$).

Patients in this study had cancer, classified as stage T1 or T2. Most patients (54.55%) had T2 cancer, which shows that the national breast cancer-screening programme still does not detect cancer in its earliest stage. An important result of this study is that of 26 patients with positive non-SLN, 24 had stage T2 tumors, indicating a statistically significant correlation between occurrence of positive non-SLNs and increasing T-stage of disease ($p < 0.001$) (13).

Most patients had luminal A and luminal B molecular subtypes (total 84.41%). The others were HER2-positive and triple negative. Patients with luminal A tumour subtype had the lowest percentage of positive non-SLN (16%). In comparison, both patients with triple negative tumour subtype had positive non-SLN. These results correlate with findings of other research in which HER2-positive and triple negative tumour subtypes are associated with a higher prevalence of non-SLN metastases (15).

Results of this study show that current practice, in which a positive SLN is always accompanied by axillary dissection, leads to unnecessary axillary dissection in over 65% of patients that had negative non-SLNs. That is, only 35% of patients in this study had positive non-SLN. This study shows that non-SLN metastases are generally found (in 73.08% of cases) in patients with a SLN capsule penetrated by tumour cells, in patients with low differentiated tumours (high grade), and in those with high-tumour T stage. Based on these findings, such patients should undergo axillary dissection due to an increased risk of non-SLN metastases. According to the updated guidelines, in other cases, axillary dissection can be spared, and substituted with conservative treatment, such as radiotherapy, to reduce the number of unnecessary operations, and to improve quality of life (9, 10).

CONCLUSION

Non-SLN metastases are generally found in patients with positive SLN capsule penetration by malignant cells, in those with low differentiated tumours (high grade), and in those with high T stage, as well as in triple-negative and HER2-positive tumours. Based on these findings, such patients should undergo axillary dissection due to an increased risk of non-SLN metastases.

AUTHORS' NOTE

Damir Grebić wrote the manuscript, participated in data analysis and interpretation, critically revised the manuscript and approved the final version. Harry Grbas participated in the interpretation of data, revision of the manuscript and approved the final version. Petra Valković Zujić performed the statistical analysis and created the figures. Matija Mavrić and Ana Marija Tomasić collected the data, participated in data analysis and interpretation. The authors declare that they have no conflicts of interest.

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ORIGINAL ARTICLE

Value of Serum Galectin 3 in Patients with Hepatocellular Carcinoma: A Meta-Analysis

L Zhang, X-J Chen, D He, T-Y Zhou

ABSTRACT

Objective: *To investigate the connection of Galectin 3 with hepatocellular carcinoma (HCC) risk.*

Methods: *Publications were searched using PubMed, MEDLINE, EMBASE and the Chinese databases (including CNKI and WanFang) up to October 2015.*

Results: *A total of four studies were included in this analysis. The pooled mean difference for HCC versus hepatitis was (1.98 (95% CI: 1.13, 2.83, Z = 4.57,* $p < 0.00001$*)) and for HCC versus healthy person was (2.29 (95% CI: 2.09, 2.5, Z = 21.78,* $p < 0.00001$*).. The serum Galectin 3 level in HCC was significantly higher than that in hepatitis and healthy person. The pooled sensitivity and specificity were 0.93 (95% CI: 0.86, 0.97) and 0.83 (95% CI: 0.74, 0.90), the pooled diagnostic odds ratio were 116.78 (95% CI: 0.13, 102122.46), the pooled positive likelihood ratio were 12.71 (95% CI: 0.12, 1374.27), and the pooled negative LR were 0.11 (95% CI: 0.00, 12.51).*

Conclusion: *The serum Galectin 3 level in HCC is higher than that in hepatitis and healthy person. Serum Galectin 3 may be a possible biomarker for diagnosis of HCC.*

Keywords: Hepatocellular carcinoma, meta-analysis, serum Galectin 3

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer, and the third most common cause of cancer-related mortality overall in the world (1). Prognosis of HCC is very poor with a 14% five-year survival rate because of rapid progression and high grade of malignancy (2, 3). Lacking novel biomarkers, HCC is frequently found in late stages. Commonly, CT, ultrasound, MRI and blood chemistry tests are used to diagnose HCC. Histopathologic assessment is necessary for confirmation and when the imaging tests and blood chemistry tests are atypical. However, biopsy of liver tissue suspected of harbouring HCC is invasive and difficult. So it would be helpful if new biomarkers can be found to improve the pre-biopsy diagnostic efficiency of HCC. In the clinic serum alpha-fetoprotein (AFP), with low sensitivity, is used to support the diagnosis of HCC (4). However, a new serum biomarker needs to be found with better performance than AFP, which is not which is not satisfactory.

Galectins are a family of β-galactoside-binding animal lectins, composed of 2 domains: a carboxyl-terminal domain and an amino-terminal domain (5). Studies suggest that Galectin 3, a unique chimaera-type member of the β-galactoside-binding soluble lectin family, has multifaceted functions including cell growth, proliferation, adhesion, differentiation, immune responses, angiogenesis, apoptosis, metastasis and tumour progression (6–8) . Expression of Galectin 3 is a promising diagnostic indicator for several kinds of carcinomas, such as carcinomas stomach (9), colon (10) and thyroid (11). However, the relationship between Galectin 3 and HCC is unclear. Our aims are to analyse the expression of serum Galectin 3 in different stages of liver diseases and evaluate the diagnostic accuracy of serum Galectin 3 in HCC patients.

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SUBJECTS AND METHODS

Search strategy

Publications searched were PubMed, MEDLINE, EMBASE and the Chinese databases (including CNKI and WanFang database) until October 2015, by using the following search terms: HCC or liver cancer or liver cell carcinoma or HCC and Galectin 3 or gal-3.

Study selection

Studies included in this meta-analysis met the following criteria::

(1) Original articles that directly directly explored serum Galectin 3 expression in different stages of diseases (including HCC, hepatic cirrhosis, hepatitis, or healthy person);
(2) Original articles that directly directly explored the diagnostic performance of serum Galectin 3 for HCC;
(3) Used ELISA to examine serum Galectin 3 expression;
(4) Sufficient information was reported to estimate a mean difference (MD), 95% confidence interval (CI), true positive (TP), false positive (FP), false negative (FN) and true negative (TN).

Studies were excluded as follows: (a) case reports, reviews, letters and editorial articles; (b) articles in which sufficient data were not reported or calculated.

Data extraction

Two independent investigators (LZ and DH) extracted all data from eligible studies to minimize bias; a third researcher (XJC) resolved disagreements through discussion. For each article, the following characteristics were recorded: first author, publication year, number of patients, test method, TP, FP, FN, PN and cut-off value.

Statistical analysis

All analysis was performed using Review Manager 5.3 and MetaDisc. Extracted data included serum Galectin 3 levels of HCC versus serum Galectin 3 levels of hepatic cirrhosis, hepatitis and healthy person in each article. Mean difference and 95% CI were applied to provide the effective values. And in order to evaluate the diagnostic efficiency of serum Galectin 3 in HCC, we also extracted the TP, FP, FN and PN to estimate the sensitivity and specificity. Initially, we retrieved 191 studies from PubMed, EMBASE and the Chinese databases (including CNKI and WanFang database) up to October 2015.

One hundred and eighty one abstracts were excluded, because they were reviews, experimental research, reports, duplicate articles or not relevant. After reading the remaining 10 full-text articles, 6 were excluded, because they used other test methods than ELISA. Finally, four articles were included for conducting the meta-analysis (see Fig. 1). One hundred and twenty patients with HCC, 68 patients with hepatic cirrhosis, 47 patients with hepatitis and 24 healthy persons in these four articles were used to explore serum Galectin 3 levels in different stages of diseases. TP, FP, FN and PN were acquired to estimate the sensitivity and specificity of HCC for detecting serum Galectin 3 expression in HCC and non-tumour. ELISA was used to detect the serum Galectin 3. A random-effects model for $I^2 > 50\%$, a fixed-effects model for $I^2 < 50\%$, and statistical significance defined as a p-value less than 0.05 (12) (Tables 1 and 2) were adopted.

Table 1: Serum Galectin 3 levels in patients with HCC, cirrhosis, hepatitis and healthy people

Reference	Year	HCC	Cirrhosis	Hepatitis	Healthy people
Nada (13)	2015	50	30	0	10
Yasunori (14)	2008	51	16	23	14
Mehmet (15)	2015	19	22	24	0

HCC = hepatocellular carcinoma.

Table 2: Galectin 3 expression in HCC and non-tumour

Reference	**Year**	**TP**	**FP**	**FN**	**TN**	**Cut-off**	**HCC/ Non-tumour**	**Detection method**
Qing-Qing Fang (16)	2011	40	1	1	89	0.62 ng/l	62/90	ELISA
Yasunori (14)	2008	34	7	14	14	2.76 ng/ml	48/21	ELISA

TP = True positive; FP = false positive; FN = false negative; TN = true negative; HCC = hepatocellular carcinoma.

RESULTS

In the four studies, the meta-analysis results (mean difference: 0.63 (95% CI: −0.61–1.87, $Z = 0.99$, $p = 0.325$)) indicated that there were no significant differences for serum Galectin 3 level between HCC and hepatic cirrhosis with an obvious heterogeneity (Tau-square = 0.92, chi-square = 9.83, $I^2 = 80\%$, $p = 0.007$) (Fig. 2A). However, we also found the serum Galectin 3 level in HCC was significantly higher than that in hepatitis and healthy person. The pooled mean difference for HCC versus hepatitis was (1.98 (95% CI: 1.13, 2.83, $Z = 4.57$, $p < 0.00001$)) without heterogeneity (chi-square = 0.21, $I^2 = 0\%$, $p = 0.64$) (Fig. 2B). The pooled mean difference

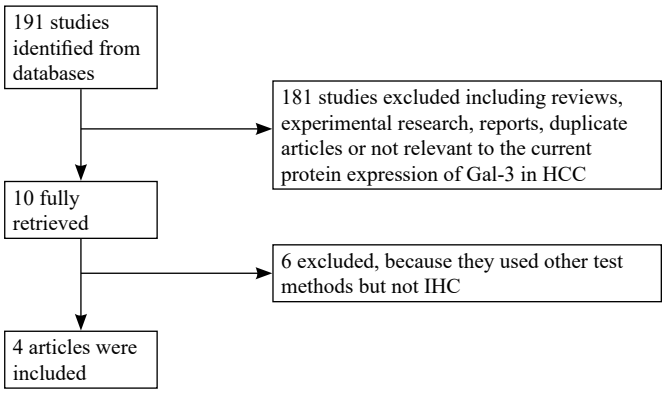

Fig. 1: The study selection process.

respectively, the pooled DOR was 116.78 (95% CI: 0.13, 102122.46), the pooled positive LR was 12.71 (95% CI: 0.12, 1374.27), and the pooled negative LR was 0.11 (95% CI: 0.00, 12.51). All the results indicated that Galectin 3 may be a useful biomarker for the diagnosis of HCC (Fig. 3).

DISCUSSION

Prognosis of HCC is very poor because of rapid progression and high grade of malignancy. Radiotherapy, chemotherapy and surgery are the main treatment methods for HCC patients in the clinic. Although therapies

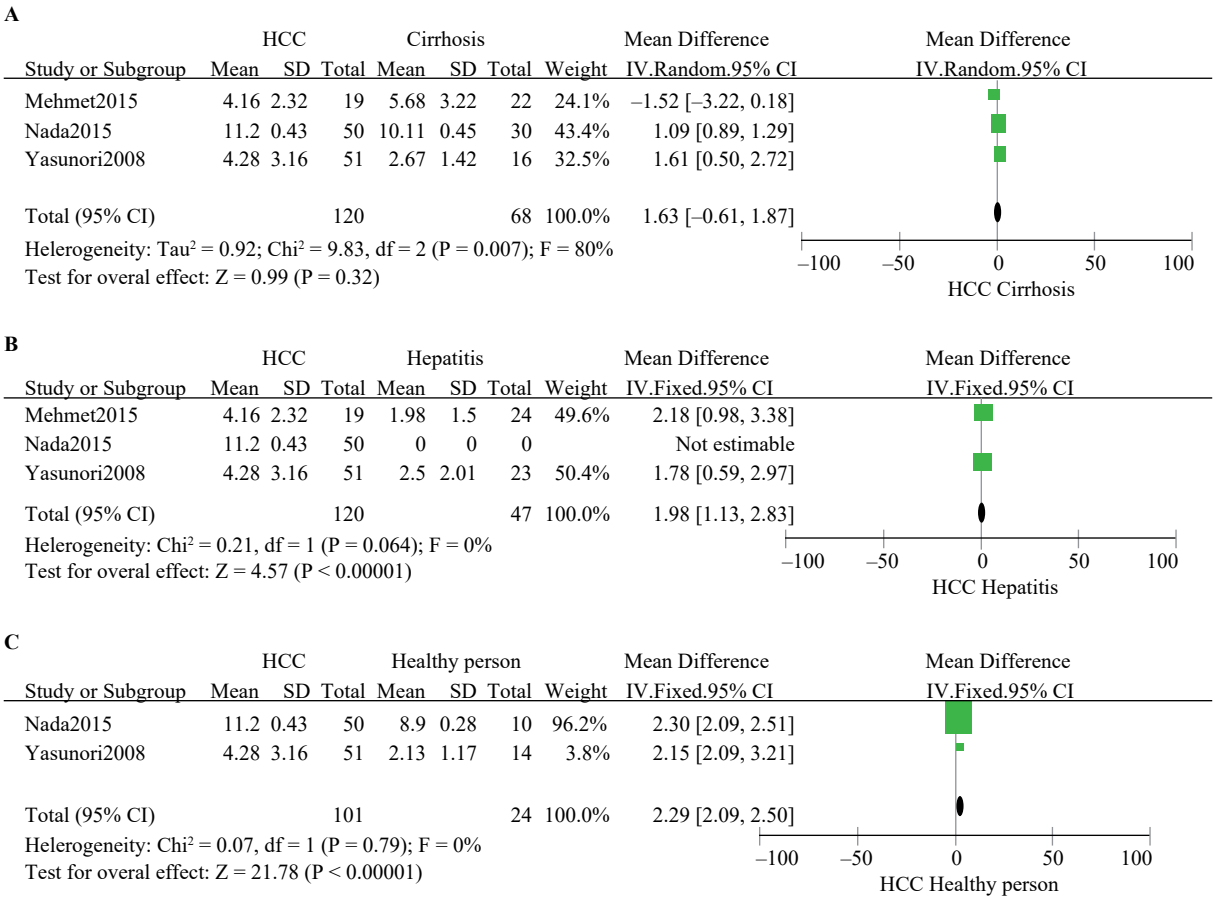

Fig. 2: (A) Forest plot for serum Galectin 3 in HCC and hepatic cirrhosis. (B) Forest plot for serum Galectin3 in HCC and hepatitis. (C) Forest plot for serum Galectin3 in HCC and healthy person. HCC = hepatocellular carcinoma.

for HCC versus healthy person was (2.29 (95% CI: 2.09, 2.5, $Z = 21.78$, $p < 0.00001$)) without heterogeneity (chi-square = 0.07, $I^2 = 0\%$, $p = 0.79$) (Fig. 2C).

In our analysis, a total of 110 HCC patients and 111 non-tumour patients were included in this meta-analysis to evaluate the diagnostic usefulness of serum Galectin 3. The overall sensitivity and specificity were 0.93 (95% CI: 0.86, 0.97) and 0.83 (95% CI: 0.74, 0.90) have been improved, the cure rate is still poor. Therefore, it is urgent to engage in finding potent factors for earlier diagnosis of HCC.

Four studies were included in this study to derive a more precise estimation of serum Galectin 3 levels in HCC patients versus serum Galectin levels in hepatic cirrhosis, hepatitis, and healthy person. The diagnostic effect of serum Galectin 3 for HCC was also estimated.

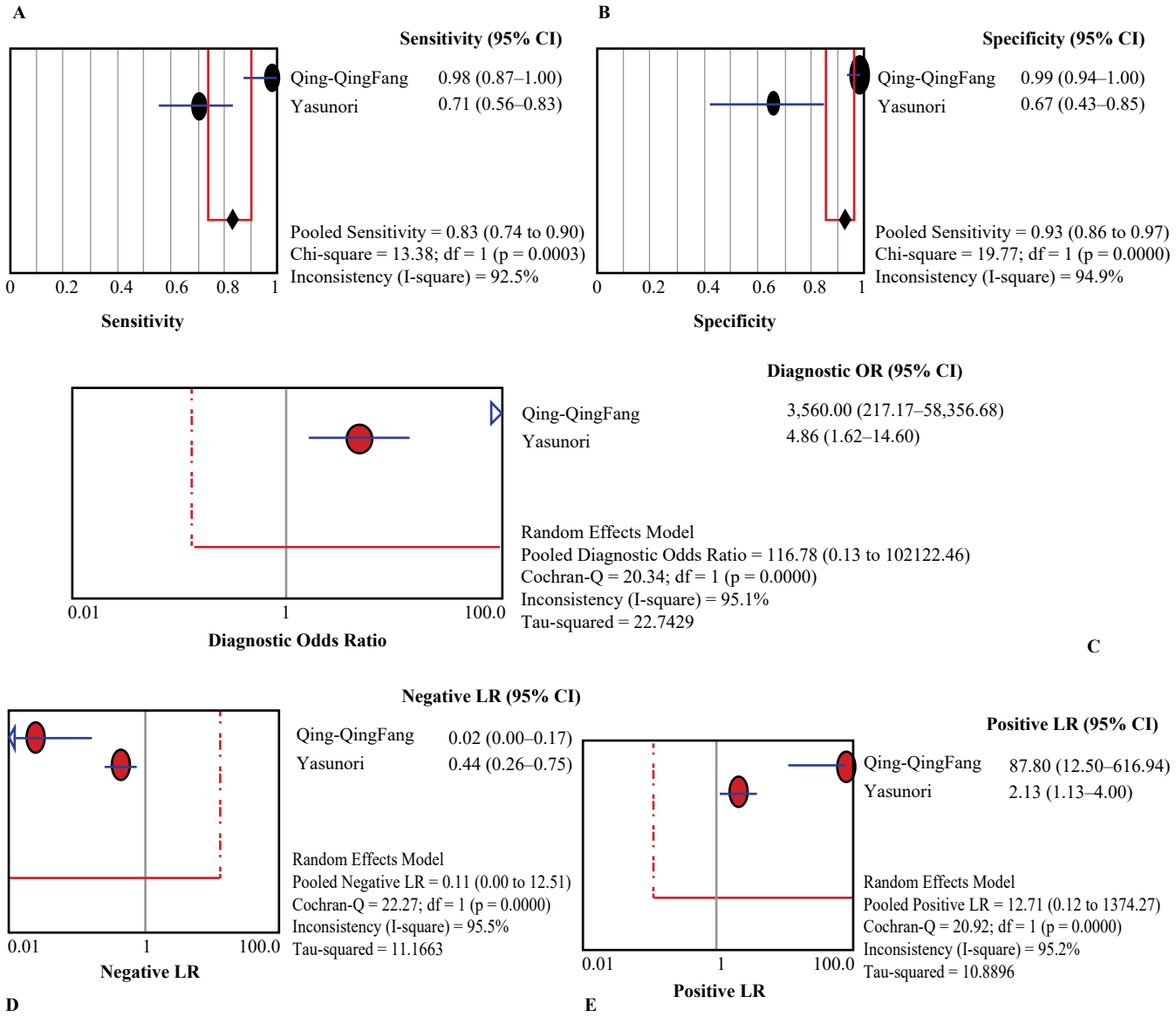

Fig. 3: (A) Forest plot of the sensitivity of serum Galectin 3 in HCC diagnosis. (B) Forest plot of the specificity of serum Galectin 3 in HCC diagnosis. (C) Forest plot of the DOR of serum Galectin 3 in HCC diagnosis. (D) Forest plot of the pooled negative LR of serum Galectin 3 in HCC diagnosis. (E) Forest plot of the pooled positive LR of serum Galectin 3 in HCC diagnosis. HCC = hepatocellular carcinoma.

The results indicated serum Galectin 3 levels in HCC were significantly increased compared to those in hepatitis and healthy persons, suggesting Galectin 3 played an important role in the pathogenesis of HCC. But there was no significant difference for serum Galectin 3 level between HCC and hepatic cirrhosis. In the study titled 'galectin 3 expression is induced in cirrhotic liver and hepatocellular carcinoma', Galectin-3 was abundantly expressed in cirrhotic liver in peripheral distribution within regenerating nodules (17). Such Galectin 3 expression in rapidly proliferating hepatocytes in cirrhotic liver may be a result of the high mitotic index. Alternatively, it is possible that proliferating cells expressing galectin-3 are in the process of being transformed, thus may indicate an early neoplastic event. Higher Galectin 3 level may be a potential biomarker for disease diagnosis. The meta-analysis showed that the overall sensitivity and specificity were 0.93 and 0.83 respectively, which implies clinical value to evaluate the diagnosis of HCC, used as an auxiliary diagnostic method. The pooled diagnostic odds ratio (DOR) reflects the accuracy of diagnostic tests as a reliable indicator; the greater its value, the stronger the diagnostic ability to distinguish. In our study the pooled DOR was 116.78, which suggested the efficiency of diagnosis was relatively high. The pooled positive LR was 12.71,

indicating the rate of detection of HCC was 12.71 times higher that of non-HCC.

The pooled negative LR implied that once the detection of Galectin 3 was negative, the risk of liver cancer is 11%. Overall, full consideration of the clinical symptoms, combined with serum Galectin 3, is helpful for early diagnosis. Zhou's study (4) included eight studies of serum AFP for diagnosis of HCC and reported as follows: sensitivity 70%, specificity 89%, and DOR 18.00 (9.41–34.46), which indicates that serum Galectin 3 may be a more useful diagnostic biomarker for HCC. The problem in our analysis is that there was no significant difference between serum Galectin 3 levels in HCC and hepatic cirrhosis, with an obvious heterogeneity. However, we did not analyse for publication bias, because the studies included were just four.

CONCLUSION

Our meta-analysis indicates that galectin3 may have good diagnostic accuracy for making the diagnosis of HCC. More studies should be done to evaluate the diagnostic accuracy of Galectin 3.

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AUTHORS' NOTE

LZ collected data and wrote the manuscript and approved the final version. XJC conducted data analysis and approved the final version. DH looked for the papers and collected the useful data and approved the final version, TYZ critically revised the manuscript and approved the final version. The authors declare that they have no conflicts of interest.

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ORIGINAL ARTICLE

What is the Diagnostic Role of Adenoid Hypertrophy and Adult-Onset Otitis Media with Effusion in Clinically Asymptomatic Nasopharyngeal Carcinoma?*

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ABSTRACT

Objectives: *To verify the role of adenoid hypertrophy (AH) and otitis media with effusion (OME) in adult patients, in relation to the diagnosis of clinically asymptomatic nasopharyngeal carcinoma (NPC).*

Methods: *One hundred and six adult patients were enrolled in this retrospective study. Of 256 cases who underwent nasopharyngeal biopsy for suspected nasopharyngeal malignancy in our clinic between January 2009 and July 2014, this subset met our criteria. We divided the patients into two groups—patients with AH only and those with synchronous presence of OME, and AH.*

Results: *Two patients out of 68 (2.9%) in the first group (only AH) and one patient out of 38 (2.6%) in the second group had NPC. There was no statistically significant difference.*

Conclusion: *We found that asymmetric AH in adult patients seems an important risk factor for NPC, and we strongly suggest that biopsy be done to rule out nasopharyngeal carcinoma, whether or not they synchronously have OME even in the absence of other clinical symptoms that would arouse suspicion of a nasopharyngeal malignancy, such as neck mass, epistaxis and cranial nerve impairment.*

Keywords: Adenoid hypertrophy, adult, nasopharyngeal carcinoma, otitis media with effusion

INTRODUCTION

Nasopharyngeal carcinoma (NPC), arising in the epithelium of the nasopharynx, is a rare malignant tumour in the United States and Europe that occurs in only 1 per 100 000 population, with a male predominance by a ratio of about two to one; however, the incidence is approximately 30-times higher in Taiwan, Hong Kong and southern China (especially the Guangdong province) which is accepted as an endemic region (1).

Although otitis media with effusion (AO-OME) is a disease that is believed to be unique to childhood it can be seen in any age group. Possible causes of AO-OME are adenoid hypertrophy (AH), nasal problems, acute respiratory tract infection, acute otitis media and secondary smoke (2, 3). The rare diagnosis of AO-OME in adults compared to children, may be an early sign of a NPC and warrants further evaluation for underlying malignant disease, especially if it is in one ear.

Nasopharyngeal carcinoma can cause OME through the following proposed pathogenic mechanisms: (a) obstruction of the Eustachian tube directly from a mass effect of the tumour and (b) tumour invasion of tensor veli palatini muscle that results in obstruction or dysfunction of Eustachian tube (4). So, a flexible, endoscopic, nasopharyngeal examination of adult patients with AO-OME is required to rule out a malignancy.

In this study, our aim was to verify the role of AH and OME in adult patients as a harbinger of clinically asymptomatic NPC, in a geographic area that is non-endemic for the disease, by comparing biopsy results of two study

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groups: group 1—patients who had only symmetrical or asymmetrical AH, and group 2—patients who synchronously had symmetrical or asymmetrical AH and OME.

SUBJECTS AND METHODS

The retrospective research protocol was approved by the local Clinical Research Ethics Committee. One hundred and six patients who underwent a nasopharyngeal biopsy, with/without insertion of grommet ventilation tube to one or both ears between January 2000 and July 2014 at a tertiary healthcare centre, were analysed in this retrospective study.

All of the patients were older than 18 years old, ranging from 18 to 76 years. They were confirmed to have AH by magnetic resonance imaging (MRI) and flexible nasopharyngoscopy; however, a suspected lesion was not identified in any patient. Patients without MRI were excluded from the study to ensure that patients were not included who might have had submucosal tumour detectable by imaging methods. Thus, only patients with clinically asymptomatic NPC by means of physical examination and imaging methods were included. Otomicroscopic examination, tympanometry and puretone audiometry were performed for each patient who had OME. All of the patients had undergone nasopharyngeal biopsy to exclude NPC.

We divided the patients into two groups according to synchronous presence or absence of OME, and AH. In the first group, there were 68 patients, who only had AH. In the second group, there were 38 patients, who had OME in addition to AH. The patients with OME underwent myringotomy and insertion of grommet ventilation tube as a standard treatment (Table 1).

Table 1: Distribution of AH, with and without OME, in patients, and side of ventilation tube insertion

	Patients number	VT side s
Group 1 (AH w/o OME)	68	None
Group 2 (AH w OME)	38	
Right		11
Left		14
Bilateral		13
Total	106	38

AH = adenoid hypertrophy; OME = otitis media with effusion; VT = ventilation tube.

Patients with AH

In the group of adult patients who had solely AH, AH was either symmetrical and generalized, or asymmetrical in which only one side of the nasopharynx was hypertrophied. All of the patients underwent nasopharyngeal biopsy under general anaesthesia. Malignancies other than NPC were excluded.

Thirty-one patients were male and 37 patients were female. The mean age of the patients was 43.2 years, with a range of 18–78 years. The cases who had signs and symptoms related to a high suspicion of malignancy, such as epistaxis, pathologic lymphadenopathy in the neck, or a malignant lesion detected at the nasopharyngeal area with flexible fibreoptic examination and/or MRI, were excluded from the study. Only patients who were apparently normal, except with asymmetrical or generalized, symmetrical, non-specific AH, were included.

Patients with AH and OME

In the group of adult patients who had OME in addition to AH, AH was either symmetrical and generalized, or asymmetrical, in which only one side of the nasopharynx was hypertrophied.

Twenty-two patients were male and 16 patients were female. The mean age of the patients was 46.6 years, with a range of 18–72 years. As in the first group, the cases with signs and symptoms highly suggestive of malignancy were excluded from the study. Only patients who were apparently normal, except for non-specific AH with synchronous OME, were included.

Statistical analysis

Data were analysed using a commercially available statistics software package (SPSS 15 for Windows). The Pearson's Chi-squared and Fisher's exact tests were used to analyse discrete variables to compare the two groups. In all analyses, values of $p < 0.05$ were considered statistically significant.

RESULTS

Two patients out of 68 in the first group had an NPC (both of them had non-keratinizing squamous cell carcinoma, WHO type II). The carcinoma ratio was 2/68 (2.9%). In the second group, one patient out of 38 (2.6%) was detected with an NPC (non-keratinizing squamous cell carcinoma, WHO type II). There was no statistically significant difference between the groups ($p > 0.05$, see Table 2). Overall, three out of 106 (2.8%) patients who underwent nasopharyngeal biopsy were diagnosed with a nasopharyngeal carcinoma.

Table 2: Comparison of patients with only AH (group 1) and patients with AH and OME (group 2)

	Value	df	Asymp. sig. (two-sided)	Exact sig. (two-sided)	Exact sig. (one-sided)
Pearson's Chi-square	0.008	1	0.927		
Continuity correction	0.000	1	1.000		
Likelihood ratio	0.009	1	0.926		
Fisher's exact test				1.000	0.708
Linear-by-linear association	0.008	1	0.927		
Number of valid cases	106				

AH = adenoid hypertrophy; OME = otitis media with effusion; NPC = nasopharyngeal carcinoma; RLH = reactive lymphoid hyperplasia; VT: ventilation tube.

In group 1, 55 patients had symmetrical, generalized AH and the remaining 15 patients had asymmetrical AH; seven had it in the right side and six had it in the left side. Nearly, half of the patients (33/68; 48.5%) had no symptoms, and AH in these subjects was detected incidentally on MRI that was performed by the neurology and neurosurgery clinics for other purposes, mainly differential diagnosis of chronic headache. These cases were referred to our clinic, and all of the patients underwent a flexible endoscopic examination. The other 35 patients (51.5%) attended our clinic for nasal obstruction and postnasal dripping, and AH was detected with an endoscopic examination of the nasopharynx; however, a suspicious lesion was not established in any patient. Magnetic resonance imaging (MRI) findings were also seemingly normal except for the AH in all of the patients.

Two out of 68 (2.9%) cases were shown to have carcinoma of the nasopharynx with biopsy results. Both of them had asymmetric AH that was right-sided with an unremarkable medical history in one female patient and left-sided in the other male patient. The female patient was consulted to our clinic for AH as an incidental finding on the MRI. On the other hand, the male patient presented to our clinic for nasal obstruction, which was progressive for the last six months. The patient had undergone a septoplasty for septal deviation in the same surgical session. None of the patients' pathologic results (those who had symmetric generalized AH in the nasopharynx) showed NPC (see Table 3).

In group 2, 25 patients (25/38; 65.8%) had symmetrical, generalized AH and the remaining 13 patients (13/38; 34.2%) had asymmetrical AH, in which seven were in the right side, and six were in the left side. All of the patients had attended our clinic for the complaints of hearing loss, aural fullness and tinnitus with/without nasal obstruction. Adenoid hypertrophy was detected with an endoscopic examination of the nasopharynx; however, a suspicious lesion was not established in any patient. Magnetic resonance imaging findings were also seemingly normal, except for the non-specific AH with synchronously present OME in all of the patients. One out of 38 (2.6%) cases was revealed to have carcinoma of the nasopharynx on biopsy. The patient was a male who had a left-sided, asymmetric AH. The patient attended our clinic for nasal obstruction, which was progressive for the last six months, and a left-sided, asymmetric AH was detected through an endoscopic examination of the nasopharynx. None of the patients' pathologic results (those who had symmetric, generalized AH in the nasopharynx), were NPC (see Table 3).

Table 3: Distribution of patients in relation to side of AH and biopsy results

Patients	Symmetrical AH		Asymmetrical AH		Total
	NPC	RLH	NPC	RLH	
Gender	M F	M F	M F	M F	M F
Patients with AH (Group 1)	None	24 29	1 1	6 7	31 37
Patients with AH and OME (Group 2)					
Right VT	None	4 2	None	3 2	7 4
Left VT	None	3 3	1 0	4 3	8 6
Bilateral VT	None	7 6	None	None	7 6
Total					22 16

AH = adenoid hypertrophy; OME = otitis media with effusion; NPC = nasopharyngeal carcinoma; RLH = reactive lymphoid hyperplasia; VT = ventilation tube, M = male; F = female.

DISCUSSION

Nasopharyngeal biopsy performed in otorhinolaryngology practice under general or local anaesthesia is not an uncommon surgical intervention in patients with suspected malignant disease of the nasopharynx. Nevertheless, the high rates of negative biopsy results question the validity of its routine implementation, which is a waste of time and cost in these circumstances. We found that asymmetric, adenoid hypertrophy in adult patients seems an important risk factor, and we strongly suggest that biopsy is needed to rule out nasopharyngeal carcinoma, whether they synchronously have OME or not, although, in the absence of other clinical symptoms, nasopharyngeal malignancy may still be present.

Two well-documented, important clinical features of NPC are firstly a high incidence in some geographic areas, such as China, Southeast Asia and North Africa, which have an incidence of up to 30-times more than low-incidence geographical areas including the United States and Europe; and secondly, there is a high incidence

in some races of persons that dwell in high-occurrence geographic areas (5). In these patients, nasopharyngeal biopsy could be performed to rule out a malignancy in clinically suspect situations, because early detection of an NPC can improve a patient's prognosis and quality of life.

Hsieh *et al* (6) evaluated a large number of patients who underwent nasopharyngeal biopsy for suspected NPC, and they assessed various clinical symptoms and signs (such as nasopharyngeal mass, neck mass, epistaxis, OME, headache, cranial nerve involvement) for relationship with the biopsy results by dividing the patients into cancerous and non-cancerous groups. They detected statistically significant differences for nasopharyngeal mass, neck mass, epistaxis and age between the groups after multivariable regression analysis. The only significant variable in the cancerous group for newly diagnosed NPC was neck mass. They found that nasopharyngeal mass had the highest sensitivity (90.7%), but lowest specificity (28.4%) due to a high rate of clinical misdiagnosis of nasopharyngeal lymphoid hyperplasia as NPC when examined with conventional white-light. On the other hand, an important clinical feature of this malignant disease is the possibility of a submucosal tumour underlying normal looking mucosa, which requires taking a biopsy, including submucosal deep tissue, up to a few millimetres (7).

Narrow-band imaging (NBI), a novel, optical technique to visualize nasopharynx, was also introduced in addition to conventional white-light endoscopes (8, 9). Narrow-band imaging (NBI) and conventional endoscopes were compared for differentiation rates of AH and NPC diagnosis in 79 consecutive, adult patients (9). They concluded that NBI was superior to the white-light endoscope for the detection of benign AH, but not that of NPC. However, NBI was not performed in our cases when we evaluated patients' files and electronic charts. Otitis media with effusion of childhood is mostly bilateral, and has numerous causes, except for tumours; however, it may be an early sign of an NPC in adults, when it is nearly always a unilateral occurrence. This warrants performing an endoscopic examination of the nasopharynx to exclude a nasopharyngeal malignancy. However, Gaze *et al* (10) detected nasopharyngeal neoplasm in adults with the only symptom being OME at an incidence of 1.4%. Similarly, they found an incidence of 1.5% in the second group of adult patients who had nasopharyngeal tumour presenting with only complaint of OME. It was concluded that the expected rate to disclose a diagnosis of NPC with isolated OME in adult patients, as presented in the literature, was between 0.4% and 5.7%, depending on population studied (4, 10–12). They suggested using clinical judgement with other clinical findings to determine whether an endoscopic nasopharyngeal examination was necessary or not in these patients.

Deeb and Ashktorab (13) concluded that bilateral AO-OME cases were usually caused by benign clinical conditions; however, unilateral cases needed nasopharyngoscopy to rule out nasopharyngeal malignancy. Glynn *et al* (14) presented 85 adult patients with isolated serous otitis media who underwent nasopharyngeal biopsy; serous otitis media was unilateral in 59 (69%) patients and bilateral in 26 (31%) patients. They detected NPC in three of 59 unilateral OME cases; one of the 26 bilateral serous otitis media cases was lymphoma.

We agree that adult patients with unilateral OME need an endoscopic examination of the nasopharynx to rule out a malignancy. Additionally, OME which is not improved with medical treatment or spontaneously, needs an endoscopic examination of the nasopharynx. For this reason, we excluded the patients in whom OME was improved with medical treatment or spontaneously and who did not need ventilation tube insertion.

All of the mentioned studies were performed in low-incidence geographic areas. Our results for prevalence of NPC in AH without/with OME are higher for both of our study groups, at 2.9% and 2.6%, respectively. A possible explanation may be that AH is present in all our patients. This difference was not statistically significant ($p > 0.05$). Ho *et al* (4) detected that five patients out of 87 with only OME were diagnosed with NPC, for a prevalence of 5.7% (5/87). They did not specifically mention AH detected by an endoscopic nasopharyngeal examination and/or MRI technique, but indicated that there were "no other apparent symptoms and signs suggestive of NPC". They concluded that the high prevalence of NPC was the result of endemicity for the disease in their population.

Magnetic resonance imaging of the nasopharynx is not only important for detection of a malignancy but also for the staging of NPC. Cui *et al* (15) found that MRI is superior to clinical detection of trigeminal nerve involvement in the untreated NPC patients. Tumour might invade deep anatomic structures, such as skull base, trigeminal nerve, cavernous sinus, intracranial region, by extending superiorly and laterally (14). Therefore, MRI is necessary in suspected cases with normal-looking nasopharyngeal mucosa, with or without adenoid hypertrophy.

CONCLUSION

We detected that asymmetric adenoid hypertrophy in adult patients seems an important risk factor requiring biopsy to rule out NPC, whether or not it is present synchronously with OME. We conclude the following regarding clinically asymptomatic NPC in a low-incidence geographic area for the disease:

(1) Asymmetric AH in adult patients indicates a high risk for NPC. We strongly suggest that this finding requires a biopsy to detect a malignancy earlier if it is present.

(2) A narrow-band imaging (NBI) endoscopic examination of the nasopharynx, coupled with conventional white-light endoscopic examination, has a higher chance of detecting benign adenoid lymphoid hypertrophy according to recently published studies (8, 9); therefore, it might decrease unnecessary nasopharyngeal biopsies.

(3) Generalized symmetric AH, as with OME in adult patients, indicates a relatively low risk for NPC. There is need for a biopsy of the nasopharynx (in the absence of other signs and symptoms) to rule out malignancy in these patients, if a neck mass or a tumourous lesion is detected on endoscopic examination of the nasopharynx. It seems that other factors are important, including clinical justification and experience of the surgeon. Patient-related factors are also important, such as age, gender, medical history, *etc*. Adult onset-otitis media with effusion (AO-OME) in non-endemic, geographic regions and in ethnic populations known to have low incidence of the malignancy for the malignancy, is more commonly due to benign diseases, such as allergic conditions and chronic infections.

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ORIGINAL ARTICLE

Cardiometabolic Risk and its Antecedents among Law Enforcement Officers in Trinidad and Tobago

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ABSTRACT

Objective: *To evaluate cardiometabolic risk and associated lifestyle behaviours among police officers.*

Methods: *Participants completed a validated self-administered questionnaire consisting of socio-demographic, dietary and physical activity items. Following this, blood pressure and anthropometry were measured using standard procedures. Participation in the study was voluntary. The study was approved by the Acting Commissioner of Police, Trinidad and Tobago Police Service.*

Results: *A total of 400 (females = 138; males = 262) officers participated in the study. Male officers were more likely than their female counterparts to have elevated blood pressures, waist circumferences and be smokers. In partial correlation analyses controlling for age, ethnicity, education level and marital status, body mass index was significantly inversely associated with the consumption of vegetables and peas and beans and positively associated with the consumption of sodas and cigarette smoking.*

Conclusion: *Our results indicate that high levels of cardiometabolic risk were associated with unhealthy lifestyle practices among participants.*

Keywords: Cardiometabolic, lifestyle behaviours, police officers, smokers.

INTRODUCTION

Globally, cardiovascular diseases (CVDs) are the leading cause of death among adults (1). In Trinidad and Tobago, over 50% of all visits to healthcare facilities are due to diabetes mellitus, hypertension and their co-morbid conditions (2). While CVDs have heredity components, unhealthy lifestyles (poor diet practices, physical inactivity, use of tobacco, excessive alcohol consumption) contribute to the development of important risk factors including hypertension, insulin resistance, altered serum lipids, and overweight and obesity (3, 4). These represent disorder metabolic processes driven by insulin insensitivity and inflammatory processes that increase the risk of cardiovascular diseases. Metabolic syndrome (the clustering of three or more of these risk factors) is a major cause of coronary heart disease. Overweight and obesity are persistent drivers of cardiometabolic risk (5).

Policing is a demanding and stressful occupation where officers are confronted with death, and threats to their well-being. The shift-based nature of their working hours is known to impact negatively on their ability to implement healthy lifestyle activity practices. It is therefore not surprising to find the rates of cardiovascular ailments are higher among police officers compared to the general public especially at retirement age (6–9). Given the role officers' well-being play in their ability to perform their duties effectively and efficiently, we sought to determine the prevalence of cardiometabolic risk factors and their lifestyle antecedents among officers of the Trinidad and Tobago Police Service (TTPS).

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SUBJECTS AND METHODS

Population

The population of interest consisted of police offers in the eight policing jurisdictions locally.

Sampling and sample size

Four of the eight jurisdictions were randomly selected and officers assigned to these jurisdictions were invited to participate. We assumed that 50% of the police officers have at least one cardiometabolic risk factor. To estimate this with a 5% precision, our calculations suggest that a minimum of 384 officers were required to participate. Altogether 400 officers participated in the survey. Prior to enrolment, the aims and objectives of the research were explained to potential participants. Those giving consent were enrolled. Participation in the study was voluntary. Approval for the study was granted by the Acting Commissioner of Police, TTPS. The study was conducted from September 1, 2013 to March 31, 2014.

Procedure

Anthropometry and blood pressure were measured using recommended procedures (10, 11). Participants' were seated in a quiet room for 10 minutes with the right arm outstretched and palm facing upwards. The upper mid-arm circumference was measured to the nearest 0.1 cm using a non-stretchable plastic tape measure. This was used to select the appropriate size cuff for blood pressure (BP) measurements. Three BP readings were then taken 3 minutes apart using standard procedures with the Omron HEM 712C (10). The average of the last two readings taken was used as the BP for each individual. Weight, height and waist circumference (WC) were measured using standard procedures (11). Percentage body fat (BF%) and lean muscle mass (LMM) were measured with the Omron Full Body Sensor HBF-510W (OMRON Healthcare, USA) according to the manufacturer's procedure manual. Population BF% estimated by these monitors are comparable to those measured with hydrodensitometry and dual-energy X-ray absorptiometry (DXA) (12).

Participants then filled out a questionnaire consisting of socio-demographic items, food frequency and physical activity items. Increased cardiometabolic risks were evaluated as follows: elevated WC of ≥ 35 inches (88 cm) for women and ≥ 40 inches (104 cm) for men; elevated systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg (13). All measurements were taken by an individual trained for the study.

Statistical analyses

Statistical analyses were performed using SPSS for Windows version 23 (IBM Corp., Armonk, NY). Prior to analyses data were checked for deviations from normality. The t-test was used to determine gender differences in continuous variables. Chi-square tests were conducted to determine association for categorical variables. Partial correlation analyses were used to assess the strength of the associations between anthropometric, body composition and physiological variables of interest.

RESULTS

Table 1 shows the socio-demographic characteristic of participants by sex. There were no significant differences in age, ethnicity, non-occupational physical activity level and marital status between male and female participants. Male officers were significantly more likely than their female counterparts to smoke cigarettes (38% *vs* 12%; $p < 0.001$).

They were also more likely than females to have elevated WC (63% *vs* 32.4%; $p < 0.001$), SBP (odds ratio [OR] = 1.80, 95% confidence intervals [95% CI]: 1.07, 3.02; $p = 0.04$) and DBP (OR = 1.62, 95% CI: 1.01, 2.60; $p = 0.005$). A BMI ≥ 30 was significantly associated with elevated SBP (OR = 4.4, 95% CI: 2.60, 7.30; $p = 0.001$), DBP (OR = 3.54, 95% CI 2.2, 5.60; $p < 0.001$) and WC (OR = 1.90, 95% CI: 1.63, 2.25; $p < 0.001$). BF% was significantly associated with BMI in males (r = 0.31; $p < 0.001$) and females (r = 0.76; $p < 0.001$).

Table 2 shows anthropometric and physiologic characteristics of officers by sex. Males were significantly taller, heavier and had higher LMM, SBP and WC than females.

Table 3 shows lifestyle practices of participants by sex. Twenty-one percent of participants had adequate levels of non-occupational physical activity at least three times per week. There were no significant gender differences in mean intakes vegetable, fruit, fish, red meat, soda and whole grain. Females were more likely than males to report adequate intakes of legumes (76% *vs* 62%; $p = 0.01$) and vegetables (51% *vs* 40%; $p = 0.03$). Males were significantly more likely than females to consume ready-to-eat meals ≥ 4 times weekly (46% *vs* 24%; $p \leq 0.001$). A total of 38% of participants consumed ≥ 48 ounces of sodas weekly.

In regression analyses adjusting for age, ethnicity, marital status, education level and money spent

Table 1: Socio-demographic characteristics of participants by sex

Variables	Female (n =138)	Males (n = 262)	*p*-value
Age group (years) (%)			
18–24	46.7	15.3	
25–34	39.9	37.5	
35–44	29.7	23.7	
45+	13.8	23.7	0.14
Ethnicity (%)			
Afro	43.5	32.8	
Indo	20.3	25.2	
Mixed	34.1	38.5	
Other	2.1	3.4	0.14
Marital status (%)			
Single	35.5	34.4	
Married	33.5	36.8	
Divorce	15.2	19.5	
Visiting	5.8	8.46	0.17
Smoking (%)			
No	87.7	61.8	
Yes	12.3	38.2	< 0.001
Non-occupational/Physical activity (%)			
Never	47.8	56.5	
Less than three times	32	22.1	
Three or more times per wk.	18.2	21.4	0.4
Education (%)			
Primary	1.4	1.4	
Secondary	71.71	61.3	
Technical	0.07	10.3	
Tertiary	26.1	22.1	0.9

Table 2: Anthropometric and physiological characteristics of participants by sex

Variable	Female (n = 138) Mean ± SD	Male (n = 262) Mean ± SD	*p*-value
Height (cm)	167.6 ± 15.7	170.6 ± 13.3	< 0.05
Weight (kg)	83.4 ± 17.4	87.7 ± 19.4	0.034
Body mass index (kg/m^2)	30.2 ± 5.5	30.0 ± 6.0	0.78
Percentage body fat (%)	41.8 (9.2%)	35.1 (10.6%)	< 0.001
Lean muscle mass (%)	25.8 (5.8%)	29.8 (6.7%)	0.002
Visceral fat (%)	8 (3.1%)	10.2 (5.4%)	< 0.001
Waist circumference (%)			
> 104 cm male	63.0	32.4	< 0.001
> 88 cm female			
Waist circumference (cm)	79.7 ± 12.3	83.3 ± 15.2	0.02
BMI > 30 (%)	46.7	44.0	0.62
SBP	124.6 ± 14.9	131.7 ± 16.9	< 0.001
DBP	82.5 ± 29.8	83.4 ± 14.4	0.72
Elevated SBP (≥ 140 mmHg) %	17.4	27.5	0.037
Elevated DBP (≥ 90 mmHg) %	23.2	32.5	0.005

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 3: Dietary pattern of police officers by gender

Variable	Female (n = 138)	Males (n = 262)	*p*-value
Fish (%)			
Twice a week	42.8	34.0	0.10
PA > 3 times a week Vegetable (%)	19.6	21.4	0.67
≥ 2 servings per day	51.4	39.7	0.03
Fruit (%)			
≥ 2 servings per day	41.31	32.4	0.08
Legumes (%)			
≥ 2 servings per day	75.5	62.1	0.01
Red meat (%)			
≥ 4 servings per week	20.3	29.0	0.07
Ready to eat meals (%)			
≥ 4 times per week	23.9	45.8	< 0.001
Soda (%)			
≥ 4 times per week	32.6	42.0	0.08
Whole grain (%)			
≥ 4 servings per week	18.8	18.3	0.89

on food each month, both BMI and WC were significantly positively associated with number of cigarettes smoked and sodas consumed and inversely associated with the consumption of vegetables, legumes, fish and whole grain products among males. Similarly, BF% was significantly inversely associated with consumption of vegetables, fruit, legumes and time spent in non-occupational physical activity and positively correlated with soda consumption. Diastolic blood pressure was positively associated with number of cigarettes smoked and the consumption of red meats, sodas and ready-to-eat meals. It was inversely associated with the consumption of vegetables, legumes and time spent in non-occupational physical activity. Among females, BMI was significantly inversely associated with vegetable and whole grain intake while WC was significantly positively associated with frequency of cigarette smoking and inversely associated with time spent in non-occupational physical activity, vegetable and whole grain consumption (Table 4).

In regression analyses controlling for age, gender, ethnicity, education level and marital status, BMI ≥ 30 was associated with elevated SBP (OR = 3.82, 95% CI: 2.92, 5.49; $p < 0.01$), elevated DBP (OR = 3.89, 95% CI: 2.88, 5.88; $p < 0.01$), vegetable intakes < 2 servings per day (OR = 1.9, 95% CI: 1.15, 3.14; $p = 0.015$), red meat intake > 4 servings per week (OR = 2.0, 95% CI: 1.04; 2.36; $p = 0.04$), soda intake > 48 ounces per week (OR = 1.9, 95% CI: 1.26, 2.88: $p = 0.002$), and lower participation in non-occupational physical activity < 3 times

Table 4: Correlations between cardio-metabolic and lifestyle factors among officers adjusted for age, sex, ethnicity, education level, marital status and monthly spent on food

Variable	BMI	WC	% Body fat	Systolic BP	Diastolic BP
Cigarette smoking					
Female	0.07	0.21*	0.04	0.05	0.10
Male	0.22***	0.23***	0.07	0.27***	0.27***
Physical activity					
Female	–0.18	–0.22*	–0.10	–0.08	–0.09
Male	–0.24***	–0.25***	–0.23***	–0.11	–0.16*
Vegetable intake					
Female	–0.21*	–0.25**	–0.14	0.02	0.16
Male	–0.25***	–0.25**	–0.19**	–0.12	–0.14*
Fruit intake					
Female	0.03	–0.02	0.04	–0.03	0.05
Male	–0.10	–0.10	–0.15*	0.07	0.006
Peas and beans					
Female	–0.09	–0.01	–0.11	0.07	–0.15
Male	–0.17**	–0.08	–0.18**	–0.13*	–0.14*
Red meat					
Female	0.02	0.04	0.10	0.08	0.18*
Male	0.08	0.10	0.01**	0.21**	0.19**
Fast food					
Female	–0.04	0.03*	0.01	–0.04	–0.03
Male	0.08	0.09	–0.07	0.23***	–0.18**
Sodas					
Females	0.10	0.13	–0.03	–0.16	0.17
Males	0.25***	0.21**	0.14**	0.29***	0.21**
Fish					
Female	0.10	0.04	–0.04	0.06	0.13
Males	–0.14*	–0.015*	–0.10	–0.13	–0.12
Whole grain					
Female	–0.18*	–0.23*	–0.23*	–0.06	–0.03
Male	–0.16*	–0.13	–0.09	–0.09	–0.13

*= $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.
BMI = body mass index; WC, waist circumference; BP = blood pressure.

per week (OR) = 4.70, 95% CI: 3.00, 10.86; $p = 0.001$). Approximately 48% of participants had one or more cardiometabolic risk factors and 7% of them had three of these risk factors. Approximately 43% of participants had BMIs ≥ 30, while 45% of them had WCs above recommended cut-offs.

DISCUSSION

Our results suggest that approximately 48% of participating officers had one or more cardiometabolic risk factors. In fact, obesity was the most prevalent risk factor. This is similar to the findings of studies conducted in other settings (6). Obesity is a consistent risk factor for the development of cardiometabolic diseases such as diabetes mellitus and hypertension, which are major contributors to the development of coronary heart disease (5). Cardiovascular diseases are the major causes of illness and death among law enforcement officers, especially among retirees (14). These results have important implication for monitoring the overall fitness of officers. Fitness is an important perquisite in policing duties, especially the detection and apprehension of criminal elements. Thus, regular monitoring of cardiometabolic risk factor with appropriate interventions is critical to effective and efficient law enforcement (8).

Importantly, these cardiometabolic risk factors were associated with important dietary and physical activity patterns in this population. In particular, consumption of unhealthy components of the diet such as convenience foods and sodas was associated with a greater risk of overweight and obesity, whereas higher consumptions of fruits, vegetables and whole grains were associated with normal weight (15). Similarly, engagement in non-occupational physical activity was associated with a protective cardiometabolic effect in this population. These findings are consistent with what is understood on the role of diet and exercise in aetiology of cardiometabolic diseases (15, 16). However, these may be symptomatic of issues related to the stressful nature of law enforcement. These must be addressed in the context of root causes to have meaningful impacts on the ability of police officers to effectively perform their duties (29, 37). This may be achieved through short educational exercises that address stress and its impact on diet and physical activity. In fact, the TTPS in 2014 has adapted lifestyle programmes to promote well-being among employees. In this regard, attention should be paid to increase risk of hypertension among males as this is the single most important risk factor for illness and death of adults globally (15–17). Hypertension is not only related to one's anthropometric stature but also to the level of stress experienced daily. Such stressful responses are typical for the profession, and therefore point to the need to provide officers with knowledge of coping strategies as part of their training.

Unfortunately, the study failed to include biochemical marks such as total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides and glucose as

ethical approval was granted for non-invasive procedures only. However, studies have shown that these are strongly correlated with level of adiposity, diet and physical activity. Notwithstanding, inclusion of biochemical markers in future studies would provide a much better profiling of the extent of cardiometabolic risk (17).

CONCLUSION

Our results indicate that high levels of cardiometabolic risk were associated with unhealthy lifestyle practices among participants. We recommend close post-recruitment monitoring and interventions to reduce the prevalence of these risk factors and promote well-being among officers.

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ORIGINAL ARTICLE

Factors Associated with Physical Activity in Jamaicans with Cardiovascular Disease

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ABSTRACT

Objective: *Cardiovascular disease (CVD) is the leading cause of death in Jamaica. Physical activity (PA) participation has positive effects on some risk factors for CVD. Despite this, many remain physically inactive. This study examined factors (social support, exercise barriers and benefits) associated with PA level in Jamaicans with CVD.*

Methods: *A total of 158 adults (112 females, 46 males), mean age 51.7 (15) years, were recruited from the medicine outpatient clinic of a large teaching hospital in Kingston, Jamaica, over the period 2012 to 2015. Exercise barriers and benefits, social support for exercise and PA level were assessed using questionnaires. Pearson's correlation coefficient was used to determine the relationship between PA level in MET-minutes/week, social support, exercise barriers and benefits. The relationship between the variables (social support, exercise barriers and exercise benefits) and categories of PA level was also determined using a one-way analysis of variance. Statistical significance was determined by* $p < 0.05$.

Results: *There was a statistically significant difference between 'family' social support scores across the three categories of PA (low, moderate, high) (F = 3.919;* $p = 0.023$*). Perceived exercise barriers and benefits had no significant association with PA level.*

Conclusion: *These results indicate that PA promotion strategies aimed at persons with CVD must consider the role of available social support.*

Keywords: Cardiovascular disease, exercise barriers, physical activity, social support.

INTRODUCTION

Non-communicable diseases (NCDs) have been reported as being the leading cause of death in Jamaica, contributing to 68% of all deaths (1); cardiovascular diseases (CVDs) accounted for 32% of these deaths. The Jamaica Health and Lifestyle Survey (2), the most comprehensive lifestyle survey performed locally, revealed that over the period 2000 to 2008, the proportion of Jamaicans who were physically inactive had increased. This pattern has likely persisted to present day, as no significant large-scale intervention to reverse it has been done. These data are disturbing in view of the fact that it is well known that the effects of these CVDs can be mitigated with exercise. Regular exercise has positive effects on some of the risk factors that contribute to CVD. It reduces blood pressure, excess weight and cholesterol levels, and increases exercise tolerance, fitness levels and insulin sensitivity (3). Other benefits include improvement in muscular function and strength, improved endothelial responsiveness (4) and muscle blood flow, increased oxygen consumption and functional endurance (5). These are important for persons with chronic CVD, whose exercise capacity is usually lower than normal (3).

Despite the benefits of exercise, many individuals in Jamaica do not engage in sufficient physical activity (PA) (2). Physically inactive persons are twice as likely to develop coronary heart disease (6, 7). While it is suspected that the level of PA in persons with CVDs will not differ from the general Jamaican population distribution, no study assessing PA level in this group has been done. In a study conducted among 48 Jamaicans with diabetes (8), researchers sought to determine how knowledgeable

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they were about the benefits of exercise and their level of exercise participation. The majority (88%) of the participants had a good knowledge of the benefits of exercise, but there was no significant relationship between knowledge and exercise participation.

Perceived barriers are known to be determinants of exercise participation (9). Some of the barriers observed in persons with CVDs include negative perception towards health and changing events as a result of cardiac events, having low mood, low motivation and lack of interest to exercise, feeling physically restricted towards or fearful of exercise, lacking knowledge regarding exercise (10), and lacking social support (11).

Social support refers to the function and quality of social relationships, such as perceived availability of help or support actually received (12). It is also related to tasks or steps that significant others take to facilitate behaviour. Social support for PA may be described as instrumental (giving a non-driver a ride to an exercise class), informational (telling a neighbour about a community exercise programme), emotional (calling a friend to see how he/she is coping with a new exercise programme) and appraisal (providing encouragement or reinforcement for learning a new activity) (13). There is still some inconsistency regarding the relationship between social support and PA. Social support from family and friends has been positively related to adult physical activity levels (9, 14–16). Eyler *et al* (11) conducted a telephone survey over a 1-year period in which they evaluated social support for PA using the Physical Activity Social Support (PASS) questionnaire. A total of 2912 women, aged 40 years and over, participated. Those with low PASS were more likely to be sedentary. In another study of 5167 Canadian men and women, aged 15–79 years, the effect of social support on PA was examined (17) and social support was not observed to have a significant effect on PA level.

Not enough research has been conducted on the factors influencing PA participation in Jamaica. While the relationship between social support and PA has been examined in other populations, the findings may be different in Jamaica given that ethnicity has been shown to influence this relationship (11). This study examined factors (social support, exercise barriers and benefits) associated with PA level in Jamaicans with CVD.

SUBJECTS AND METHODS

Ethical approval was obtained from the university's ethics committee and permission was received from the hospital's senior medical officer and head of the department of Medicine. Persons were included if they attended the hospital's medicine outpatient department and had at least one chronic CVD. Participants who gave informed consent were asked to complete interviewer-administered questionnaires. The Social Support Survey for Diet and Exercise Behaviors (18) comprises two sections: for assessing social support for exercise behaviours, only items 11 to 16 and 20 to 23 were used (19). The scale consists of Likert-type items with responses ranging from 1 (none) to 8 ('does not apply'). Social support scores from 'friends' and 'family' were summed separately.

The scale has been found to be valid and reliable for use in adults 18 years old and over (20). The Exercise Barriers and Benefits Scale (21) comprises 43 items that evaluate the perceived barriers and benefits from exercise participation. The instrument may be scored and used in its entirety or as two separate scales. The instrument has a four-response, Likert-type format with responses ranging from 4 (strongly agree) to 1 (strongly disagree). When the 'benefits' items are used alone, the score range is between 29 and 116. When the 'barriers' is used alone, scores range between 14 and 56. In this instance, the higher the score on the barriers items, the greater the perception of barriers to exercise. Test–retest reliability assessment yielded a reliability coefficient of 0.953 for the benefits and 0.886 for the barriers scale which suggests it is a reliable instrument for assessing perceived benefits and barriers to PAs among different populations (21). The benefits and barriers scales were used separately in this study.

The International Physical Activity Questionnaire (22) was used to assess PA level (vigourous walking, sitting and moderate exercise) by self-report in persons aged 18–69 years. Physical activity was scored as 'low', 'moderate' and 'high' and in MET-minutes/week.

Data analysis

Pearson's correlation coefficient was used to determine the relationship between PA level in MET-minutes/week, social support, exercise barriers and benefits. The relationship between the variables (social support, exercise barriers and exercise benefits) and categories of PA level was also determined using a one-way analysis of variance. Statistical significance was determined by $p < 0.05$. Statistical analysis was done using the Statistical Package for the Social Sciences, version 19 (IBM Corp., Armonk, NY).

RESULTS

A total of 158 persons (112 females, 46 males), mean age 51.7 (15) years, participated. Approximately 50% of the respondents were unemployed or retired. A total of 57 respondents (36%) fell in the 'low' PA category, while 32 (20.3%) were in the 'moderate' PA group and 21 (13.3%) were in the 'high' PA category. The mean (SD) PA score in MET-minutes/week was 1239.9 (2865.3). The mean (SD) for social support, exercise barriers and benefits is shown in Table 1.

Table 1: Mean (SD) for variables

Variable	Mean (SD)
Physical activity level (MET-minutes/week)	1239.9 (2865.3)
Social support (family)	17.94 (8.98)
Social support (friends)	17.47 (9.18)
Exercise barriers	27.7 (7.5)
Exercise benefits	94.0 (12.5)

Relationship with PA

There was a negative correlation between age and the mean PA score (r = –0.007), but this was not significant (p = 0.951). There was no significant relationship between gender and PA level. The mean PA score was not significantly related to social support, exercise barriers and exercise benefits (see Table 2).

Table 2: Relationship between mean PA score and social support, exercise barriers and benefits

Variable	*r*	*p*-value
Family social support	0.06	0.579
Friends social support	0.069	0.524
Exercise barriers	–0.127	0.241
Exercise benefit	0.201	0.062

There was no significant difference in PA scores across employment status (retired, unemployed, employed) (F = 1.802; p = 0.153).

There was a statistically significant difference between 'family' social support scores across the three categories of PA (low, moderate, high) (F = 3.919; p = 0.023). Post-hoc tests revealed that the 'family' social support was significantly higher in the 'high' PA group compared to the 'low' PA group (p = 0.018). There was also a statistically significant difference between 'friend' social support scores across the three categories of PA (F = 7.000; p = 0.001). The 'friends' social support was significantly higher in both the high (p = 0.004) and moderate PA (p = 0.026) groups compared to the low PA group.

When exercise barriers were compared across the three PA categories, there was no significant difference (F = 0.122; p = 0.885). Neither did perceived exercise benefits differ across PA categories (F = 0.998; p = 0.372).

DISCUSSION

Cardiovascular disease is the leading cause of death globally. Physical inactivity is one of the major behavioural risk factors for CVD (1). This study sought to determine the correlates of PA in persons with chronic CVD. Approximately 50% of the participants were found to be in the low PA category. This was in keeping with data from a large population-based study in which approximately 45% of the Jamaican population was reported as physically inactive (2).

Although the perception of barriers to exercise was low, this did not translate to persons achieving the recommended levels of PA. The mean PA level (in MET-minutes/week) fell within the low PA category. This was surprising given that there was a high perception of the benefits of exercise. There are, however, many other determinants of PA and exercise, such as self-motivation, social reinforcement, family influences and access to exercise facilities (23), which were not examined in this study.

Social support has been defined as non-verbal or verbal communication which aims to improve feelings of coping and competence (24). Social support for exercise was poor, overall. The mean scores from family and friends were 36% and 35%, respectively. This is similar to findings from the Adeniyi *et al* (25) study which states that 99.8% of participants experienced low social support for exercise. This study found that social support from friends and family was a positive influence on PA. Other studies have also reported similar findings (11, 22, 25). Healthcare and exercise professionals must evaluate the social support for exercise that is available, in attempting to influence exercise behaviours of persons with cardiovascular conditions.

Our study revealed a negative correlation between perceived barriers and PA (MET-minutes/week); however, this trend did not achieve significance. These findings conflict with those of Adeniyi *et al* (25) who found that higher perceived barriers were significantly related to low PA level. This may have been due to the differences in sample size.

To our knowledge, this is the first study that has assessed factors influencing PA in Jamaicans with CVD. A few limitations must be mentioned. The PA

level was measured by self-report. Respondents are known to overestimate their PA participation by this method. The cross-sectional nature of the study does not allow us to determine causal relationships between the factors and PA.

CONCLUSION

Engagement in PA is a major factor affecting cardiovascular risk. Social support has a strong influence on PA participation in Jamaicans with CVD. Health promotion strategies should encourage friends and family of persons with CVD to offer support for exercise.

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AUTHORS' NOTE

Both authors contributed to the development of the manuscript. The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Prevalence of Multiple Miliary Type of Osteoma Cutis in the Maxillofacial Region as an Incidental Finding: A Retrospective Cone Beam Computed Tomography Study

K Gunduz[1], G Serindere[2], H Avsever[3], K Orhan[4]

ABSTRACT

Objective: *Miliary osteoma cutis (MOC) is a rare variant of osteoma cutis in which multiple fragments of bone formations are embedded in the skin. In general, they are asymptomatic, benign and detected incidentally on radiographic examination.*

Methods: *This prevalence study was made by using cone beam computed tomography (CBCT) scans. A total of 893 CBCT scans were evaluated. A total of 202 of them were excluded because of poor diagnostic quality. The occurrence frequency of incidentally found multiple miliary type of osteoma cutis in head and neck area was noted. Median and range were used to describe the age of the patients.*

Results: *A total of 691 CBCT images were screened. Of these, 268 (38.8%) were from female patients and 423 (61.2%) were from male patients. The median age of patients referred for CBCT was 45.0 (IQR=30.0) years and within the age range of 5–84 years. A total of 22 (3.2%) multiple MOC cases in the maxillofacial region were discovered on 691 patients' CBCT scans.*

Conclusion: *Calcified lesions in the head and neck region were commonly seen in CBCT images. Although most of the calcifications are asymptomatic and require no treatment, diagnosis should be carefully made to avoid unnecessary further diagnostic assessments. It will also provide the ability to comprehensively evaluate underlying diseases.*

Keywords: Multiple miliary osteomas, osteoma cutis, prevalence.

INTRODUCTION

Multiple miliary osteoma cutis (MOC) is one of four subtypes of osteoma cutis, a rare skin disorder characterized by the bone formation within the dermis or subcutaneous tissue. Osteoma cutis is benign with limited and non-invasive growth as well as its subtypes (1). It may be primary or secondary, but a secondary form in association with a pre-existing inflammatory skin condition is mostly seen. In the majority of cases, it is clinically asymptomatic and may be detected incidentally on radiographic examination (2, 3).

Recently, the use of cone beam computed tomography (CBCT) for various diagnostic purposes is more common in dentistry. There are two major advantages of CBCT compared to 2D radiographic modalities. One of them is the elimination of geometric distortion and the second one is the reduction of structural superimpositions (4). Additionally, in comparison with computed tomography, CBCT has a lower radiation dose between 29 and 577 μSV. Computed tomography has radiation exposures of about 2000 μSV (5). It can provide precious diagnostic information not only from interested area but also out of the region. The out-of-interested region findings which are described as incidental findings may sometimes have greater importance in determining an appropriate treatment plan. The purpose of this study

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was to investigate the characteristics and frequency of multiple MOC which is incidentally detected.

SUBJECTS AND METHODS

This prevalence study was made by using CBCT scans. CBCT images used in the study were acquired on a 3D Accuitomo 170 (3D Accuitomo; J Morita Mfg. Corp., Kyoto, Japan), which were obtained between 2011 and 2016. A total of 893 CBCT scans were evaluated and 202 of them were excluded because of the poor diagnostic quality of small field of view size. The study sample (n=691) consisted of CBCT scans of patients who were referred for CBCT evaluation to the Department of Dentomaxillofacial Radiology, Gulhane Faculty of Dentistry, Health Sciences University, Ankara, Turkey. All CBCT images were evaluated by a dentomaxillofacial radiologist who has 12 years of experience on the basis of multiple miliary type of osteoma cutis, which were detected incidentally (Figs 1–3).

For CBCT evaluations, proprietary manufacturer software (i-Dixel 2.0/One Data Viewer/One Volume Viewer; J Morita Mfg. Corp., Kyoto, Japan) was used. Images were viewed in a dimly lit room on a 30-inch Dell™ 3008WFP Flat Panel Monitor (Dell Inc., Round Rock, TX, USA) at a screen resolution of 1920 × 1200 pixels and 32-bit colour depth.

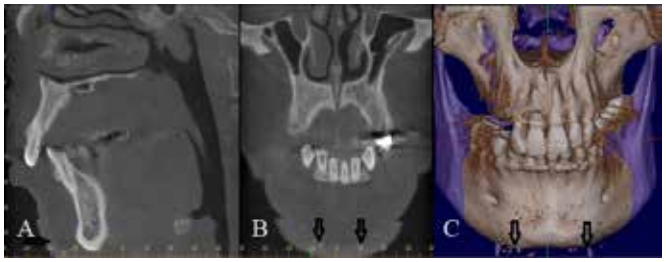

Fig. 1: A 45-year-old female referred for implant rehabilitation. On CBCT examination, multiple dot-like radiopaque masses were detected around the chin (arrow). (A) Sagittal view. (B) Coronal view. (C) Three-dimensional reconstruction.

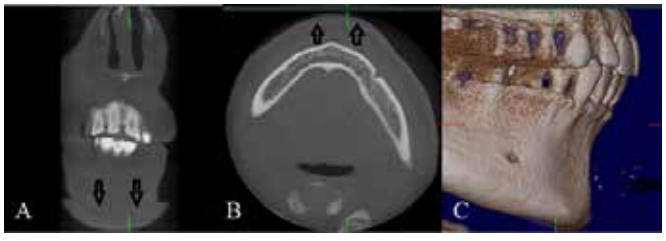

Fig. 2: A CBCT view of a 35-year-old male patient showing multiple radiopaque masses around the chin (arrow). (A) Coronal view. (B) Axial view. (C) Three-dimensional reconstruction.

Statistical analyses

Data were analysed by descriptive statistics. The occurrence frequency of incidentally found multiple MOC in head and neck area was noted. Median and range were used to describe the age of the patients. Statistical analyses were performed using the SPSS software (version 15.0; SPSS Inc., Chicago, IL, USA) and MS Excel 2003.

RESULTS

A total of 691 CBCT images were screened. Of these, 268 (38.8%) were from female patients and 423 (61.2%) were from male patients. The median age of patients referred for CBCT was 45.0 (IQR=30.0) years and within the age range of 5–84 years. A total of 22 (3.2%) multiple MOC cases in the maxillofacial region were discovered on 691 patients' CBCT scans. Of 22 patients, 14 (63.6%) were males and 8 (36.4%) were females. A predominance of males was found with a ratio of 14:8 over females. The median age of patients was 49.6 years, within the age range of 21–81.

The age–gender distribution and frequency distribution of the sample with multiple MOC are shown in Table 1. According to Table 1, multiple MOC was seen most frequently at 41–50 (n=7, 31.8%) and 51–60 age groups (n=7, 31.8%). The least frequent age group was found as 71–81 (n=1, 4.5%).

Table 1: The age-gender distribution and frequency distribution of the patients with multiple miliary osteoma cutis

Age groups	**21–30**		**31–40**		**41–50**		**51–60**		**61–70**		**71–81**	
Gender	M	F	M	F	M	F	M	F	M	F	M	F
	2	–	1	1	4	3	4	3	2	1	1	–
Total	2		2		7		7		3		1	

DISCUSSION

Osteoma cutis is true bone formation of the skin and is classified as primary and secondary (metaplastic) ossification (6). Secondary osteomas constitute 85% of cutaneous ossifications and develop in pre-existent neoplastic or inflammatory skin lesions (7). Primary

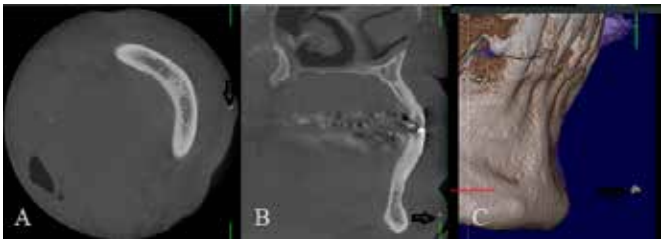

Fig. 3: A CBCT view of a 41-year-old male patient. The arrows point to radiopaque lesion around chin. (A) Axial view. (B) Sagittal view. (C) Three-dimensional reconstruction.

osteoma cutis accounts for approximately 15% of cutaneous ossifications and develops in itself (8). Classification of osteoma cutis is shown in Table 2. Principal causes of this condition are progressive osseous heteroplasia, Albright's hereditary osteodystrophy and multiple MOC in the face (6).

First, Virchow, in 1864, determined this condition as MOC (9). In 1928, the role of acne was first suggested by Hopkins in the development of multiple MOC (10).

The pathogenesis of this condition is unknown. Some hypotheses were present about the origin of the cell-forming osteoma. Fibroblast metaplasia is the most accepted theory (11, 12). According to *in situ* hybridization techniques, dermal fibroblasts have the talent to differentiate into osteoblasts and to produce collagen type 1 and osteonectin (11).

There is another hypothesis. According to this hypothesis, embryonic mesenchymal cells, faultily migrated to the dermis, might differentiate into the osteogenic lineage. Gene mutations in syndromes of cutaneous ossification can be one of the reasons (11).

Multiple MOC is an uncommon situation that generally affects middle-aged women associated with a history of severe acne (13). However men were more frequently affected than women in our study.

Miliary osteoma cutis is generally observed as skin coloured papules in the scalp, the face as well as the trunk, the breast, the extremities and the buttocks. In patients who have chronic acne, the differentiation between microcomedones and macrocomedones can be difficult (12).

Miliary osteoma cutis is an infrequent condition, with approximately 50 cases in the literature (11). After an extensive literature search, a few studies that have evaluated the prevalence rate were found about osteoma cutis in the maxillofacial region. According to the study of Safi *et al* (2), 6500 CBCT scans were evaluated and multiple MOC was found in 130 (2%) cases. Kishi *et al* (14) evaluated 2089 individuals and calculated the incidence of multiple miliary osteomas as 2.2%. Similar to our study, Kishi *et al* (14) reported that males were more frequently affected than females. In our study, multiple MOC was observed at the rate of 3.2%. This result is close to the results of Safi *et al* (2) and Kishi *et al* (14). Shigehara *et al* (15) assessed 33 cadavers and 158 living subjects. They detected multiple miliary osteoma in 27.8% (44/158) of the living subjects. Similar to our study, Shigehara *et al* (15)reported that incidence was higher in males than in females and multiple miliary osteomas were seen most frequently in the 40–59 age group. Kim *et al* (16) evaluated 1315 consecutive sinus computed tomography scans. Among the total number of males and females, they found in 252 males and 301 females who had small facial calcified nodules (42.1 and 42.0%, respectively). In comparison with our study, these rates were so higher than our study rates. In the study of Shigehara *et al* (15), this higher rate may result from the preference technique. As for the study of Kim *et al* (16), it was hypothesized that this encountered facial calcification represents primary MOC. According to our opinion, this may explain the high result of the study of Kim *et al* (16).

The patient may have an aesthetic problem because of multiple MOC. Until today, no curative treatment for multiple MOC has been found. However, different treatments with different results have been mentioned in the literature such as oral isotretinoin or tetracycline, the method of needle microincision–extirpation, surgical treatment and carbon dioxide laser (17, 18).

CONCLUSION

In conclusion, it was decided that CBCT provides more accurate detection of soft tissue calcifications such as osteoma cutis than conventional radiographic methods and additionally provides extensive information for accurate diagnosis. Thus, it assures the patients. However, the knowledge of calcified lesions improves the extensive evaluation of underlying diseases. It is very important that early diagnosis will save the life of the patients.

Table 2: Classification of osteoma cutis (based on 7, 8)

Primary		Secondary
Albright's hereditary osteodystrophy	Not associated with Albright's hereditary osteodystrophy • Multiple miliary osteomas of the face • Isolated osteoma • Widespread osteoma • Congenital plaque-like osteoma	(1) Inflammatory skin disease • Progressive systemic sclerosis and CREST syndrome Dermatomyositis Morphea (2) Tumours/Neoplasms Basal cell carcinoma, pilomatricoma, *etc* (3) Trauma and scars

AUTHORS' NOTE

KG conceived paper, oversaw data collection and revision of manuscript and approved final version. GS participated in study design, wrote manuscript and approved final version. HA participated in study design, data analysis and interpretation of data and approved the final version. KO participated in study design, data analysis and interpretation of data and approved final version. The authors declare that they have no conflicts of interest.

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ORIGINAL ARTICLE

The Efficacy of H89 on Aquaporin 5 Levels in Asthmatic Rat Models

M Saygin[1], O Ozturk[2], H Asci[3], D Bayram[4], İA Candan[5]

ABSTRACT

Background: *The effect of a specific protein kinase A inhibitor H89 on Aquaporin 5 (AQ5) levels, which has a role in the inflammation of asthma pathogenesis, was investigated in this study.*

Objective: *To prove that H89, which was thought to be a promising agent, may show anti-inflammatory activity in the treatment of asthma by causing inhibition of the protein kinase A enzyme that is involved in inflammation.*

Methods: *Thirty-two Wistar-Albino adult male rats, ranging between 250 and 350 g, were divided into four groups: (a) control group; (b) sham group, administration of 1 ml ovalbumin (OVA) solution intraperitonal (IP) and 0.1 ml OVA dissolved in dimethyl sulfoxide intranasally; (c) asthma group, IP + intranasally OVA administration; and (d) H89 group, (IP + intranasally OVA) + 0.1 ml H89. The lungs of the rats were evaluated histopathologically and immunohistochemically at the end of the study.*

Results: *The histopathological changes and AQ5 levels of the sham and asthma groups were not statistically different (*$p > 0.05$*). However, the parameters were found to be increased in the asthma group compared with the control group (*$p < 0.001$*). The alveolar degeneration and vascular congestion were statistically significantly decreased in the H89 group (*$p < 0.05$*). The AQ5 levels were reduced in the H89 group, but the difference was not statistically significant.*

Conclusion: *Aquaporin 5 levels and histopathological changes were increased in asthmatic patients, and an improvement was detected with H89 treatment. H89 has an effect on the inflammation of asthma pathogenesis, so it can be thought to be used in asthma treatment. However, more studies are needed to find out the therapy duration and ideal doses of H89 treatment.*

Keywords: Asthma, aquaporin 5, H89, ovalbumin, protein kinase A

INTRODUCTION

Asthma is a disease that progresses depending on the increased sensitivity in the respiratory tract and hypersecretion by goblet cells in bronchia. Inflammation sources that play a role in asthma's physiopathology are T lymphocytes, mast cells, eosinophils and macrophages. Biopsy studies have revealed that there are correlations between the density of inflammation and intensity of the diseases (1). The most prominent part is played by the corticosteroid in the suppression of inflammation in asthma treatment (2). These kinds of situations require new modalities to be applied in asthma treatment.

Protein kinase A (PKA) causes specific genes to be overly expressed, and it also causes intracellular effects by phosphorylating-specific proteins that bind to deoxyribonucleic acid-binding sites (3). Aquaporin 5 (AQP-5) is a member of the aquaporin family that is closely linked with the secretion of the serous glands (4). It has been demonstrated that AQP-5 levels are related with increased secretion, and AQP-5 secretion

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is regulated with the cyclic adenosine monophosphate (cAMP)–PKA pathway (5, 6). In cell culture studies relevant to H89, a potent PKA inhibitor, important results on the PKA pathway have been attained, and these findings should be supported with *in vivo* studies.

We researched the H89 effect on AQP-5 levels that have a role in inflammation in asthma pathogenesis.

MATERIALS AND METHODS

Experimental group

This study was conducted in the Suleyman Demirel University Experimental Animals Laboratory. In total, 32 white albino Wistar rats that weighed between 250 and 350 g were included in the study. Rats were separated into four groups:

Group 1 (Control): this is the group in which no action was taken.
Group 2 (Sham): asthma was created by giving asthma with chicken serum albumin (ovalbumin [OVA], grade III) and dimethyl sulfoxide (DMSO) to this group.
Group 3 (Asthma): an experimental asthma model was constructed after the rats were sensitized with chicken serum albumin (OVA, grade III), and no other medicine was given to this group.
Group 4 (H89): this is the group that received only the medicine called H89 (LC Laboratories, Woburn, MA, USA) in the form of topical intranasal spray after being sensitized with chicken serum albumin.

Ketamine (Alfamin, Alfasan, Holland) intraperitoneal (IP) at a dose of 90 mg/kg and xylazin IP at a dose of 10 mg/kg 24 hours after the last use of H89 anaesthesia were applied to all of the rats. Following the anaesthesia, lung tissues were placed in formaldehyde and examined histopathologically.

Preparation of medicines

For the sham group, a 0.9% physiological saline solution of 200 ml that contained OVA (25 μg/ml) and aluminium hydroxide (5 mg/ml) was prepared. On days 1, 2, 3, 7 and 10, 1 ml (IP) of solution was given. Prepared DMSO solution 8, 9, 10 and 14 days after the first use of OVA (IP) was applied to each nostril in two doses. Thus, two doses of 0.1-ml DMSO solution were applied in each nostril. Then, 1 hour after each DMSO application, the OVA solution, in which 0.02-g OVA was solved in 20-ml sulfide, was again given to each nostril in two doses.

The OVA sensitization method was employed, and the OVA solution was given to groups 2–4 on days 1, 2, 3, 7 and 10 in 1 ml (IP) in order to generate an experimental asthma model in rats. From day 7 on for inhalation use, the OVA solution was given to each rat's nostrils on days 8, 9, 10 and 14 in two doses of 0.1 ml each twice a day in groups 2–4.

The OVA solution was given to group H89 on days 1, 2, 3, 7 and 10 in 1 ml (IP). Prepared H89 solution (Sigma-Aldrich) (15 ml solution of 30 μM) on 8, 9, 10 and 14 days after the first use of OVA (IP) was applied to each of the nostrils in two doses. Then, 1 hour after each H89 use, OVA solution was applied given to each nostril in two doses. The lungs of the rats were examined histopathologically and immunohistochemically after the experiment.

All procedures in this study were conducted in accordance with the National Institutes of Health laws and approved by the Suleyman Demirel University Animal Research Ethical Committee.

Histopathological and immunohistochemical analysis

Tissues were fixed with formaldehyde for histological parameters and examined under a normal tissue microscope by staining with hemotoxylin and eosine. Stained samples were examined under an Olympus BX50 binocular microscope and evaluated by taking microphotographs from fractions. Fractions of each rat were scored separately from the point of the alveoli degeneration, mononuclear cell infiltration (MCI) and vascular congestion. Lung tissues were fixed with 4% paraformaldehyde solution for immunohistochemical analyses, and their AQP-5 levels were observed.

Histopathological and immunohistochemical scoring was performed semi-quantitatively as in the study by Ercan *et al* (7) and presented as follows:
(0) score (negative score), no structural damage;
(1) score (one positive score), minimal damage;
(2) score (two positive scores), middle damage;
(3) score (three positive scores): severe damage.

Statistical analysis

Statistical analyses were carried out by taking the benefit of Statistical Package for Social Sciences version 15.0 (IBM, Chicago, IL, USA) for Windows program. Histopathological and immunohistochemical results were evaluated statistically with the Mann–Whitney U-test, and correlations were evaluated with the

parametric *t*-test. The *p*-value less than 0.05 was considered significant and was accepted as meaningful for the different results.

RESULTS

Histopathological and immunohistochemical scoring was shown in Table. Histopathological findings were not confronted in lung tissue samples of rats in the control group (Fig. 1A). In the sham group, histopathological changes, such as alveolar degeneration, vascular congestion, haemorrhage and MCI, were observed ($p < 0.05$) (Fig. 1B). A meaningful increase was determined in histopathological findings acquired in the asthma group called OVA ($p < 0.05$) (Fig. 1C). A meaningful decrease existed in alveolar degeneration and vascular congestion in the treatment group called H89 ($p < 0.05$) (Fig. 1D).

In immunohistochemical analysis of tissue sections, it has been observed that AQP-5 staining is slightly present in the alveolar of lung tissue in the control group and is light (+) in the sham group (Fig. 2A and 2B). A non-statistically significant increase with AQP-5 staining was detected in the alveolar cells in the asthmatic group ($p > 0.05$) (Fig. 2C). However, it has been observed as decreasing to the levels of AQP-5 staining in the alveolar cells in the treatment group to whom we gave H89 compared with the asthma group ($p > 0.05$) (Fig. 2D).

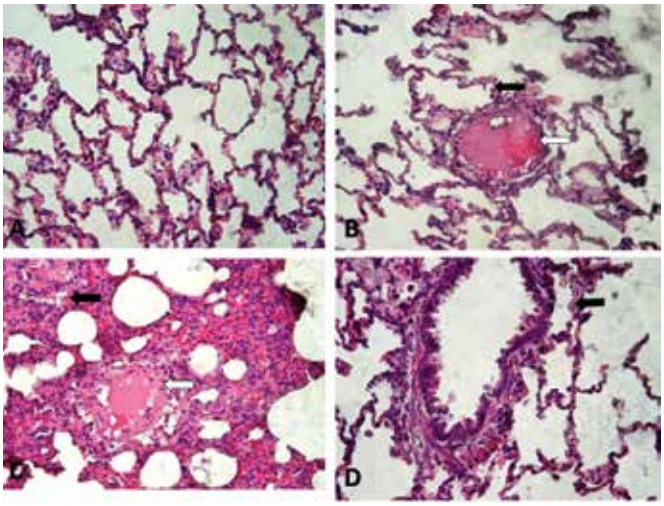

Figure 1. (A) Image of lung tissue in the control group (H&E; 40×). (B) Image of lung tissue in the sham group: haemorrhage (white arrow) and alveolar degeneration (black arrow) (H&E; 40×). (C) Image of lung tissue in the asthmatic group: haemorrhage (white arrow) and alveolar degeneration (black arrow) (H&E; 40×). (D) Image of lung tissue in the asthmatic + H89 group: alveolar degeneration (black arrow).
H&E = hemotoxylin and eosine.

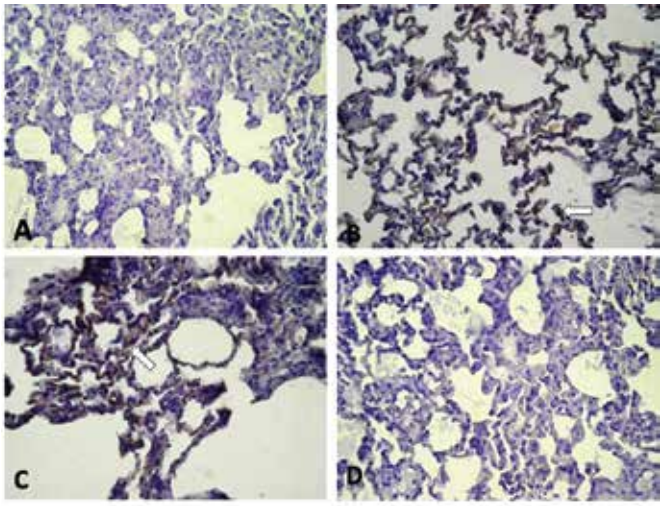

Figure 2. (A) Image of lung tissue in the control group: AQP-5 staining negative immunohistochemical staining; 40×). (B) Image of lung tissue in the sham group: AQP-5 staining positive (appearing as brown in the cell membranes of the alveoli (white arrows), (immunohistochemical staining; 40×). (C) Image of lung tissue in the asthmatic group: AQP-5 staining positive (appearing as brown in the cell membranes of the alveoli (white arrows) (immunohistochemical staining; 40×). (D) Image of lung tissue in the asthmatic + H89 group; decreasing in AQP-5.
AQP-5 = aquaporin 5.

Table: Histopathological and immunohistochemical analysis of lungs

	Control (n = 8)				Sham (OVA + DMSO) (n = 8)				Asthma (OVA) (n = 8)				H89 (OVA + H89) (n = 8)			
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
Alveolar degeneration	8	0	0	0	0	1[a]	5[a]	2	0	0	6[b]	2[b]	0	5[c]	3[c]	0
Mononuclear cell infiltration	8	0	0	0	0	1[a]	6[a]	1[a]	0	2[b]	5[b]	1[b]	0	5	3	0
Vascular congestion	4	4	0	0	0	3[a]	5[a]	0	0	1[b]	6[b]	1[b]	0	6[c]	2[c]	0
Haemorrhage	4	4	0	0	0	1 a	6 a	1 a	0	2 b	5 b	1 b	0	5	3	0
AQP-5 staining	6	2	0	0	2[a]	5[a]	1[a]	0	0	6[b]	2[b]	0	2	5	1	0

AQP-5 = aquaporin 5; DMSO = dimethyl sulfoxide; OVA = ovalbumin.

[a]Sham group induced lung injury, $p < 0.05$ *vs* control.
[b]Asthma induced lung injury, $p < 0.05$ *vs* control.
[c]Protective effect of H89, $p < 0.05$ *vs* asthma.

DISCUSSION

Because asthma is a chronic inflammatory disease, existing drugs must be used effectively and over the long term (8). The significant side effects have risen due to the chronic usage of these drugs, which has led us to develop new therapeutic drugs. In the treatment of allergic and inflammatory diseases, the prolonged usage of glucocorticoids has limited the use of drugs because they cause major side effects, such as suppression of the immune system, peptic ulcer, hypertension and osteoporosis. In addition, these drugs have ultimately created non-response to treatment due to glucocorticoid resistance evolving over time. This is the reason of the need to develop new drugs, which have fewer side effects and are as effective as steroids (9–11). Due to all of this information, the main objective of this study is to prove that H89, which was thought to be a promising agent, may show anti-inflammatory activity in the treatment of asthma by causing inhibition of the PKA enzyme that is involved in inflammation.

In the asthma study induced with OVA and conducted with this inflammation that occurs in asthma carried out by Rogerio *et al* in 2006, MCI was observed in lung histopathology. In addition, the substances called quercetin and isoquercitrin were found to significantly suppress this inflammation (12).

In the study carried out by McKay *et al* (13), it was found that the perivascular and peribronchial cell infiltration was suppressed by simvastatin in an OVA-induced asthma model. In another OVA-induced study, it was discussed that the protein kinase enzyme inhibition had reduced the T-helper 2 cytokine production in asthma, the pulmonary eosinophilia, serum IgE and IgG1 synthesis and mucus hypersecretion, and it also led to the increased sensitivity of the respiratory tract (14). It was shown that the phosphodiesterase type 4 inhibitor, rolipram, and the adenylate cyclase activator forskolin, PKA inhibitor H89, had suppressed the cAMP-induced eosinophilic infiltration (15). Hsieh *et al* (16) damaged the liver with oestradiol and bovine serum albumin and found that the protein kinase inhibitor H89 reduced the damage and haemorrhage. In a study in which the steroid was used together with the H89, it was found that the airway inflammation and hyper-responsiveness reduced. It was supposed that this dual therapy might cause a reduction in the therapy dose and the duration of glucocorticoid, so that the steroid-related side effects might be reduced. It had been pointed out that H89 could be used in steroid resistance asthma treatment, depending on the results of this study (17).

In this study, in the OVA-induced asthma model, a statistically significant reduction was present in the histopathological findings, such as alveolar degeneration, vascular congestion, haemorrhage and MCI, which occurred in the lung tissue with the H89 treatment.

As associated with inflammation developed on the basis of the disease, an increase in the level of AQP-5 was formed (4–6, 18). The water channel protein AQP-5, which was first detected in the submandibular gland (19), was also found in many tissues, such as apical membranes of the submucosal gland secretory cells, corneal epithelium, type I alveoli, and the lacrimal and salivary glands (20). The dysfunction of AQP-5 has been associated with many diseases, such as asthma, hyperhidrosis, hipohidrosis, salivary disorders and Sjögren's syndrome (21–23). In human beings, AQP-5 is important, especially in the cases of lungs and respiratory tract diseases. Aquaporin 5 has been localized in rat lungs in the epithelial cells' apical membranes lining type 1 alveolar (24). According to recent studies, the abundance and distribution of AQP-5 are regulated through the cAMP–PKA pathway (21, 25). The implementation of an anti-inflammatory property drug by inhibiting this cAMP–PKA pathway can lead to decreased levels of AQP-5. For example, Yang *et al* (25), in their cell culture study, found that AQP-5 messenger ribonucleic acid's protein levels and translocation of AQP-5 to the apical plasma membrane had increased fourfold in cells inserted with chlorophenylthio-cAMP (cpt-cAMP), and they also showed that a specific PKA inhibitor (H89) added to the cell culture decreased this effect. Sidhaye *et al*'s cell culture study (26), which included lung epithelial cells, showed that terbutaline and forskolin, which raised cAMP levels, increased the amount of AQP-5 and H89, which reduced the increased AQP-5 levels. Parvin *et al* (27) also showed that AQP-5 significantly increased and H89 blocked the increased expression when H89 was inserted in vitro into the cell culture of duodenal sections of an apical cell membrane that was treated with vasoactive intestinal polypeptide. It was observed that AQP-5 inhibited the feature of H89 in all of the mentioned studies, which were compatible with our study. In the in vivo study of the OVA-induced lung inflammation model, it was revealed that the increased AQP-5 levels in type I alveolar cells decreased as a result of the H89 treatment.

CONCLUSION

In light of all these findings, the reduction of the AQP-5 expression, which is one of the indicators of inflammation, may be important in the anti-inflammatory activity

and may contribute to the development of new drugs. Thus, we think that in an experimental OVA-induced asthma model, the PKA enzyme inhibitor H89 suppresses inflammation; thus, it may be an alternative agent in the treatment of asthma. It is obvious that this suppression should be supported by the studies with different doses and durations in the future.

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ORIGINAL ARTICLE

Histopathological Examination of the Effects of Butane Gas on Nasal Mucosa in Rats

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ABSTRACT

Background: *Butane is present as propellant gas in deodorants, shaving foam tubes and air fresheners. In our study, potential allergic effects of chronic inhalation of butane on nasal mucosa of rats were evaluated.*

Objective: *To discover the effects of butane gas on nasal mucosa in rats and determine its potential allergic effects.*

Methods: *An experimental study was conducted on Wistar Albino rats. Animals were divided into two groups as experimental and control. The experimental group was exposed to butane for 100 days. Coronal slices of 5 µm thickness were taken from the nasal cavities of the animals. Eosinophils, goblet cells, lymphocytes and eosinophil exocytosis were evaluated in slices.*

Results: *An increase was found in eosinophil counts in the experimental group (*$p < 0.001$*); between the groups, lymphocyte infiltration, amount of goblet cells and eosinophil exocytosis were similar (*$p > 0.05$*). A positive correlation was observed between lymphocyte infiltration and eosinophil exocytosis in the experimental group (*$p = 0.0001$*).*

Conclusion: *According to our study, butane may create inflammation in nasal mucosa.*

Keywords: Butane, eosinophil, goblet, nasal

INTRODUCTION

Nowadays, development of industrial production is accompanied by extensive environmental pollution. Various gases, the effects of which we do not yet know, are are emitted as a result of industrial production. Although the effects of these gases are not specifically well known, they generally cause air pollution and it is already well known that air pollution exacerbates allergic symptoms (1–3).

Butane gas, a member of the saturated aliphatic hydrocarbons, is encountered frequently in daily life, and humans are exposed to it. Butane is a compressed gas that is used as an aerosol propellant in deodorants, shaving foam tubes, air fresheners, etc. Liquefied petroleum gas contains butane gas in variable proportions. Acute and high dose inhalation of butane may lead to fatal arrhythmias and sudden death in a healthy heart (4–6). Recent animal studies found out that acute inhalation of extremely high concentrations of butane gas may adversely affect the central nervous system. Scattered symptoms of exposure to high concentration of butane include headache, nausea, dizziness, drowsiness, confusion and unconsciousness (7–9). However, there is no study regarding the effects of chronic inhalation of butane gas in the literature.

Allergic rhinitis is a global health problem that negatively influences social life, sleep, school and occupational life (10). In histopathologic studies concerning allergic rhinitis, increase of eosinophils and eosinophil exocytosis, lymphocyte infiltration and goblet cell hyperplasia have been observed (11–14).

In our study, we aimed to determine the effects of butane gas on nasal mucosa and its potential allergic effects in rats.

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MATERIALS AND METHODS

This study was conducted in animal laboratory of the Experimental Medical Research Institute of Istanbul University, obeying the Declaration of Helsinki. Prior to the trial, consent from Animal Experiments Local Ethics Committee of Istanbul University was received (Ethics Committee number: 30.03.09-42). In this study, animal experiment ethics board guidelines of Istanbul University were followed.

The study was conducted on 20 healthy adult female Wistar albino rats. Animals were obtained from the animal laboratory of the Experimental Medical Research Institute of Istanbul University. Rats were 7–8 months old, and their weights were varied between 200 and 250 gms. Animals were divided with random choice into two groups of 10, as experimental group and control group. The rats were locked inside the cages so that each cage contained five rats. All rats were harboured in a surrounding which was artificially illuminated and darkened equally for 12 hours. The temperature was set to 21°C–22°C. The rats were allowed to eat and drink freely. Adjustment of illumination and darkness were carried out by a timer installed to the lighting system. In addition, for the experimental group, an acrylic glass cabin with 20 circular ventilation holes with a diameter of 2 cm and dimensions of 40 × 40 × 50 cm was used. Since rats are more active during night, the experimental group was taken into this cabin which was placed in another room, during the darkness period. Also, an automatic spray machine (Discover automatic spray dispenser; Guler electronic, cosmetic, chemical company, Istanbul, Turkey) with day–night adjustment and timer was installed into the cabin to emit butane gas. During the experiment, lighter gas tubes (Jumbo lighter gas; Unver group, Istanbul, Turkey) that contained purified butane gas were used. Duration of the experiment was 100 days. During the study, butane gas was given as one spray (0.6 mL) in 5-minute intervals during the 12-hour darkness period into the cabin, where the experimental group was harboured. Gas measurement was performed in the geology lab of Istanbul University Faculty of Engineering. A gas chromatograph (Agilent 6890N, Agilent technologies, Santa Clara, CA, USA) fitted with a thermal conductivity detector, and flame ionization detector was used to identify the hydrocarbon and other noble gases in the cabin.

At the end of the experiment, all animals were sacrificed using intraperitoneal sodium pentobarbital (100 mg/kg). Then, upper jaws of the animals were removed by incising in front of the orbit on coronal plane so as to contain the nose. Coronal slices of 5 μm thickness were taken from the nasal cavities of the animals. Slices were stained with haematoxylin-eosin stains. Decalcification with a 20% formalin–formic acid solution was applied to slides for 12 hours, in order to better visualize the goblet cells in slices. All slices were evaluated microscopically in 10 magnified areas for eosinophil count, amount of goblet cells, lymphocyte infiltration and eosinophil exocytosis (Figure 1). Magnified cross sections most representative of each cell group were evaluated. Eosinophils in the magnified areas were counted; on the other hand, amount of goblet cells, lymphocyte infiltration and eosinophil exocytosis were determined semi-quantitatively. During the experiment, two rats from the experiment group and two rats from the control group died due to unknown reasons. Dead animals were not subjected to histopathological evaluation.

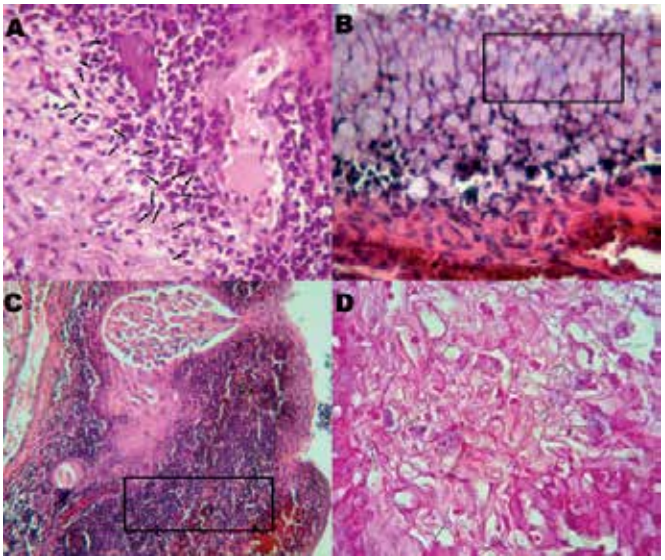

Figure 1: (A) Eosinophilia in nasal mucosa. Arrows show some of the eosinophils (experimental group; haematoxylin-eosin stains, magnification ×100). (B) Goblet cells in nasal epithelia. Inside the rectangle, a group of goblet cell is seen with translucent cytoplasm (experimental group; haematoxylin-eosin stains, magnification ×400). (C) Lymphocyte infiltration in nasal mucosa. A large number of lymphocytes are seen inside the rectangle (experimental group; haematoxylin-eosin stains, magnification ×100). (D) Eosinophil exocytosis in nasal mucosa. Arrows show some of the exocytosis areas (experimental group; haematoxylin-eosin stains, immersion magnification ×1000).

Statistical analyses

Because variables did not provide assumption of normality and numbers of subjects were low in groups, whether histopathological changes differed for the experimental and the control groups was evaluated with Mann–Whitney *U* test. In addition, the relationship

between lymphocyte infiltration and eosinophil exocytosis was determined with Pearson Correlation test. The significance level was set at 5% ($p \leq 0.05$).

RESULTS

Butane gas is heavier than air, and it may accumulate in a closed place. For this reason and due to the ventilation holes of the cabin, amount of butane gas detected in the cabin was variable. The amount of butane gas detected in the cabin was between 1350 and 2000 ppm (1.35%–2%). Rats showed no symptoms of central nervous system depression.

In the histopathological examination of the slices of the experimental group, it was observed that eosinophil counts vary between 24 and 75 (mean ± SD, 42.4 ± 18.9). This count ranges from 2 to 9 (mean ± SD, 4.25 ± 2.8) in the control group. In the experimental group, a significant increase in eosinophils was seen ($p < 0.001$). The amount of goblet cells in slices range between '+' and '+++' (mean ± SD, 1.75 (+) ± 0.88 (+)) in animals from the experimental group, and between '+' and '++' (mean ± SD, 1.125 (+) ± 0.125 (+)) in the control group. When groups were compared, the amount of goblet cells was found to be similar ($p > 0.05$). When lymphocyte infiltration was compared, whereas it ranged from '+' and '++++' (mean ± SD, 2.25 (+) ± 1.28 (+)) in animals from the experimental group, the range in the control group was found to be between '+' and '++' (mean ± SD, 1.375 (+) ± 0.517 (+)). When these differences were evaluated, the amount of lymphocyte infiltration was found to be similar ($p > 0.05$). As for eosinophil exocytosis, whereas values between '+' and '+++' (mean ± SD, 1.875 (+) ± 0.83 (+)) were observed in the experimental group, values between '+' and '++' (mean ± SD, 1.375 (+) ± 0.517 (+)) were observed in the control group. Eosinophil exocytosis was found to be similar between groups ($p > 0.05$) (Table). When two groups were compared, in slices where the lymphocyte infiltration was more in the experimental group, eosinophil exocytosis was also found to be more. A positive correlation was observed between lymphocyte infiltration and eosinophil exocytosis in the experimental group ($r = 0.987$ $p = 0.0001$).

DISCUSSION

There are various gases that are introduced into the atmosphere, thereby increasing air pollution. This results in respiratory and allergic diseases (1–3). Despite an increase in the development of allergic rhinitis with exposure to air pollution in some studies (1–3, 15), in others, this relationship could not be established (16). The relationship between outdoor pollutants and rhinitis of unknown origin has also been reported (17–20). We are exposed to butane gas in many areas of life and effects of this gas on living creatures are not well known.

In the literature, there are studies about butane gas related to acute, accidental exposure or exposure due to its abuse. When butane gas is inhaled, it makes myocardium sensitive to catecholamines and accumulates in fat-rich tissues and especially in brain (7, 23). Following the inhalation of butane gas, cases in which ventricular fibrillation and encephalopathy occur have been reported (6, 24–26). Rhabdomyolysis, multiple organ failure and death due to exposure to butane gas may also develop (4, 5, 27, 28). However, the possible effects of chronic and low-dose exposure to butane gas are not well known. In this study, allergic effects in nasal mucosa of rats as a result of exposing rats to butane gas at low dose and for longer duration, instead of acute and high doses, were histopathologically investigated.

Eosinophils and T lymphocytes are among the major cells of allergic inflammations. In allergic diseases, T lymphocytes, eosinophils and products have been shown to be increased and found to be related to severity of the disease (29–33). In patients diagnosed with

Table 1: Histopathologic changes in nasal mucosa between the experimental and control groups

	1st Rat	2nd Rat	3rd Rat	4th Rat	5th Rat	6th Rat	7th Rat	8th Rat	*p* value
Eosinophil counts in E.G.	30	32	65	28	24	75	50	35	<0.0001
Eosinophil counts in C.G.	3	2	2	5	9	8	2	3	
Amounts of goblet cells in E.G.	+	+	+	++	++	+++	+	+++	NS
Amounts of goblet cells in C.G.	+	+	++	+	+	+	+	+	
Amounts of lymphocyte infiltration in E.G.	++++	++++	++	++	+	+	+++	+	NS
Amounts of lymphocyte infiltration in C.G.	+	+	+	++	++	++	+	+	
Amounts of eosinophil exocytosis in E.G.	+++	+++	++	++	+	+	++	+	NS
Amounts of eosinophil exocytosis in C.G.	+	+	+	++	++	++	+	+	

E.G. = experimental group; C.G. = control group; NS = non-significant; *p* value: between rats in the experimental group and rats in the control group.

allergic rhinitis, a significant increase in numbers and activities of eosinophils and CD_4+ T lymphocytes have been found in nasal biopsy and lavage applications when an allergen is encountered (11, 12). It has been shown that in bronchoalveolar lavage fluids taken from asthmatic patients 24 hours after allergens are encountered, local CD_4+ T lymphocytes were activated, m-RNA expression for TH_2-type cytokines was increased and eosinophils piled up (34). Also, in experimental studies, eosinophils and CD_4+ T lymphocytes are found to be increased in the nasal cavity and lungs once allergy is induced (35, 36). Additionally, CD_8+ T lymphocytes are known to have a regulatory role in allergic diseases (37, 38). In many slices in the experimental group, we have observed an increase in eosinophils and lymphocytes in nasal mucosa. The presence of a significant increase ($p < 0.001$) in eosinophils in nasal mucosa shows the relationship of this gas with eosinophilic inflammation. Although there was a more obvious increase in lymphocyte infiltration in the experimental group, a similar increase was found in the control group ($p > 0.05$).

Eosinophil exocytosis has an important role in allergic reactions. As a result of exocytosis, cytotoxic proteins such as major basic protein, eosinophil cationic protein, eosinophil peroxidase, eosinophil-derived neurotoxin, enzymes and also cytokines are released out of the cell, and as a result tissue damage and inflammation develop (29, 39, 40). In the experimental group, we detected eosinophil exocytosis in many slices. In slices in which there is more lymphocyte infiltration, we observed that there was also more eosinophil exocytosis. In the experimental group, a positive correlation was observed between the increase in lymphocyte infiltration and the eosinophil exocytosis ($r = 0.987$, $p = 0.0001$). This result supported our thought that exposure to butane gas might induce inflammation.

Goblet cells that form a substantial part of respiratory epithelium are present in almost every site of the mucosa of the respiratory tract and are responsible for production and secretion of mucus. Many inflammatory and humoral mediators that include environmental antigens stimulate mucus production (41). Inflammatory molecules stimulate mucus production from epithelial cells in the protective immune response and inflammatory allergic airway diseases by activating interleukin-13 and the epidermal growth factor receptor (EGFR). The expression and activation of EGFR promote goblet cell hyperplasia and metaplasia (42, 43). In studies conducted by inducing allergic inflammation, increase in goblet cells in the respiratory epithelium has been encountered (13, 14, 44). Also, the amount of goblet cells was found to be similar in patients with allergic rhinitis both before and after high pollen periods (45). In our study, we encountered increase in goblet cells in many slice areas in the experimental group, but this increase was found insignificant. However, a direct proportional relationship has been determined between duration of exposure to antigen and increase in goblet cells (13). We think that butane gas might create an allergic effect on respiratory epithelium if the duration of exposure is increased.

CONCLUSION

Butane gas is a substance that we frequently encounter in our daily life. Allergic diseases constitute very important health problems worldwide, influencing domestic, educational, and social lives of individuals and accounting for a significant part of healthcare costs. Therefore, eliminating the causes that may have effect on development of allergic diseases is crucial. According to our study, we have concluded that chronic inhalation of butane gas may create inflammation and might generate allergic effects in nasal mucosa due to significant increase in eosinophils and significant correlation between lymphocyte infiltration and eosinophil exocytosis in the experimental group. Although more detailed studies are needed in order to definitively determine the inflammatory and allergic effects of butane gas, our study is important due to it being the first study of its kind in the literature, as far as we are aware.

AUTHORS' NOTE

SY conducted the experiment, conceived paper, oversaw data collection, conducted data analysis, wrote the manuscript and approved the final version. IT participated in study design, data analysis and interpretation, critically revised the manuscript and approved the final version. GH participated in study design, data analysis and interpretation of data and revision of the manuscript and approved the final version. The authors declare that they have no conflicts of interest.

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ORIGINAL ARTICLE

Maternal and Foetal Outcome of Anti-epileptic Drug Use in Pregnancy in Afro-Caribbean Patients

S Rowe-Gardener[1,2], F Gayle[1,2], N Johnson[3]

ABSTRACT

Objective: *To determine the maternal and foetal outcomes of anti-epileptic drugs (AEDs) use during pregnancy, in women of Afro-Caribbean descent, seen at the University Hospital of the West Indies (UHWI).*

Methods: *A retrospective observational study was conducted for the period of 2002-12. From the records received, 40 cases were identified from the labour ward admission books and the Codes and Ethics Department. The controls were sought from the labour ward records and were matched for year of delivery, age ± 6 years and co-morbidities.*

Results: *An adverse foetal outcome was higher in infants exposed to AEDs in utero and was found to be statistically significant (*p *= 0.04). The occurrence of minor malformations in infants exposed to AED was determined to be more than two-times (14.2%) compared to the occurrence in infants from the control group (6.1%). The maternal outcomes from an exposure to AED in pregnancy were not found to be significantly different between cases and controls. (*p *= 0.06).*

Conclusion: *There are additional adverse effects of AED use in pregnancy, other than major congenital malformations (MCMs), such as an increased risk of foetal demise. Similar to the previous reports, there are adverse maternal outcomes of AED use, though the differences did not achieve conventional levels of statistical significance in this study.*

Keywords: Anti-epileptic drugs (AEDs), Afro-Caribbean, major congenital malformations (MCMs), maternal outcomes

INTRODUCTION

Epilepsy is the most common serious chronic neurological condition, affecting between 4 and 10 people per 1000 (1). Most of those affected, including women of childbearing age, will require a long-term treatment with anti-epileptic drugs (AEDs) to prevent seizures (1). It is widely accepted that the prenatal exposure to AEDs increases the risk of a major congenital malformation (MCM) from the background risk of 1%–2% to 4%–9% (1). However, the medical literature does note that more than 90% of pregnancies will be free of MCMs (1). There are other effects of AEDs such as respiratory distress (2), foetal demise (3) and neurodevelopmental effects that have been identified by following the infant from 2 years to several years after the birth (3–12). It is recommended that women who have to use AEDs take the smallest effective dose and/or utilize monotherapy as much as is possible (13, 14).

The mechanisms for the teratogenicity of AEDs are most likely multifactorial and may include genetic susceptibility, free radical intermediates of AEDs, enzymatic deficiencies causing accumulation of toxic intermediates of medications and AED-induced folate deficiencies (15). Despite the lack of irrefutable evidence, the American Academy of Neurology recommends that every woman with epilepsy of childbearing age receives

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folate supplementation of at least 0.4 mg/day for primary prevention of neural tube defects and 5 mg/day for secondary prevention (13, 15, 16). Furthermore, women with epilepsy have an approximately twofold increased risk of certain obstetrical complications including hyperemesis gravidarum and abruptio placentae (17). It is uncertain as to whether or not these adverse effects are due to epilepsy or the use of AEDs in pregnancy.

The development of international pregnancy registers has generated useful information towards a greater understanding of the impact of AED exposure on immediate birth outcomes (18). Nevertheless, there were no data found looking at the difference in adverse effects among the different ethnic groups in either mother or child. This study aims to identify the adverse effects of AED/s use in pregnancy on mother and foetus in an Afro-Caribbean population. The statistical method used is the ANOVA analysis to determine the correlation between the AED use and the adverse effects identified. It is hoped that this study will encourage Jamaica and other Caribbean countries to consider starting a registry of pregnant women on AEDs. The results from such a registry could help many local neurologists and obstetricians to treat pregnant women, who require AEDs, with more confidence.

SUBJECTS AND METHODS

Study design

This is a retrospective observational case–control study conducted at the University Hospital of the West Indies (UHWI). The UHWI is a tertiary academic referral hospital with over 400 beds serving the capital city and its surrounding areas in Jamaica.

The cases were chosen based on the following inclusion criteria: All pregnant women who had epilepsy and were using AEDs or had epilepsy but were not using AEDs or those who do not have epilepsy but were using AEDs for conditions other than epilepsy, and were seen at the antenatal clinic (ANC) or admitted at the UHWI between 2002 and 2012. For each of the enrolled women, one woman was chosen who does not have epilepsy and is not taking AEDs. These controls were within a ± 6-year age range and were delivered the same year as the enrolled case. They were also matched for co-morbidities.

Patients were excluded if they: were not known to have epilepsy but had one seizure episode in the past and were not using AEDs; were not known to have epilepsy and not on AED but had eclampsia; had congenital malformations or family history of congenital malformations; had multiple gestations, alcoholic consumption or smoking during pregnancy; had acute infections during pregnancy.

Data collection

Forty index cases were identified from the labour ward admission books between 2002 and 2012. The cases were identified from a search of the labour ward admission books and the Codes and Ethics Department based on the code for pregnancy and epilepsy, migraine, bipolar disorder and neuropathic pain. The controls for each index case were sought from the labour ward records in the same year of delivery as the index case and were also matched for comorbid diseases. These controls did not have epilepsy and were not taking AEDs. Once the dockets were obtained, the pre-natal and post-natal notes up to six weeks following delivery were reviewed.

The maternal and foetal outcomes of the controls were then compared to the index cases. The study was approved by the University Hospital of the West Indies/University of the West Indies/Faculty of Medical Sciences Ethics Committee. Data were entered into a Microsoft Access database (see Appendix A) and included: medication regime, *i.e.*, single or polytherapy; time instituted prior to or during pregnancy. Polytherapy is defined as taking two or more AEDs concurrently regardless of the time, the subsequent drug was added. The maternal and foetal outcomes observed for were similar to the outcomes found in the previous studies to be associated with AED/s use in pregnancy.

RESULTS

Of the forty records reviewed, seven cases were rejected and omitted from the final analysis due to the inadequate antenatal records or unavailable dockets. The final review was conducted on 33 index cases and 33 controls. The categories of women analysed in this study are shown in Table 1. Most (63%) women who used AED used monotherapy and 55% used multiple drugs including the combination therapy throughout pregnancy.

A total of 27 women were identified who had taken one or more anti-convulsant drugs during pregnancy, 17 of whom took only one drug and 10 of whom had taken two or more drugs. Carbamazepine was the most commonly used drug, used by 14 women, followed by valproic acid, used by 13 women, phenytoin by 9 women, phenobarbital by 2 women and diazepam by 2 women. Three women used newer types of AEDs, one woman used lamotrigine and two used topiramate. Among the 27

Table 1: Types of seizures occurring during pregnancy and AED use

Category	Women used AED		Women did not use AED		Total
	Seizure	No seizure	Seizure	No seizure	
Identified cases	21	6	6	33	66
Seizure Dev[1] in pregnancy	1	0	0	0	1
Seizure during pregnancy	9	0	0	0	9
Partial seizure	3	0	0	0	3
Generalized tonic clonic seizure	5	0	0	0	5
Not indicated	1	0	0	0	1
AED drug use					
Mother took only 1 AED	11	6			17
Mother took only 2 AED	6	0			6
Mother took only 3 AED	3	0			3
Mother took only 4 AED	1	0			1
Mother took AED in comb[2]	5	0			5

[1] Refers to seizures developed in pregnancy.
[2] Refers to women who used more than one AEDs in combination.
AED = anti-epileptic drug.

women who used at least one anti-convulsant drug, six used the drug for migraine. Of that number, four (66.7%) used valproic acid and two (33.3%) used topiramate.

The foetal outcomes in each category of women are shown in Table 2. The records of 66 infants were reviewed, 33 infants from each group. Major congenital malformations were not observed in any of the groups; however, seven minor congenital malformations and three other adverse foetal outcomes were seen. Minor congenital malformations were seen in 14.2% (3/21) of infants whose mothers used AEDs and had seizures compared to 16.7% (1/6) of infants whose mothers took AED but had no seizures. Minor congenital malformations were seen in 6.1% of foetuses in the control group. There were no minor congenital malformation seen in foetuses whose mothers had seizures but took no AED. A single-factor ANOVA analysis was performed to determine if there was any correlation between the AED use in pregnancy and the overall adverse foetal outcomes. A p-value of 0.04 was obtained at a confidence level of 95%. This suggests that there is a relationship between the AED use in pregnancy and the overall adverse foetal outcome.

Carbamazepine, phenytoin and valproic acid were the AEDs used in women whose infants were found with minor congenital malformation.

Most (45.5%) of the women who took AED during pregnancy for seizures had delivery via a caesarean section versus 33.3% of controls. The women who took AED for migraine had six cases that were analysed; the delivery record for the remaining case was unavailable. Within this group, 50% had induced vaginal delivery and 50% had spontaneous vaginal delivery.

Table 3 shows the maternal outcomes in all groups. Most adverse maternal outcomes were seen in women who did not take AEDs and did not have seizure. However, most of the adverse maternal outcomes seen in women who took AEDs were seen in those who took carbamazepine. The single-factor ANOVA analysis was performed to determine if there was any relationship

Table 2: Foetal outcomes in each category of infants

Category	Women used AED		Women did not use AED		Total
	Seizure	No seizure	Seizure	No seizure	
Foetal outcome					
Foetal Death	2	1	0	1	4
Intrauterine growth restriction	0	0	0	1	1
Microcephaly	0	0	0	1	1
Undescended testes	0	0	0	1	1
Premature birth	1	1	1	2	5
Umbilical hernia	2	0	0	0	2
Tapered superior helix of left ear	1	0	0	0	1
Over folded superior helix of the right ear	1	0	0	0	1
Posteriorly rotated low set ears	0	1	0	0	1
Slightly posteriorly rotated ear	1	0	0	0	1

AED = anti-epileptic drug.

Table 3: The maternal outcomes in each group of women

Category	Women used AED		Women did not used AED		Total
	Seizure	No seizure	Seizure	No seizure	
Maternal outcomes					
Uterine haemorrhage > 500 cc	4	0	2	6	12
Premature rupture of membrane	0	0	0	1	1
hyperemesis gravidarum	1	0	1	1	3
Abruptio placentae	0	0	1	0	1
mechanical rupture of membranes	7	3	1	12	23
Pre-eclampsia	0	0	1	2	3

AED = anti-epileptic drug.

between the AED use in pregnancy and the adverse maternal outcome. A *p*-value of 0.06 was obtained at a confidence level of 95%. This would suggest that there is no correlation between the AED use and the adverse maternal outcome.

DISCUSSION

This study sought to identify major and minor congenital malformations that may be present in infants who were exposed to AEDs in utero and the maternal outcomes that may be associated with their use. It was found that infants exposed to AEDs in utero had only minor congenital malformations and no major congenital malformations. This is a variation of what was seen in previous similar observational studies of women who were exposed to AEDs during pregnancy (1, 13, 19). This difference in outcome could be due to the small-sample size. The results are not unexpected, given the relatively few pregnancies complicated each year by AEDs use (20). As a result, multicentre design studies are the only feasible approach to gather unbiased data on a significant number of pregnancy outcomes (20).

In this study, the infants who were not exposed to AEDs had minor congenital malformations that were not seen in the infants exposed to AEDs in utero. This is not an unusual occurrence. Though previous studies reported that more malformations were seen in infants of mothers exposed to AEDs, they also reported that most of the major malformations identified were types of abnormalities that also occurred in infants whose mothers have not taken an anti-convulsant drug (19).

The difference in population could also affect outcome. Previous studies and registries were based on populations that were likely of mixed ethnicity, as they were of multicentre design involving women from different regions and countries (1, 2, 19). This study was composed primarily of women of the African descent. The Jamaican population is primarily of the African descent (90.9%) with people of mixed ethnicity making up 7.3% (21).

The use of the newer AEDs was not significant but as they become more available, it is expected that their use will increase among this population of patients and the foetal and maternal effects can then be appreciated.

Our study findings suggest that though MCMs are important adverse foetal outcomes to be aware of there are other significant adverse foetal outcomes that both the physicians and the pregnant women on AEDs are to anticipate and aim to mitigate against.

There were several limiting factors in this study. The study outcomes were hinged on the documented examination findings made by the attending physicians who were not following the guidelines recommended for assessing infants with in-utero exposure to AED/s. The New Born Services guideline is a recommended protocol for evaluating such infants (22). Furthermore, the physicians' documentation and their various opinions on the women was the only method of collecting information.

Regarding the anti-epileptic medications they were using, it is possible that non-compliance and adherence to prescribed medication by the mothers could also have impacted on the study outcome. Maternal complications of AEDs could possibly have been observed but not routinely documented by the obstetricians or the neurologists.

CONCLUSION

The study revealed that there are adverse effects, other than MCMs, of AED use in pregnancy on the foetal outcome. The adverse maternal outcomes were similar to those previously documented. It also demonstrates that the ongoing screening of mothers with epilepsy on AEDs is relevant to identify the foetal and maternal effects of AED use in pregnancy. It is, therefore, recommended that the guidelines for examining foetuses of mothers who use AED during pregnancy be followed so as to identify foetal anti-convulsant syndromes and, those infants that will go on to develop motor, language and cognitive abnormalities.

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AUTHORS' NOTE

SRG participated in the study design, oversaw data collection, conducted data analysis, wrote manuscript and approved final version. FG conceived paper, participated in the study design, oversaw data collection, critically review and approve final draft of manuscript. NJ oversaw data collection, critically review and approve final draft of manuscript. The authors declare that they have no conflicts of interest.

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ORIGINAL ARTICLE

The Perception of Pharmacists and Physicians about Generic Drugs on Drug Price Lists in Trinidad

AR Villarroel Stuart

ABSTRACT

Objective: *To determine the perception and concerns physicians and pharmacists have about generic drugs on three annual drug price lists in Trinidad.*
Method: *Windows® Excel 2007 and Minitab® version 17 examined the price lists and a self-administered questionnaire was used to perform a non-randomized, cross-sectional study with a convenient sampling of physicians and pharmacists after obtaining written consent.*
Results: *Physicians (78.6%) and pharmacists (87.1%) agreed and strongly agreed respectively that there are medical conditions for which brand name drugs are preferred including cardiovascular conditions and diabetes; which were comprised in the five major medication categories on the national drug price lists. Overall, physicians and pharmacists showed a 'Good' to 'Excellent' perception of generic drugs but had some safety and efficacy concerns. Lack of reporting of adverse drug reactions and quality issues by health professionals was also observed.*
Conclusion: *Education and communication among patients, physicians and pharmacists can improve the perception of generic drugs; hence, increase confidence in prescribing, dispensing and patient management.*

Keywords: Drug list, generic drugs, perception of pharmacists and physicians, Trinidad.

INTRODUCTION

The World Health Organization's (WHO's) Essential Medicines List helped develop national drug lists that addressed major health needs of a country's population and provided WHO's recommendations of safe, effective, affordable and good quality medicines (1–4). Drug lists guide prescribing patterns, address morbidity and mortality diseases, assist in medication consumption, manage drug acquisition and distribution, and make necessary medicines available and accessible to those who require them (1–3). However, some physicians indicated that a drug list restricts their practising (3).

In Trinidad and Tobago, as in Jamaica, there is no Essential Medicines list, however, the national drug list contains drugs classified as Vital, Essential and Necessary (VEN) for public sector use, commonly referred to as the 'VEN' list (4, 5). The annual drug price lists consist of items from the VEN list tendered for a particular year with the inclusion of manufacturer, brand name and distributor (6–8). Generic drugs are defined as being similar to their brand name counterparts in dosage form, performance, route of administration, strength, quality, safety and indicated use (9).

Trinidad and Tobago and other countries have included multi-source/generic drugs on their national drug list because these decrease the price to patients or government; therefore, increase medicine access (10–14). The Ministry of Health of Trinidad and Tobago has guaranteed that the medicines provided to its population are safe, efficacious and of superior quality (15, 16). Nevertheless, Trinbagonian physicians have indicated that the generic drugs used in the public health sector are not as effective as the brand name drugs (17).

Perception refers to the process of receiving data, analysing it and then producing a response (18). Researchers have identified various factors that may

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influence perception including prior experience, emotions, culture and knowledge (19). The perception of generic drugs can affect the prescribing behaviour of physicians; the ordering and procuring of generic drugs by the pharmacists and the adherence of patients to their medications (12, 20, 21).

MATERIALS AND METHODS

National drug lists investigation

Annual national drug price lists for 2008–2011 were obtained from the internet and the respective hardcopy booklets for the relevant years (6–8). The items were entered in Windows® Excel 2007; recoded and descriptive analyses were performed on the data using Minitab® version 17. Internet searches were used to confirm data including that of manufacturers and drugs.

Survey

Design and collection tool

A non-randomized, cross-sectional study was performed from June to August 2010. Research done by Kersnik and Peklar (2006), Shrank *et al* (2011), Sharrad *et al* (2011), Chong *et al* (2010), Chua *et al* (2010) and others were used to develop the self-administered questionnaires (12, 20–25). Open-ended questions, Likert scales and Visual Analog scales (VAS) were applied to acquire the necessary data. Visual Analog scale ranged from 0, which represented 'Poor', to 10, which represented 'Excellent'. The question items aimed to obtain data on variables such as cost; efficacy and safety of generic drugs; support of switching from a brand name drug to a generic or generic to generic; if generic drugs are the same as brand name ones; knowledge, understanding and views of generic drugs and communication of healthcare professionals and patients. Some items of the questionnaire were combined to create specific categories such as cost, safety and total perception and these combinations were referred to as domains (groups of questions). The domains and the single item for perception utilized the quartile method which divided the responses into four groups—Poor, Fair, Good and Excellent.

The questionnaires were pre-piloted among supervisors and colleagues and they were then piloted prior to the beginning of the study. Face validity ensured that the questions measured what it was supposed to measure, therefore, certifying the collection of meaningful data.

Sampling method

The North Central Regional Health Authority (NCRHA) and institutions in Trinidad were conveniently selected from the five Regional Health Authorities (RHAs) in Trinidad and Tobago. The list of the health institutions within the NCRHA was obtained from the Trinidad and Tobago, Ministry of Health website and three health centres and five district hospitals were chosen (26, 27). Participants included both genders, all ethnic/racial composition, at least 18 years of age, willing to give written informed consent and employed at the various health institutions.

Statistical analysis

Data entry was done *via* the computer using Microsoft Office Excel® 2007 then transferred into Minitab® version 17 and Statistical Package for Social Sciences (SPSS®), versions 11 and/or 12, for data analysis incorporating a coding scheme.

Reliability analysis was performed to verify the internal consistency of each item within the different domains and Cronbach's alpha coefficients were calculated in SPSS 11 and/or 12. A reliability coefficient of 0.8 and more was necessary to confirm the reliability of a domain while those that did not meet the requirement were considered as individual items in the analyses. Additionally, some of the questions were asked in a different part of the questionnaire so as to confirm the reliability of the items. Various analyses were achieved including descriptive statistics, correlations and ordinal logistic regression.

Ethical approval

The research was approved by the Ethics Committee of The University of the West Indies. Respect for persons included a written informed consent from the physicians and pharmacists and confidentiality was maintained. In addition, permission was granted from NCRHA and the selected health institutions prior to the initiation of the study.

RESULTS

Thirty-one pharmacists and 70 physicians participated in the study and most were of East Indian ethnicity from each group. Pharmacists were predominantly females (77.4%) of 31–40 years (38.7%) while physicians were chiefly males (51.4%) of 21–30 years. Pharmacists (40%) and physicians (53.0%) mainly had 5 years or

less working experience and 63.3% of the pharmacists and 54.0% of the physicians worked in the public health sector for this same period.

About 64% of the physicians compared to 48.4% of the pharmacists agreed that generic drugs can be used for all chronic diseases. Both physicians (78.6%) and pharmacists (87.1%) agreed that there are medical conditions for which brand name drugs are preferred such as cardiovascular conditions, diabetes mellitus, infections and cancer. The main classes of medications on the drug price lists were the central nervous system (293/1473), anti-infectives/antibiotics (226/1473), cancer (177/1473) and cardiovascular (139/1473). The major routes of administration on the national drug price lists were the oral (50.94%) and parenteral (31.50%) while the rectal route (0.54%) was the least.

Most pharmacists (67.7%) and physicians (42.4%) estimated the percentage of generic medicines stocked at their pharmacies as 76%–100% and 51%–75%, respectively. Approximately 54% of pharmaceuticals on the drug price lists were generic formulations. Pharmacists (27/31) and physicians (65/70) believed that India was the main country from which most generic drugs originated while the second choice was Canada for pharmacists (51.6%) and South America for physicians (14.3%). The five main countries that manufactured the pharmaceuticals on the drug price lists were India (395/1499), the United States of America (266/1499), the United Kingdom (172/1499), Switzerland (110/1499) and Canada (85/1499).

Physicians rated their general understanding of generic drugs as predominantly 'Good' (33/70); whereas most pharmacists rated their understanding as 'Very Good' (12/31).

Doctors (51.4%) and pharmacists (41.9%) agreed that they were comfortable prescribing/dispensing generic drugs from the Trinidad and Tobago drug listings. Prior experience influenced prescribing/dispensing behaviour while 87.1% of pharmacists and 51.4% of physicians were concerned about the difference in colour, shape, size, taste and packaging of generic medicines.

Pharmacists (38.7%) showed a 'Poor' perception about generic drugs in the Cost domain, in respect to value and price, as opposed to the physicians (34.8%) who demonstrated a 'Good' perception.

Physicians (39.4%; 37.3%) and pharmacists (50.0%; 38.7%) demonstrated an 'Excellent' and 'Good' perception for the safety and efficacy domains respectively.

Doctors (80%, 51.5%) and pharmacists (67.7%, 48.4%) agreed that pharmacist should only substitute a brand name drug with a generic one with doctor's and patient's consents correspondingly.

On a VAS, the most responses were of the score 5 (20.6%) followed by 6 (19.6%). This single perception item showed a mean score of 5.58, median and mode scores of 6 and 5 respectively, and standard deviation of 2.0. Physicians (20/70) and pharmacists (14/31) mainly showed an 'Excellent' perception of generic drugs in the single item. However, for the perception domain pharmacists (10/29) had an 'Excellent' perception while physicians (20/62) had a 'Good' perception of generic drugs.

Physicians (23.7%) and pharmacists (26.45%) made recommendations to diminish poor perception of which education was the most popular. Most physicians (37.1%) and pharmacists (45.2%) indicated that they sometimes communicate with their patients regarding generic drugs. More physicians (44.3%) declared that doctors/dentists should be the chief educators for patients about generic drugs whereas pharmacists (67.7%) stated that it should be the pharmacists.

Pharmacists (35.5%) and physicians (21.4%) stated that they seldom report any complaints of generic drugs; in contrast to 29% of pharmacists and 64.3% of physicians who have never made a report.

DISCUSSION

The medicines referred to by the participants, in our study, were those on the annual national drug price lists. The pharmacists and physicians shared comparable perception of generic drugs but highlighted specific concerns about efficacy, safety and difference in the physical appearance of generic medicines compared to their counterparts.

Management of medication safety and efficacy includes reporting adverse effects and quality issues, however, our study demonstrated poor reporting by physicians and pharmacists (28, 29). Our study observed other factors that influenced the perception of generic drugs which were also seen in studies from New Zealand and Malaysia (13, 20). However, where cost can affect some countries, in Trinidad and Tobago, various medications to patients in the public sector are supplied gratis by the government (10, 11).

Our study stated that education within the healthcare system would improve perception and each group stated that they were the main person to educate patients about generic drugs (13, 20). Studies in Iraq and South Africa showed that patients were more likely to agree to generic substitution if it was suggested by a physician

as opposed to a pharmacist (22, 25). Nevertheless, the study from Iraq and other studies stated that education of generic drugs should be from both physicians and pharmacists (13, 20, 25). Furthermore, a Malaysian study indicated that communication between pharmacists and physicians can better the perception of generic drugs and their partnership can improve the quality of generic drugs (20, 28).

Physicians and pharmacists stated that there are some medical conditions where generic drugs should be restricted. Other researchers have encountered similar concerns and have identified certain diseases such as cardiovascular conditions and epilepsy (30, 31).

Limitations of the study included a small sample size and convenient sampling. A larger study comprising all the RHAs and private sector will obtain enough data to represent the pharmacists and physicians of the Republic of Trinidad and Tobago.

CONCLUSION

The single item and domain perception of generic drugs were mainly 'Excellent' for pharmacists and physicians but they had concerns about safety and efficacy. However, a safety and efficacy mechanism of reporting adverse drug reactions and quality matters was not performed sufficiently by the healthcare professionals. Education and communication can provide valuable information for physicians and pharmacists; thus, address their apprehension of generic drugs and ensure medicines on the national drug price lists are safe and effective for patients.

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AUTHOR'S NOTE

AR Villarroel Stuart conceived paper; performed study design; conducted data collection, analysis and interpretation; and wrote, revised and approved final version of the manuscript. The author declares no conflict of interest.

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ORIGINAL ARTICLE

An Investigation of Serum Magnesium and Red Blood Cell Distribution Width Values in Patients with Obstructive Sleep Apnoea Syndrome

K Kilic[1], MS Sakat[1], O Araz[2], MS Gozeler[1]

ABSTRACT

Objective: *Obstructive sleep apnoea syndrome (OSAS) leads to complications in several systems. The purpose of this study was to examine serum magnesium and red cell distribution width (RDW) values in OSAS, a chronic inflammation, and thus to reveal the relations between these two parameters and with other sleep parameters.*

Methods: *A total of 160 patients diagnosed with OSAS and 50 controls were enrolled in this retrospective study. Study and control groups were constituted using the medical records. Age, gender, magnesium and RDW values were obtained from all patients' medical records. Values for apnea–hypopnea index (AHI), SpO_2, mean desaturation level, total sleep time (TST) and total sleep time in which oxygen saturation is below 90% (TST90) were also obtained from the polysomnography records.*

Results: *Red cell distribution width values of the patients in the study group were statistically significantly higher compared to those of the control group ($p < 0.001$). The magnesium levels of the patient group were significantly lower compared to those of the control group ($p < 0.001$). Also, serum RDW and Mg levels were negatively correlated.*

Conclusion: *We determined that serum magnesium levels decreased in the presence of OSAS and that this is related to the severity of OSAS. Similarly, we observed that RDW values increased in patients with OSAS and exhibited a significant correlation with AHI. Also, RDW and Mg levels were found to be negatively correlated. To our knowledge, this is the first study in the literature that demonstrates the association between RDW and Mg levels in the same patient population.*

Keywords: Inflammation, magnesium, obstructive sleep apnoea syndrome, red blood cell distribution width.

INTRODUCTION

Apnoea refers to the interruption of respiration exceeding 10 seconds during sleep. Obstructive sleep apnoea syndrome (OSAS) is a syndrome characterized by apnoea throughout sleep, periods of hypopnea and accompanying decreased blood oxygen saturation, daytime sleepiness, interruptions of sleep and collapse in the upper airways (1). The severity of the disease depends on the hourly number of apnoea/hypopnoea events during sleep. The mean hourly number of apnoea/hypopnoea events is known as the apnea/hypopnea index (AHI). An AHI of 5–15 is defined as mild OSAS, 15–30 as moderate OSAS and higher than 30 as severe OSAS (2). Obstructive sleep apnoea syndrome leads to complications in several systems. Oxidative stress and chronic inflammation are involved in the pathogenesis of these complications. Inflammatory biomarkers such as interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-α) have been shown to increase in patients with OSAS (3).

Red blood cell distribution width (RDW) is a numerical value providing information concerning erythrocyte

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dimensions in complete blood counts. This value showing erythrocyte variability in the circulation is generally used to determine types of anaemia (4). However, studies in recent years have shown that RDW values also increase in the event of chronic inflammation, hypoxia and oxidative stress. Özsu *et al* reported an increase in RDW values in OSAS patients compared to the normal population (5).

Magnesium is the second most abundant cation in intracellular fluid and plays an active role in several biochemical and enzymatic reactions in the body. Magnesium deficiency has been shown to be associated with several diseases (6–8). Low levels of magnesium have also been shown in OSAS, a chronic inflammatory disease (9).

The purpose of this study was to examine serum magnesium and RDW values in OSAS, a chronic inflammation, and thus to reveal the relations between these two parameters and with other sleep parameters. To our knowledge, this is the first study in the literature that demonstrates the association between RDW and Mg levels in the same patient population.

SUBJECTS AND METHODS

The study was performed by examining the records of 360 patients undergoing polysomnography between June 2015 and January 2017 at the Sleep Disorders Laboratory. Ethical committee approval was granted from local Ethics Committee with admission number 2017:1-1. Anamnesis is routinely taken from patients presenting to our Sleep Disorders Laboratory, and a detailed physical examination is performed at which they are weighed and measured, and their body mass index (BMI) values calculated. Blood is also collected from all patients before polysomnography, complete blood count and broad biochemical tests, and medical records are established from these.

Study and control groups were constituted using these medical records in this study. Age, gender, magnesium and RDW values were obtained from all patients' medical records. Values for AHI, SpO_2, mean desaturation level, total sleep time (TST) and total sleep time in which oxygen saturation is below 90% (TST90) were also obtained from the polysomnography records. Based on the polysomnography results, patients with AHI < 5 were enrolled as the control group and those with AHI > 5 as the study group. The medical records of both groups were examined, and subjects with any known haematological disease, diabetes mellitus or kidney disease, rheumatologic and allergic diseases, periodontal diseases, with a history of alcohol use of, with infection findings, with a history of drug intakes such as antihypertensives, inhibitors of proton pump and corticosteroids were excluded.

Polysomnography

Full polysomnography was carried out with the Compumedics E-series Sleep System (Compumedics Sleep, Melbourne, VIC, Australia). Electroencephalography (EEG), electrooculography, electromyography and electrocardiography were performed concurrently. Surface electrodes were attached for the recording of EEG channels, right and left electro-oculographies and submental electromyography. Respiratory flow through one or both nostrils and the mouth was measured using airflow. Inductive plethysmography bands were employed to observe thoracic and abdominal breathing movements, in addition to body position. In terms of pulse oximetry, arterial oxygen saturation was determined from the subject's fingertip. Apnoea was defined as uninterrupted cessation of airflow exceeding 10 seconds in duration, and hypopnea as a 30% or greater decrease in airflow exceeding 10 seconds in duration accompanied by an oxygen desaturation of ≥ 3% or a decrease in thoracic wall movement. AHI was calculated as the total number of apnea and hypopnea events per hour of sleep.

Blood samples

Ten cubic centimetre blood specimens were collected from all patients. These were divided into two parts and placed into blood count and biochemistry tubes. After being kept at +4°C for 1 hour, they were centrifuged at 3000 rpm for 10 minutes. Red cell distribution width levels were studied from the plasma obtained using an autoanalyzer (Sysmex XN 9000, Kobe, Japan) and magnesium tests were performed from the serum using an autoanalyzer (Beckman Coulter AU 5800, Brea, California, USA).

Statistical analysis

Statistical analysis was performed on SPSS 17.0 software. The Mann–Whitney *U* test was used for comparisons between the groups. Spearman's correlation test was used for correlation calculations $p < 0.05$ was regarded as significant for all calculations.

RESULTS

Out of 360 patients, 150 patients, whose medical records were examined, were excluded for meeting exclusion

criteria. One hundred sixty patients (99 male, 61 female) aged between 22 and 69 (51.1 ± 12) and a 50-member control group (34 male, 16 female) aged between 37 and 68 (49.9 ± 4.8) were included in the study. There was no significant difference between the groups in terms of gender or age ($p > 0.05$). Also, there was no statistically significant difference in haemoglobin values between the control and study group ($p = 0.54$).

Red cell distribution width values of the patients in the study group were statistically significantly higher compared to those of the control group ($p < 0.001$). The magnesium levels of the patient group were significantly lower compared to those of the control group ($p < 0.001$) (Figure).

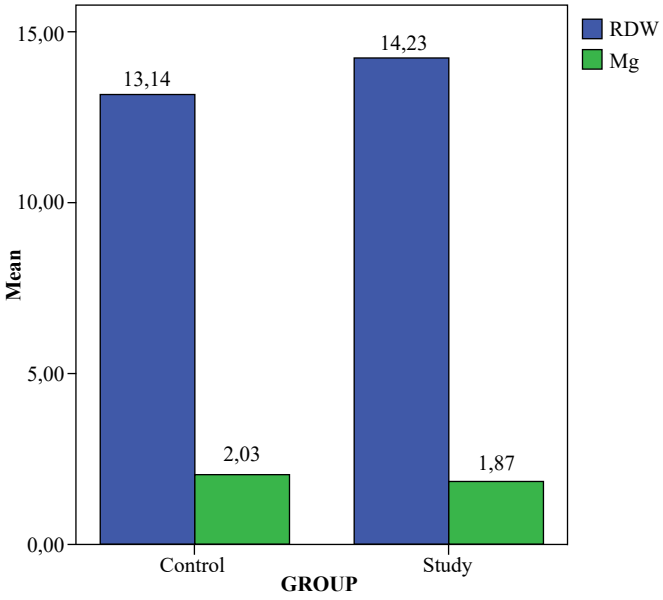

Figure: Mg and RDW values of groups. RDW = red cell distribution width.

In terms of study and control group polysomnography data, AHI was 41.6 ± 29.7 in the study group and 2.5 ± 1.2 in the control group. Desaturation rates and TST90 values were significantly higher in patients with OSAS compared to the control group, while TST and SpO_2 were significantly lower ($p < 0.001$). Demographic data, laboratory and polysomnographic parameters for the two groups are shown in Table 1.

Table 1: Comparison of parameters of OSAS and control groups

	Control (n = 50)	Study (n = 160)	*p*
Age	52 ± 5	51.1 ± 12	= 0.89
Gender (M/F)	34/16	99/61	> 0.05
BMI	27.4 ± 2.3	28.2 ± 2.7	= 0.06
RDW (%)	13.1 ± 0.8	14.2 ± 1.5	< 0.001*
Hgb (g/dL)	13.5 ± 0.9	13.7 ± 1.1	= 0.54
Mg (mg/dL)	2 ± 0,1	1.8 ± 0.1	< 0.001*
AHI	2.5 ± 1.2	41.6 ± 29.7	< 0.001*
SpO_2	93.3 ± 1.5	85.9 ± 8.3	< 0.001*
TST (minute)	341.8 ± 60.9	311.9 ± 76.5	= 0.01*
Desaturation ratio	3.4 ± 0.9	6.9 ± 3.1	< 0.001*
TST90 (minute)	5.2 ± 18.7	139.1 ± 108.6	< 0.001*

*: Statistically significant.
AHI = apnea–hypopnea index; BMI = body mass index; RDW = red cell distribution width; TST = total sleep time; TST90 = total sleep time in which oxygen saturation is below 90%.

The results of Spearman correlation analysis performed to identify correlations between variables are summarized in Table 2. Positive correlation was observed between RDW and AHI ($r = 0.349$, $p < 0.001$), BMI ($r = 0.434$, $p < 0.001$), desaturation rate ($r = 0.378$, $p < 0.001$) and TST90 ($r = 0.334$, $p < 0.001$), while negative correlation was observed between RDW and SpO_2 ($r = -0.425$, $p < 0.001$) and total sleep time ($r = -0.142$, $p < 0.05$). Magnesium was negatively correlated with AHI ($r = -0.285$, $p < 0.001$), BMI ($r = -0.282$, $p < 0.001$), desaturation rate ($r = -0.233$, $p < 0.001$) and TST90 ($r = -0.230$, $p < 0.001$), and positively correlated with SpO_2 ($r = 0.234$, $p < 0.001$) and total sleep time ($r = 0.170$, $p < 0.05$). In addition, negative correlation was determined between RDW and magnesium ($r = -0.266$, $p < 0.001$).

DISCUSSION

Our study findings showed that magnesium levels were significantly lower in patients with OSAS compared to the control group, while RDW values were significantly higher compared to the control group. The RDW and Mg levels were found to be related to the severity of OSAS. Also, we have found a negative correlation

Table 2: Spearman correlation test between serum Mg level, BMI, RDW and polysomnographic parameters

		AHI	SpO2	BMI	TST	Desaturation ratio	TST90	Mg
RDW	*r*	0.349**	−0.425**	0.434**	−0.142*	0.378**	0.334**	−0.266**
Mg	*r*	−0.285**	0.234**	−0.282**	0.170*	−0.233**	−0.230**	

**: Correlations significant at 0.01 level.
*: Correlations significant at 0.05 level.
AHI = apnea–hypopnea index; BMI = body mass index; RDW = red cell distribution width; TST = total sleep time; TST90 = total sleep time in which oxygen saturation is below 90%.

between serum RDW and Mg levels. To our knowledge, this is the first study in the literature that demonstrates the association between RDW and Mg levels in the same patient population.

Obstructive sleep apnoea syndrome is a syndrome characterized by obstruction of the upper airway that causes complete interruption of airflow in the mouth and nose during sleep (apnoea) or a decrease (hypopnoea). The episodes of apnoea/hypopnoea are generally accompanied by loud snoring and a reduction in blood oxygen saturation. These episodes typically conclude with sleep interruptions and short arousals, leading to a decrease in REM sleep (10). Patients with OSAS are generally unaware of these sleep interruptions, and this condition is the main cause of daytime sleepiness. Obstructive sleep apnoea syndrome affects 4% of males and 2% of females in the adult population (11). It is significantly associated with morbidity and mortality. Excessive daytime sleepiness may lead to impairments in cognition and social performance and a serious lowering of quality of life. It may even lead to an increase in traffic accidents.

The inflammatory process leading to endothelial dysfunction plays an important role in the pathogenesis of OSAS. In addition, while sympathetic stimulation, oxidative stress, increased coagulation and metabolic impairment have been implicated in the pathogenesis, considering the complex nature of OSAS, the pathogenesis is probably multifactorial. The hypoxia that occurs in OSAS is intermittent hypoxia characterized by reoxygenation cycles following brief desaturations. Intermittent hypoxia plays an important role in the start of the inflammatory process in OSAS (12, 13). The importance of the inflammatory process in the pathogenesis of OSAS has been supported by studies showing high levels of proinflammatory cytokines, chemokines and adhesion molecules in the circulation (14). However, the mechanism underlying the inflammatory process has not yet been fully explained.

Several parameters have been investigated in studies performed in order to elucidate the pathogenesis of chronic inflammation in OSAS, one such being the acute phase reactant CRP. The results of studies concerning CRP levels in OSAS are questionable. There are studies reporting an increase in CRP levels. At the same time, CRP levels have also been reported to be correlated with the severity of OSAS (15). In contrast, there are also studies showing no increase in CRP levels (16, 17). However, in a meta-analysis by Nadeem *et al*, higher CRP values were reported in patients with OSAS in the majority of studies (18).

C-reactive protein is more an inflammatory mediatory marker of acute inflammatory events. Red cell distribution width can provide more important information than CRP in the evaluation of chronic inflammatory events. RDW is an inexpensive, easily obtained parameter that that provides information about erythrocyte dimensions. Several studies performed in recent years have reported that RDW increases in conditions such as coronary artery disease, cerebrovascular diseases, heart failure and diabetes, and also that high RDW values in these diseases are correlated with mortality and morbidity (19–21). In the light of these studies, RDW emerges as a novel prognostic marker reflecting chronic inflammation and oxidative stress. Since OSAS is also a condition characterized by increased oxidative stress and chronic inflammation, increased RDW levels in these patients may be associated with the severity of the disease and the development of complications. In this study, we determined significantly higher RDW values in patients with OSAS compared to the control group. Additionally, we determined that RDW levels were positively correlated with AHI, mean desaturation rate and TST90. These results show that RDW values are directly associated with disease severity.

Our results showed that magnesium levels in patients with OSAS were significantly lower compared to the control group. At the same time, we determined that magnesium levels were associated with the severity of the disease. Various studies have shown that magnesium deficiency is a risk factor, as a cause of chronic inflammatory stress, in several diseases including metabolic syndrome, cardiovascular diseases and diabetes mellitus (22–24). Karamanlı *et al* reported significantly lower magnesium levels in patients with OSAS compared to a control group and that this exhibited a negative correlation with AHI and CRP (9). We also determined a negative correlation between magnesium levels in patients with OSAS and AHI, mean desaturation rate and TST90.

We also determined that magnesium levels exhibited a negative correlation with RDW. However, the reason for this change in magnesium levels in patients with OSAS has not yet been explained. The most commonly implicated factor is inflammation, although we do not yet know whether low magnesium in OSAS is a cause or the result of inflammation. From another perspective, considering the role of magnesium in muscle activity, we thought that low magnesium in patients with OSAS might be associated with muscle overactivity in order to overcome apnoea. However, since our study contains no

detailed information capable of illuminating this, further studies concerning the role of muscle activity in patients with OSAS in low magnesium levels are now needed.

CONCLUSION

We determined that serum magnesium levels decreased in the presence of OSAS and that this is related to the severity of OSAS. Similarly, we observed that RDW values increased in patients with OSAS and exhibited a significant correlation with AHI. Also, RDW and Mg levels were found to be negatively correlated. To our knowledge, this is the first study in the literature that demonstrates the association between RDW and Mg levels in the same patient population. Polysomnography will remain the gold standard in the diagnosis of OSAS, but low magnesium values and elevation in RDW values in a patient with suspected OSAS must alert the clinician to the administration of polysomnography.

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AUTHORS' NOTE

Compliance with ethical standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statement of Author Contributions: All authors participated in the design, interpretation of the studies, analysis of the data, review of the manuscript and approved final version; KK, MSS, OA and MSG conducted the study. KK and MSS wrote the manuscript. The authors declare that they have no conflicts of interest.

Human Research Ethics Clearance: Ethical committee approval was granted from the local Ethics Committee with admission number 2017:1-1.

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ORIGINAL ARTICLE

Brain Magnetic Resonance Imaging Findings and Distribution of the Findings According to the Age Groups in Childhood Epilepsies

SK Balık[1], M Öztürk[2], C Göya[3], F Ekici[3]

ABSTRACT

Objective: *To retrospectively analyse the magnetic resonance imaging (MRI) observations and the distribution of etiological factors according to age groups in cases with MRI examinations for an epilepsy diagnosis.*

Methods: *The brain MRI of 606 cases from the 0–17 years age group were analysed retrospectively, and the findings were evaluated according to the age group.*

Results: *In 274 cases (45.2%) at least one lesion from different pathology groups was observed. The most frequently observed pathologies were parenchymal damage, hippocampal sclerosis and cortical developmental anomalies.*

Conclusion: *An MRI is a non-invasive, irradiation-free imaging method that can be used in the follow-up of epileptic patients to detect underlying pathologies and treatable causes of epilepsy.*

Keywords: Children, epilepsy, magnetic resonance imaging.

INTRODUCTION

A seizure is a paroxysmal attack caused by a cerebral neuron, abnormal and excessive release of neurotransmitters and is symbolized by a sudden modification in sensory-motor functions, behaviour, memory or consciousness. Epilepsy may be defined as the tendency of the brain to create epileptic seizures, and this situation may have conscious, psychological and social results and may be defined as a clinical pattern (1). Seizures may be observed at a rate of 3%–5% during childhood. While epilepsy occurs at 0.5%–1% in the general population, it starts during childhood in 60% of patients (2). Epilepsy is considered a genetic or acquired disease and is believed to be multifactorial (3). In various studies and in 30%–35% of cases, the original aetiology has been determined (4). The determination of the aetiology is important in the planning of the treatment.

Imaging methods are required in patients believed to be epileptic as a result of physical and neurological examinations and laboratory analyses for epileptic patient evaluations (5). Magnetic resonance imagings are performed more than other methods for the evaluation of epileptic patients in which the diseases are associated with cerebral structural impairments. Magnetic resonance imagings hold the most important place among radiological imaging methods for the evaluation of epileptic patients due to their high resolution of soft tissue and multi-planar imaging capacity. There are few extended MRI studies concerning imaging method epilepsies and the distribution of etiological factors according to age.

The aim of our study was to diagnose early MRI observations and treatable causes of epilepsy and to determine the etiological factors according to age group.

SUBJECTS AND METHODS

This retrospective study was carried out following the approval of the local institutional review board. Adherence to principles announced in the Declaration of Helsinki was observed. The study included 606 cases

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between 0 and 17 years of age who were submitted to brain MRI examinations and diagnosed as having epilepsy in the Paediatric Neurology Department of our hospital between June 2008 and August 2012. The patients who underwent operations and were non-conforming for imaging procedures due to movement artefacts were not included in the study.

Brain MRI observations were performed using 1.5 and 3.0-T (Achieva; Philips Medical Systems, Best, the Netherlands) devices and head coils. All observations were performed according to the epilepsy protocol. In Dicle University, Medical Faculty Hospital, Diyarbakir, Turkey, the MRI protocol used as a routine in 1.5-T and 3.0-T MRI devices presents the T2-weighted fast spin-echo sequence (FSE) in the axial and coronal planes, sequence fluid-attenuated inversion recovery (FLAIR), and non-contrast T1-weighted 3D turbo field echo sequences. In examinations performed in the 1.0-T MRI device, T1-weighted spin echo (SE), T2-weighted FSE, proton-weighted FSE in the coronal plane, and T1-weighted SE sequences in the sagittal plane were used. According to the pathology determined during the examination, 0.1 mmol/kg of an intravenous paramagnetic contrast substance (gadodiamide [Omniscan; Amersham Health, Cork, Ireland], gadopentetate dimeglumine [Magnevist; Schering AG, Berlin, Germany] and gadobutrol [Gadovist; Schering AG, Berlin, Germany]) was administered at 2 ml/sec via the antecubital vein and the SE sequence T1-weighted axial, coronal and sagittal plane images were obtained. To reduce movement artefacts in children, chloral hydrate (50 mg/kg) was given orally to help the patient sleep. No sedatives were used in older children who cooperated. Two radiologists with 10 and 3 years of experience of neuroradiology reviewed the MRI images in consensus and blind to diagnosis.

Statistical analyses

The computer program SPSS 22.0 for Windows (IBM Corporation, Armonk, New York, NY, USA) was used to perform the statistical analysis (descriptive study).

RESULTS

A total of 606 cases including 369 boys (60.9%) and 237 girls (39.1%) from the 0–17 years age group (mean age: 7.4 years) were included in this study. In our study, there were 79 cases in the infant age group (13.2%), 358 cases in the children age group (59%),and 169 cases in the adolescent age group (27.8%). No lesions were detected in the brain MRIs of 332 cases (54.8%). In 274 cases (45.2%), at least one lesion from different pathology groups was observed. The distributions of the lesions detected in the MRIs according to age and the pathology groups are given in Table 1.

When we classified the cases of our study according to age groups (Table 2), the most important proportion of pathologic findings was for the infant group and the most frequent pathology encountered in all groups was parenchymal damage with 118 patients (43%) (Fig. 1). The MRI observations detected in these cases were encephalomalacia and gliosis development in the pre-natal-perinatal-post-natal periods due to ischemic, toxic, infectious, inflammatory and traumatic causes.

The second largest group was the cortical developmental anomalies group with 34 (12.5%) cases in our study (Fig. 3). The pathologies we determined were cortical dysplasia (n = 10), heterotopia (n = 8), polimicrogiria (n = 7), corpus callosum agenesis/dysgenesis (n = 4), holoprosencephaly (n = 2), hemimegalencephaly (n = 1), schizencephaly (n = 1) and Aicardi syndrome (n = 1). The most frequently observed pathologies in this group were cortical dysplasia, heterotopia, and

Table 1: Distribution of lesions detected in MRI according to the pathology groups

Pathology Groups detected in MRI	Infants (n = 42)	Children (n = 160)	Adolescents (n = 72)	Number of cases	Percentage of cases
Parenchymal damage	22	64	32	118	43
Hippocampal sclerosis	2	18	12	32	11.7
Cortical developmental anomalies	5	22	7	34	12.5
Cerebral atrophy	4	16	6	26	9.5
Tumour/cyst	1	17	10	28	10.3
Neurocutaneous syndromes	1	8	1	10	2.7
Myelinization disorder	4	4	1	9	3.3
Vascular anomalies	2	5	1	8	2.9
Metabolic-degenerative diseases	1	6	2	9	3.3

MRI = magnetic resonance imaging.

Table 2: Number of cases and proportion of pathologic findings according to the age group

	Total number of cases	Cases with no pathology	Cases with pathology	Parenchymal damage
Infant (1–12 months)	79 (13.2%)	37 (47%)	42 (53%)	22 (52.3%)
Children (1–10 year)	358 (59%)	198 (55.5%)	160 (44.5%)	64 (40%)
Adolescent (10–17 years)	169 (27.8%)	97 (57.4%)	72 (42.6%)	32 (44.4%)

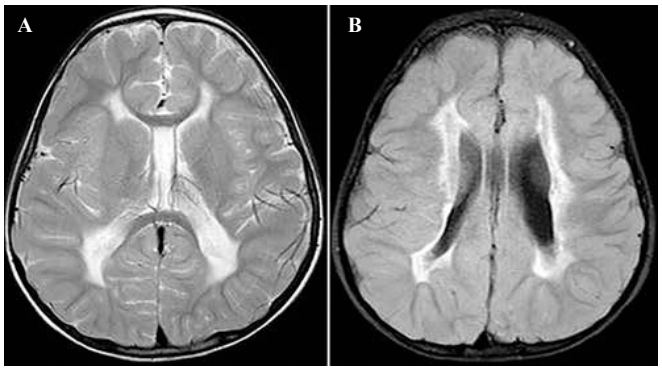

Fig. 1: Leukomalacia/gliosis with ventricular enlargement and volume loss at transverse T2-weighted fast spin-echo MR (A) and transverse fast fluid-attenuated inversion recovery (FLAIR) MR images (B). MR = magnetic resonance.

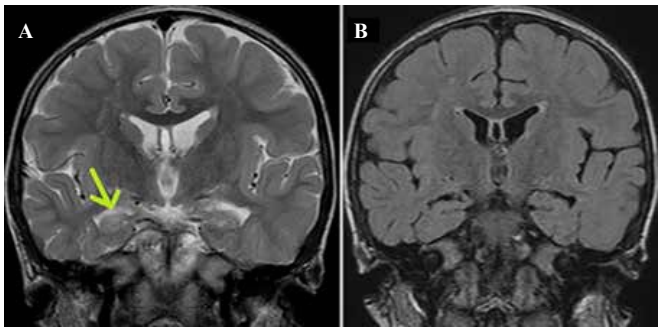

Fig. 2: Right hippocampal signal abnormality and volume loss in a 9-year-old boy. Increased signal with a volume loss in the right hippocampus at coronal T2-weighted fast spin-echo MR (A) and a volume loss at coronal fast fluid-attenuated inversion recovery (FLAIR) (arrow) MR images (B). MR = magnetic resonance.

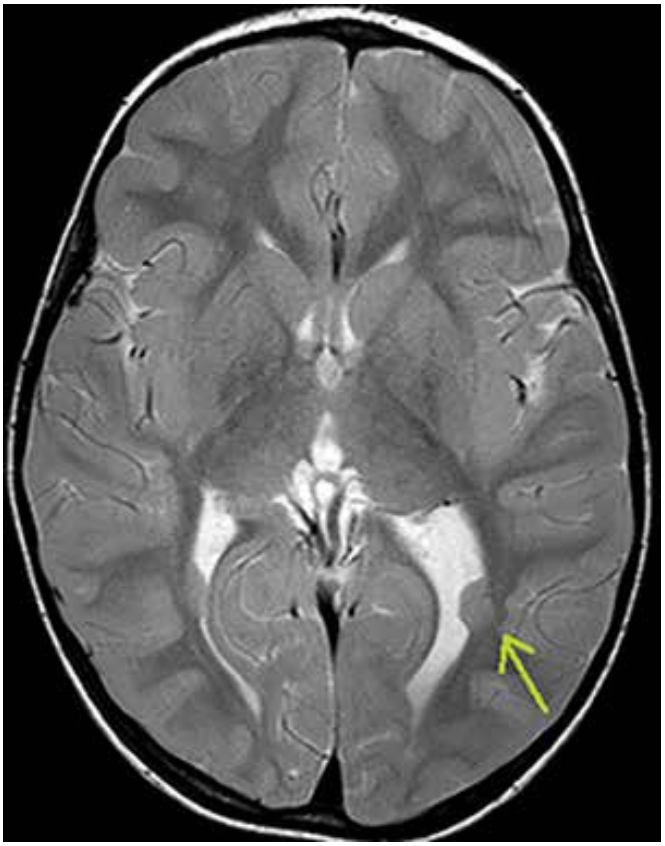

Fig. 3: Subependymal nodular lesions that were isointense with grey matter extending into the lateral ventricles (arrow) at a transverse T2-weighted fast spin-echo MR image (subependymal heterotopia). MR = magnetic resonance.

polimicrogiria. Congenital bilateral perisylvian syndrome was associated with five cases of polimicrogiria.

The other largest group was the hippocampal sclerosis group with 32 cases (11.7%) (Fig. 2). Of these cases, we determined bilateral hippocampal sclerosis in 10 cases, left hippocampal sclerosis in 12 cases and right hippocampal sclerosis in 17 cases.

In 26 of our patients (9.5%), we observed increases in the depth and width of the cerebral fissure and sulcus. These were associated with diffuse cerebral atrophy and enlargements at various levels of the ventricular system.

In our study, arachnoid cysts were detected in 16 cases. Arachnoid cysts were present in the left temporal fossa (n = 6), retrocerebellar region (n = 5) and in the right temporal fossa (n = 2). Moreover, there were choroid fissure cysts in three patients. In 12 cases in which we detected tumour lesions (4.01%), hamartom (n = 5), low-grade glial tumour (n = 3) and dysembryoplastic neuroepithelial tumour (DNET) (n = 4) were present. In the cases with low-grade glial tumour, masses were present in the left temporal lobe in one patient, and in the left globus pallidus in the other. In two of the four DNET cases detected, the lesions were localized in the left temporal gyrus and in the left median temporal lobe. In a case believed to be DNET, masses were present in the right temporal lobe, and in another case, cortical masses were present in the right parietal parafalcine.

We determined there were eight patients in the neurocutaneous syndrome group (2.7%). Tuberosclerosis

(n = 5), neurofibromatosis (n = 3) and Sturge–Weber syndrome (n = 2) were observed in the neurocutaneous group.

In our study, myelination defects were observed in eight patients (3.3%). Furthermore, regions with modifications in hyper-intense signals in the white matter in T2 imaging, considered as dysmyelination, were observed.

There were nine cases (3.3%) in the metabolic-degenerative group. Three of these patients presented with Van der Knapp disease, while the other two presented with Leigh disease, four cases glutaric aciduria type 2. We determined that there were eight patients (2.9%) in the vascular anomaly group. Sinus vein thrombosis (n = 2), venous angioma (n = 2), cavernous angioma (n = 2) and arteriovenous malformation (AVM) (n = 2) were observed in this group.

DISCUSSION

In 45.2% of the epilepsy cases during childhood, we detected pathologies using MRIs. The most frequently determined pathologies were parenchymal damage, hippocampal sclerosis and cortical developmental anomalies. Cerebral atrophy, tumours/cysts, myelinization defects, vascular anomalies, neurocutaneous syndromes and metabolic-degenerative disorders were also detected. When considered according to age groups, the most important proportion of pathologic findings was observed in the infant group. The most frequent pathology encountered in all groups was parenchymal damage.

Early diagnosis and treatment are very important in the control of seizures during childhood and also for the protection of neuronal damage due to repetitive seizures, normal development, reduction of drug side effects and increasing the quality of life (6). Imaging methods are not needed in the idiopathic epilepsy group. The diagnosis is established according to the seizure type and the electroencephalography observations. There is no structural damage in the brain of such patients (7, 8). In the symptomatic epilepsy group, there is structural damage that leads to frequent seizures. In patients with symptomatic seizures, imaging methods, especially MRIs, are required (5).

One of the important causes of neurological damage developed during the pre-perinatal period is hypoxic-ischemic events (9). The maturation state of the brain during the period of brain damage development is related to the intensity and duration of the event. Hypoxic-ischemic encephalopathy developing in early pregnancy before the 20th week leads to periventricular white matter damage [periventricular leukomalacia] (10). Hypoxic-ischemic event rates during childhood epilepsy vary between 8% and 23% (11–13). In our study, this rate was 19.7%, which is consistent with the results reported by previous studies.

Hippocampal sclerosis is the most frequently observed pathologic lesion in patients with temporal lobe epilepsy and is the cause of 60%–80% of complex partial seizures (14). The surgical success rate in patients with hippocampal sclerosis is relatively high; thus, a pre-operative diagnosis is very important. The most reliable qualitative MRI observations in a FLAIR sequence in hippocampal sclerosis are atrophy and signal changes in the hippocampus (15, 16). The hippocampal sclerosis rate in epilepsy cases in the children's group varies between 50% and 70% (17–20). In a similar study by Kalnin *et al* (11), this rate was 14.9%. In our study, this rate was 11.7%. The differences in the rates may be associated with differences in age groups and patient populations.

Cortical developmental anomalies may be defined as the most frequent epileptogenic lesion in chronic extratemporal epilepsies. An MRI is a valuable method in the diagnosis of cortical developmental malformations and allows for the determination of 50%–70% of the anomalies (21). Kalnin *et al* (11) studied childhood epilepsy and reported a cortical development anomaly rate (12%) similar to our results. Cerebral/cerebellar atrophy is characterized by non-recoverable brain tissue loss, is associated with enlargements in regions with intra- and extracerebral cerebrospinal fluid (CSF) and has many causes including metabolic, demyelinating, degenerative and cerebrovascular diseases (22). The cerebral/cerebellar atrophy rate for childhood epilepsies is reported to be between 10% and 19% (11, 13). In our study, this rate was similar at 9.5%.

The brain tumour rate in the general epilepsy population is 2%–4%, and the sensitivity of MRI use for their detection is about 100%. The tumour lesions leading to epilepsy are usually close to the cortex and temporal lobe. Low-grade lesions such as low-grade astrocytoma, oligodendroglioma, ganglioglioma, ganglioneuroma, DNET and mixed gliomas have been detected in one-third of the children submitted to temporal lobectomy due to epilepsy (23, 24). The brain tumour rate in the children's epilepsy group is 3.2%–4.6% (25, 26). In our study, this rate was 4%, which confirms the literature data. Arachnoid cysts are arachnoid membrane congenital lesions with CSF secretion. They constitute 1% of all intracranial masses (27).

In a similar study by Amirsalari *et al* (13), the cyst determination rate (5%) was similar to our value. The development of normal myelin may be monitored by conventional MRI. Ischemia, infection, myelin damage associated with toxins (demyelination) and modifications related to the construction of damaged myelin (dysmyelination) may be easily detected by MRI, but these two situations may not be differentiated. Cerebral MRI examinations present a high sensitivity for complex neuronal development disorders and neurodegenerative diseases; unfortunately, they also have low specificity (28). In our study, myelination disorders were present in 3.3% of cases and there is no data about the rate of myelinization disorders in the literature.

One of the etiological groups causing epilepsy is vascular anomalies. Presentation types include seizures, progressive neurological deficits, restless headaches, intracranial haemorrhages and hydrocephaly (29). Extensive studies concerning the imaging of epileptic diseases (26, 30) have reported that they have roles in 2%–5% of cases, but this rate is expected to be lower during childhood. In our study, this rate was 2.9%.

Metabolic and neurodegenerative diseases may affect grey and white matter, or both. Magnetic resonance imaging observations are mostly non-specific. A primary cortical block leads to epileptic seizures and mental destruction. In our study, the rate of metabolic-degenerative diseases was 3.3%, and there is no data concerning the rate of metabolic-degenerative diseases in the literature.

Dura´-Trave´ *et al* (12) reported that the pathology detection rate with MRIs is higher in the infant group than in both the children and adolescent groups. In our study, the rate of MRI pathology detection was higher in the infant group. The most frequent pathology determined in all age groups was parenchymal damage, similar to the study by Dura´-Trave´ *et al* (12).

CONCLUSION

Magnetic resonance imaging is a non-invasive imaging modality that does not contain any ionizing radiation and may be used to determine pathologies leading to epileptic attacks during childhood. The most frequent pathologies in all age groups were signs of parenchymal damage. Other common pathologies were hippocampal sclerosis and cortical developmental anomalies.

AUTHORS' NOTE

SKB Ferguson conceived the paper, oversaw data collection, conducted data analysis, wrote the manuscript and approved the final version. MÖ Tulloch-Reid participated in study design, data analysis and interpretation, critically revised manuscript and approved the final version. CG Younger participated in study design, data analysis and interpretation of data and revision of the manuscript and approved the final version. FE Wright-Pascoe participated in study design, interpretation of data and revision of the manuscript and approved the final version. MÖ Boyne participated in study design and interpretation of data, critically revised the manuscript and approved the final version. SKB Soyibo participated in study design and interpretation of data, critically revised the manuscript and approved the final version. CG Wilks provided oversight to the study, participated in data interpretation and revision of the manuscript, and approved the final version. The authors declare that they have no conflicts of interest.

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ORIGINAL ARTICLE

Israel Exhibits a Homogenous Male-to-Female Ratio at Birth for All Races and Religions

V Grech

ABSTRACT

Objective: *Male live births occur in excess of female live births and their ratio (M/F) is usually expressed as male divided by total births. The value of M/F varies, declining with stress. Israel has been shown to have a relatively stable M/F. This study was carried out in order to ascertain whether there were any racial or religious differences in M/F in Israel, and to compare with totals for Europe and North America.*

Methods: *Annual data for male and female live births were available from the Israel Central Bureau of Statistics for the period 2002–2011. Excel was used for data entry, overall analysis and charting. For race, data were available as Jews and others, and Arabs. For religion, data were available as Jews and Moslems.*

Results: *There were a total of 1 523 956 live births. Overall M/F was 0.5127 (95% CI: 0.5119, 0.5135). There were no significant differences between the races and no significant trends with time. Male-to-Female Ratio (M/F) is mid-way between that of Europe and North America.*

Conclusion: *The psychological and psychiatric effects of stress in Israel are well documented. However, there was no apparent effect on M/F that is manifested as racial or religious differences in M/F. This could be due to equal levels of stress in all groups or insufficient levels of stress or insufficient births to demonstrate M/F differences.*

Keywords: Birth rate trends, infant, Israel, newborn, politics, gender ratio

INTRODUCTION

Male live births occur in excess of female live births and their ratio (commonly referred to as M/F) is usually expressed as male divided by total births. The value of M/F varies. It has been shown to exhibit broad secular trends (1) and to be sensitive to stress (2). Indeed, all forms of stress have been shown to reduce M/F and these include natural calamities (3, 4).

Man-made events, such as terrorist attacks, have also been shown to reduce M/F. For example, following the September 11 attacks, M/F was shown to have dropped not only in the New York (5) but also in the entire United States (6). Short periods of war have also been shown to reduce war (7) as has economic turmoil and uncertainty (8).

Overall, Israel has been shown to have a relatively stable M/F with no influence from maternal or paternal age, gravidity or parity over the period 2003–2006 (9). However, a study over a longer period showed a significant decline in M/F from 1950 to 1989 with one outlier year (1981) in temporal relation to the destruction of a nuclear reactor that was still under construction near Baghdad. It was speculated that the spectre of war may have resulted in sufficient stress to cause a dip in M/F in this year (10).

Racial differences in M/F have also been demonstrated in countries wherein such races coexist (11). This study was carried out in order to ascertain whether there were any racial or religious differences in M/F in Israel.

SUBJECTS AND METHODS

Annual data for male and female live births were available from the website of the Israel Central Bureau of Statistics for the period 2002–2011. Excel was used for

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data entry, overall analysis and charting. For race, data were available as Jews and others, and Arabs. For religion, data were available as Jews and Moslems.

The quadratic equations of Fleiss were used for exact calculation of 95% confidence intervals for ratios (12). Chi tests and Chi tests for trends for annual male and female births were used throughout using the Bio-MedStat Excel add-in for contingency tables (13). A p-value ≤ 0.05 was taken to represent a statistically significant result.

Overall M/F for Israel was also compared to amalgamated data for the European and the North American Continents (14).

RESULTS

There were a total of 1 523 956 live births for the period 2002–2011. Overall M/F was 0.5127 (95% CI: 0.5119, 0.5135). Annual M/F for the study period overall, and by race and by religion are shown in Table 1. There were no significant differences between races and religions and no significant trends with time.

For the European Continent, M/F over the period 1950–1999 was 0.5142 (95% CI: 0.5142–0.5143), and for the North American Continent, M/F over the period 1958–97 was 0.5112 (0.5111–0.5112). Male-to-female ratio for Israel was significantly less than for Europe ($p = 0.0002$) but significantly greater than North America ($p = 0.0001$), as per Table 2.

DISCUSSION

Man-made stress is known to reduce M/F. This may be due to contracting economies (15), hotly contested political referenda (16) and even civil strife (17) that falls short of actual warfare (7).

Male-to-female ratio in Israel appears to be mid-way between that of the European and the North American Continents, with no racial or religious differences within the country and significant time trends over the period studied.

The psychological effects of stress in Israel (manifesting even in psychosomatic manifestations) (18) along with the outright psychiatric effects have been well documented in this region (19). However, there was no apparent effect on M/F that is manifested as racial or religious differences in M/F. This could be due to one or more of the following reasons:

All individuals may be equally stressed, so that there may be no difference in M/F outcomes. Another alternative is that the stress levels present are insufficient to affect M/F. Another possibility is that the number of births available for study is too small to detect M/F changes, which may be subtle and require larger numbers of births in order to manifest.

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Table 1: M/F overall and by race and by religion, 2002–11

All	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
M	71 318	74 272	74 694	73 956	76 078	77 830	80 254	82 398	85 415	85 162	781 377
F	68 217	70 664	70 513	69 957	72 092	73 849	76 669	78 644	80 840	81 134	742 579
Total	139 535	144 936	145 207	143 913	148 170	151 679	156 923	161 042	166 255	166 296	1 523 956
UCI	0.5137	0.5150	0.5170	0.5165	0.5160	0.5156	0.5139	0.5141	0.5162	0.5145	0.5135
M/F	0.5111	0.5124	0.5144	0.5139	0.5135	0.5131	0.5114	0.5117	0.5138	0.5121	0.5127
LCI	0.5085	0.5099	0.5118	0.5113	0.5109	0.5106	0.5089	0.5092	0.5114	0.5097	0.5119
Jews and others	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
M	50 480	53 220	53 554	54 062	56 136	57 697	60 018	62 158	64 572	64 626	576 523
F	48 124	50 379	50 803	51 050	53 052	54 846	57 455	59 085	60 933	61 924	547 651
Total	98 604	103 599	104 357	105 112	109 188	112 543	117 473	121 243	125 505	126 550	1 124 174
UCI	0.5151	0.5168	0.5162	0.5174	0.5171	0.5156	0.5138	0.5155	0.5173	0.5134	0.5138
M/F	0.5119	0.5137	0.5132	0.5143	0.5141	0.5127	0.5109	0.5127	0.5145	0.5107	0.5128
LCI	0.5088	0.5107	0.5101	0.5113	0.5112	0.5097	0.5080	0.5099	0.5117	0.5079	0.5119
Arabs	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
M	20 838	21 052	21 140	19 894	19 942	20 133	20 236	20 240	20 843	20 536	204 854
F	20 093	20 285	19 710	18 907	19 040	19 003	19 214	19 559	19 907	19 210	194 928
Total	40 931	41 337	40 850	38 801	38 982	39 136	39 450	39 799	40 750	39 746	399 782
UCI	0.5140	0.5141	0.5224	0.5177	0.5165	0.5194	0.5179	0.5135	0.5163	0.5216	0.5140
M/F	0.5091	0.5093	0.5175	0.5127	0.5116	0.5144	0.5130	0.5086	0.5115	0.5167	0.5124
LCI	0.5042	0.5044	0.5126	0.5077	0.5066	0.5095	0.5080	0.5036	0.5066	0.5118	0.5109
Jews	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
M	48 365	50 915	51 319	51 742	53 729	55 377	57 600	59 764	62 085	62 051	552 947
F	45 962	48 212	48 743	48 915	50 784	52 609	55 203	56 835	58 588	59 469	525 320
Total	94 327	99 127	100 062	100 657	104 513	107 986	112 803	116 599	120 673	121 520	1 078 267
UCI	0.5159	0.5167	0.5160	0.5171	0.5171	0.5158	0.5135	0.5154	0.5173	0.5134	0.5138
M/F	0.5127	0.5136	0.5129	0.5140	0.5141	0.5128	0.5106	0.5126	0.5145	0.5106	0.5128
LCI	0.5095	0.5105	0.5098	0.5109	0.5111	0.5098	0.5077	0.5097	0.5117	0.5078	0.5119
Moslems	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
M	18 439	18 588	18 683	17 579	17 560	17 796	17 857	17 868	18 481	18 207	181 058
F	17 760	17 841	17 555	16 638	16 777	16 776	17 003	17 385	17 740	17 040	172 515
Total	36 199	36 429	36 238	34 217	34 337	34 572	34 860	35 253	36 221	35 247	353 573
UCI	0.5145	0.5154	0.5207	0.5191	0.5167	0.5200	0.5175	0.5121	0.5154	0.5218	0.5137
M/F	0.5094	0.5103	0.5156	0.5138	0.5114	0.5148	0.5122	0.5069	0.5102	0.5166	0.5121
LCI	0.5042	0.5051	0.5104	0.5084	0.5061	0.5095	0.5070	0.5016	0.5051	0.5113	0.5104

M/F = male to female ratio; M = male; F = female; UCI = upper 95% confidence interval; LCI = lower 95% confidence interval.

Table 2: A comparison of M/F for Israel *vs* amalgamated data for the Europe and the North American Continents

	Europe	**Israel**	**North America**
Years	1950–1999	2002–2011	1958–1997
M	159 194 981	781 377	127 034 732
F	150 384 968	742 579	121 488 464
Total	309 579 949	1 523 956	248 523 196
UCI	0.5143	0.5135	0.5112
M/F	0.5142	0.5127	0.5112
LCI	0.5142	0.5119	0.5111
Chi	13.7		15.0
***p*-value**	0.0002		0.0001

M/F = male-to-female ratio; M = male; F = female; UCI = upper 95% confidence interval; LCI = lower 95% confidence interval.

ORIGINAL ARTICLE

A Review and Nested Case Study of Special Study Modules in Undergraduate Medical Education at the University of the West Indies, Jamaica

D Ragoobirsingh[1], TJ Paul[2], MJ Branday[2]

ABSTRACT

Objective: *To evaluate the Special Study Modules (SSMs) that were developed with the aim that students should have learnt new skills, adopt new attitudes and acquire knowledge in areas outside the mainstream of medical education that enrich and enhance their professional development.*

Methods: *A review of records in the office of curriculum affairs was undertaken to identify and categorize all topics administered as SSMs to medical students since the last revision of the curriculum. Additionally, a nested case study was done on one of the modules on 'taking a spiritual history'.*

Results: *The SSMs were divided into three broad subject panels. Each SSM regardless of its subject panel had expressed goals, a set of objectives, and a defined development structure. The nested case study revealed that 40 students took part in the SSM on spiritual health. Overall, students reported positive feedback on the experience and there has been a growing demand for this SSM.*

Conclusion: *From all indications, this programme ensures development of lifelong skills, transferable or generic, associated with opportunities to explore topics outside the core of the undergraduate medical curriculum.*

Keywords: Medical curriculum, Mona Campus, nested case, Jamaica, Special Study Module, University of the West Indies.

INTRODUCTION

In the field of education, the British General Medical Council has recognized the value of a broader based education experience and advocated the introduction of areas such as the arts and humanities into medical curricula (1, 2).

The undergraduate medical curriculum at the University of the West Indies (UWI), Mona, was designed to produce competent graduates with skills that equip them for lifelong learning. It is comprised of core modules and a series of Special Study Modules (SSMs). The structure and delivery of SSMs is designed to promote self-learning and develop understanding rather than just the acquisition of knowledge.

The philosophy and aim of the SSMs is to provide students with an opportunity to explore subjects of particular interest to them in greater depth than the core course allows, and to assist them in developing analytical and communication skills.

This article describes the range of topics covered in the delivery of SSMs to students from the inception of the programme and looks at the value of SSMs in enhancing curriculum diversity.

MATERIALS AND METHODS

A review of records in the office of curriculum affairs was done to identify and categorize all topics that have been administered as SSMs to medical students since the

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last revision of the curriculum. The topics were sorted by subject area and a content analysis was done to group learning outcomes into common themes. Additionally, a nested case study was done on one of the modules covering 'taking a spiritual history'.

Forty students took part in this SSM which ran for 6 weeks on a part-time basis. The aim was for students to develop knowledge and skills on the assessment of spiritual health. Each student took two in-depth patient histories using a structured spiritual assessment tool. Their written feedbacks were reviewed and collated to highlight the key reflections.

RESULTS

Special Study Modules

List of SSM offered are as follows:

- Ethical Dilemmas in Medicine
- Environmental Hazards affecting the Human Foetus—the Effect of Heavy Metals
- The History of Medicine
- The Use of Radio in Health Promotion/Education
- Screening for Obesity and Diets for Management
- Ethical Issues at the End of Life
- Sports Injuries affecting the Knee
- Gender, Sexuality and Behaviour Change Communication
- Current Thinking on Nutrition and Child Development
- Drug Discovery; Ethnopharmacology and Other Approaches
- Substance Abuse: Caribbean Issues and Responses
- Port Health and Quarantine
- Health Promotion: Teach and Learn
- Continuing Medical Education—a Needs assessment
- Creative Photography
- Spiritual Health
- Introduction to Telemedicine
- Emerging Parasitic Infections in the Caribbean
- Designer Drugs—the Way Forward
- Sign Language
- Spanish
- Evaluating Research in the Faculty of Medical Sciences, UWI
- Functional Determinants of Autonomic Control of the CVS
- Eating Disorders—their Effects on Nutrition and Health Status
- Male Sexual Function and Dysfunction
- Approaching Dilemmas in Clinical Ethics through Film
- Wine making
- Creative Writing
- Medicine, Law and Ethics

(i) Subject panel

The SSMs were divided into the following broad subject panels:

- Arts and the Humanities
- Basic Sciences
- Clinical care

(ii) Goals

The expressed goals of each SSM, regardless of the subject panel, were to provide opportunities for students to:

- source, process and critically evaluate information
- develop the skills of group work and group leadership
- develop and maintain oral and written presentation skills

(iii) Objectives

To achieve the above goals, the candidates adhered scrupulously to the stated objectives which emphasized that on completion of this series of modules the student should be able to:

- retrieve information
- evaluate and critically appraise both written and oral communication
- demonstrate the ability to work as a team
- demonstrate the ability to carry out self-directed learning

(iv) Development structure

As such each module was designed to include as many of the following elements as possible:

- Subject material with some relevance to the practice of medicine
- A method of learning that promotes self-direction
- Defined times for contact with the coordinator
- An allocated number of hours per week for completion
- A written overall aim
- Written student centered objectives
- A defined method of assessment which matches the objectives of the module.

Nested case study

Forty students took part in the SSM on spiritual health. The main reflections reported by these students were as follows:

'Understanding of spiritual health has broadened beyond Christianity. It provided an opportunity to look at the person behind the illness and to connect'.

'What was most challenging was determining what spiritual health meant to me'.

'This was a stimulating experience for me as my journey through medical school is a spiritual one. I see the benefits of incorporating spiritual aspects of medicine into my history. This will undoubtedly be listed among my most meaningful undertakings in medical school'.

Overall, students had positive feedback on the experience and there is a growing demand for this SSM.

DISCUSSION

The wide range of topics developed into SSMs by faculty highlight an avenue for enriching and building diversity in the undergraduate medical curriculum. It must be admitted that the SSM programme at Mona does not adhere scrupulously to the recommendations of the GMC, practiced by many UK medical schools. The latter involves modules of varying length which are in subjects directly related to medicine, whether laboratory based or clinical, biological, or behavioural, research oriented or descriptive (3). It is noteworthy, however, that students in these schools have to do an SSM in each of the first 3 years, if not more, of their curriculum. As such in the 1st year of their 5-year medical course, the SSMs focus on information retrieval and presentation; information technology and skills in data analysis. Early in 2nd year, another SSM is primarily a literature review related to a particular medical or biomedical science topic. It is only at this juncture that students are thought to be mature enough to gain broader experience in a topic not necessarily directly allied to medicine. At Mona, on the other hand, the students are required to do just one for the entire duration of their programme. The philosophy underpinning SSMs was to introduce alternative educational climates early, as suggested by Roff and McAleer, which can be motivating and the mature learner, wants progressively different types of teaching, learning, and environment (4).

Qualitative student feedback, for the most part, reflected satisfaction with the experience gained. They appreciated that they were being exposed to other learning methods that they may not be able to access otherwise. They were intrigued by the opportunity provided for them to set their own objectives and explore their own interests. The need for teamwork was also highlighted. Among all the positive reports received and recorded was the refrain expressed by nearly all the students of the workload that SSMs imposed on their already packed timetable. From the supervisors' perspective the experience was very rewarding. The diligence and commitment of the students motivated the former to persevere.

The nested case study that follows gives a more in-depth look at the Mona SSM experience. The nested case study, although not a representative sample of SSMs, provides some qualitative insights into the students' response to what may be deemed a non-mainstream curriculum. The main reason for using nested study was to reduce the labour and cost of data collection by collecting data only for those subjects who are chosen for the nested study (5). This form of analysis is used widely (6, 7).

Exposure to spiritual history taking is seen as a positive one by students with perceived benefits to both patients and students. Students saw benefits to this exposure while at the same time reported challenges with applying the concept to themselves suggesting the deeper application of the material. It also highlights values implicit to molding well-rounded physicians as they looked at the 'person behind the illness' and sought to connect.

Teaching about spirituality in medical school training is lacking. Spirituality is a dimension of humanity that can put experiences of health and illness into a meaningful context. Medical students might benefit from understanding spirituality as an important element in learning to care for patients. Spirituality also provides a context for medical students to explore their own motivations for doctoring (8).

The relationship between spirituality and health is receiving increased attention; consequently, medical schools have begun asking how and in what manner these issues should be addressed in medical education. Unfortunately, student beliefs concerning spirituality and health have not been adequately assessed.

Selecting this SSM for the nested study is proving to be instructive in curriculum review and possible revision going forward. The Mona medical school can learn invaluable lessons from the study done by Guck and Kavan (9). This study examined medical students' beliefs regarding the relationship between spirituality and health and the level of instruction spirituality should receive in the curriculum. Spiritual practices were seen as more helpful for acute and mental health conditions

than for chronic or terminal conditions and believed to be more helpful for coping with a health condition than for healing tissue. Students believed that patients could benefit from spiritual practices more than they could for their own health conditions. Most students endorsed a lecture or 1–2-week seminar with instruction in the 1st or 2nd year of medical school. Student spirituality was the only predictor of the required level of instruction in the medical school curriculum.

Mona can further learn from the model employed in the Diploma nursing curriculum at the University of Malta (10). The aim was to increase students' awareness about the essence of spirituality in care to enable them to implement holistic care. Spirituality may or may not incorporate religiosity. Apart from the use of traditional teaching methods such as lessons and a seminar, other methods were also used constantly throughout the study unit, for example, self-reflection exercises, case studies and small group discussions to enhance learning.

The Mona Medical Education Unit may wish to consider the recommendations proposed in the aforementioned studies with a view to introduce other teaching methods for effective learning. However, it will be prudent to evaluate if an intervention in teaching spirituality and health fosters competence changes in healthcare students (11). In fact, Mona can further learn from the Neely and Minford study that investigated the status of teaching on spirituality in medicine in UK medical schools to establish if and how medical schools are preparing future doctors to identify patients' spiritual needs (12). They found that there was little uniformity between medical schools with regard to content, form, amount, or type of staff member delivering the teaching. It was suggested that it would be beneficial to introduce a standardized curriculum on spirituality across all UK medical schools. Rather than reinventing the proverbial wheel, Mona could possibly adopt and adapt the latter if, and when, it decides to incorporate spirituality and health in the curriculum.

From the analysis of the range of topics provided to students and the qualitative nested case analysis, this aspect of the undergraduate medical curriculum appears to provide a useful opportunity for personal and professional development and self-growth. In this sense as much as it is provided in a peripheral manner to the core biomedical content of the early years of training it can play an integral part in molding the future physician.

The SWOT analysis revealed a wide range of benefits to participating students. Opportunities for curriculum diversification through external stakeholders were also identified. The main weaknesses that were identified resulted from a lack of resource support and the threat of an expanding core curriculum eroding time for non-core activities.

CONCLUSION

Given the students' interest and perceived benefits, the maintenance of non-core subject teaching require greater buy-in from staff, and will depend largely on increased resource support and allocation of time. In 2010, the SSM initiative was adapted to a student self-crafted community service experience. This came about because of increasing class sizes and the challenges with providing SSMs to all students.

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AUTHORS' CONTRIBUTIONS

D Ragoobirsingh, who was the original coordinator of the SSM module, conceived paper, wrote the manuscript, and approved the final version.

TJ Paul, the then Director of the MBBS programme, collected and analysed the data, conducted the nested case analysis and reviewed the final manuscript.

MJ Branday, one of the main architects of the new curriculum, provided invaluable information on the conceptualization, subject panels, goals, objectives and the structure of the SSMs and reviewed the final manuscript.

The authors declare that they have no conflicts of interest.

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REVIEW

Cardiac Involvements of Fabry Disease

S-M Yuan

ABSTRACT

Fabry disease is a rare, inherited metabolic disorder caused by deficient activity of α-galactosidase A, which leads to cellular and multiorgan dysfunction due to progressive intracellular globotriaosylceramide accumulation, extensive interstitial fibrosis and smooth muscle cell proliferation, mostly due to accelerated cellular apoptosis and/or necrosis. Cardiac involvements are frequent in Fabry disease. The patients may develop hypertrophic cardiomyopathy, arrhythmias, conduction abnormalities, valvular abnormalities and coronary heart disease. The diagnosis of Fabry disease is challenging due to the protean manifestations, which often lead to delayed diagnosis. Enzyme replacement therapy with the administration of agalsidases α and β may lead to the clearance of globotriaosylceramides from the cardiac capillaries and therefore result in left ventricular structural and functional improvements. Anticoagulant treatment is necessary for patients with Fabry disease to prevent ischaemic events. Symptomatic bradycardia and heart block frequently warrant pacemaker implantation and malignant arrhythmias may require an implantable cardioverter-defibrillator. Surgical interventions including valvular operation, myectomy and coronary artery bypass or coronary angioplasty have been attempted in a limited number of patients with Fabry disease alongside enzyme replacement therapy. The early and mid-term follow-up results have been satisfactory. This article presents a review of the pathogenesis, clinical features, diagnostic approaches and treatment strategies of the heart involvements of Fabry disease.

Keywords: Enzyme replacement therapy, left ventricular hypertrophy, lysosomal storage diseases

INTRODUCTION

Fabry disease is a rare inherited metabolic disorder caused by the deficient activity of α-galactosidase (Gal) A, which degrades the globotriaosylceramides (Gb3) and other glycosphingolipids into lower molecular weight products (1). Deficient α-Gal A activity leads to cellular and multiorgan dysfunction due to progressive intracellular Gb3 accumulation in the organs (2). Globotriaosyloceramides deposits cause extensive interstitial infiltration (3), thereby leading to smooth muscle cell proliferation and increased intima-media thickness of the arteries, including common carotid, brachial and radial arteries, *etc* (4). Globotriaosyloceramides often deposits within the cells and interstitial fibrosis frequently develops due to accelerated cellular apoptosis and/or necrosis (5). Both Gb3 deposits and elevated plasma endothelin-1 levels contribute to myocardial architectural remodelling (6).

Globotriaosylsphingosine (lyso-Gb3) is a degradation product of Gb3, and it increases dramatically in classical Fabry patients (7). Lyso-Gb3 has high diagnostic sensitivity and correlates with the left ventricular (LV) mass in late-onset Fabry disease patients (8). A comparative study revealed that the plasma sphingosine-1 phosphate levels were significantly higher in the Fabry disease patients than in those of healthy controls. In addition, a positive correlation between plasma sphingosine-1 phosphate levels and both common carotid artery intima-media thickness and LV mass index was found (9). Inhomogeneous properties of cells with

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normal X-chromosome and those with X-chromosome with α-Gal A mutations are associated with random X-chromosome inactivation (10). Various cell types can be affected by metabolite storage, and renal epithelial, myocardial and neuronal cells are the most often affected (11). As a result, 70% of patients with Fabry disease had electrocardiographic abnormalities, 60% had proteinuria and 40% had a reduced glomerular filtration rate (2).

The incidence of Fabry disease is not well defined; and neonatal screenings showed a higher incidence than cited in the literature due to detection of late-onset variants (12). Fabry disease is found in approximately 1:117 000 people or 1:40 000 males (13). It was reported that 98% of the patients had a positive family history (2). The diagnosis in female patients is often delayed, due to mild symptoms, slow progression and isolated organ involvement (2). Cardiac involvement is frequent in Fabry disease (3), accounting for 46% of the cases (2). The patients may develop hypertrophic cardiomyopathy, arrhythmias, conduction abnormalities, valvular disorders and coronary heart disease. It has been noted that Fabry cardiomyopathy with valvular disorders correlates with the severity of the disease (14). The diagnosis of Fabry disease is challenging and a delayed diagnosis is usually the case due to the protean manifestations. In order to have a better theoretical knowledge and to improve the diagnosis and treatment of the disease, the cardiovascular aspects of Fabry disease are highlighted in this article.

Cardiac manifestations

Left ventricular hypertrophy

Left ventricular dilatation and aneurysms are not typical, but they can be seen in terminal patients. The cardiomyopathy in Fabry disease is a progressive infiltrative hypertrophic cardiomyopathy characterized by LV dilatation with global or regional wall motion abnormalities and aneurysm formation (15). Concentric LV hypertrophy is a key feature in Fabry disease (16).

The underlying mechanism for LV hypertrophy in Fabry disease patients is still unknown. Gb3 accumulation is unlikely to be directly involved in the development of Fabry cardiomyopathy, but it may induce cardiomyopathy by activating certain signalling pathways (17). The myocardial energy depletion in Fabry cardiomyopathy is similar to that found in other metabolic diseases and hypertrophic cardiomyopathies (18). The patients with Fabry cardiomyopathy may have mild diastolic dysfunction at the early stage, and they may evolve into exceptional restrictive cardiomyopathy at the late stage with a probable infiltrative pathogenesis of the endothelium of the arterioles (18).

In a majority of the patients, the LV hypertrophy is concentric; however, an asymmetrical variety with septal thickening and posterior wall fibrotic thinning may present in about 5% of the cases (14). Left ventricular hypertrophy in Fabry patients is usually not associated with significant systolic or restrictive diastolic dysfunction. Instead, the LV function correlates well with the severity of the disease (19). The deposits of Gb3 represent only about 1% of the increase in the LV mass (6). The fibrotic process in Fabry cardiomyopathy starts with intramural involvement with later transmural involvement. Fibrosis is invariably present in the basal posterolateral segments (20). Magnetic resonance imaging showed increased gadolinium uptake involving the basal segment of the LV posterolateral wall, typical for myocardial fibrosis in advanced Fabry cardiomyopathy patients, in whom the end-diastolic thicknesses of the LV septum and posterolateral walls were measured to be 16 mm and 15 mm, respectively (21). Gb3 accumulation had been observed in vascular endothelial and smooth muscle cells, cardiomyocytes, conduction tissues and valvular fibroblasts (22).

Sachdev *et al* (23) reported that about 6% of male patients with late-onset and about 1% of patients with early-onset hypertrophic cardiomyopathy had a low α-Gal activity and the incidence of Fabry disease was 4%. They screened for plasma α-Gal activity in male patients with hypertrophic cardiomyopathy diagnosed before and after 40 years of age, and noted that all six patients with low α-Gal values had α-Gal gene mutations. Monserrat *et al* (24) screened the genotype of 508 patients with hypertrophic cardiomyopathy and found that the prevalence of Fabry disease was 1% (0.9% in men and 1.1% in women). The prevalence of Fabry disease gene mutations in the patients with unexplained hypertrophic cardiomyopathy was 0.5%–4% (25, 26).

Valvular changes

Valvular changes in Fabry disease patients are believed to be caused by lipid storage and fibrosis in the valvular tissue (13). The incidence of valvular changes did not differ between the hemizygotes and the heterozygotes (27). The post-mortem examinations of the heart of patients with Fabry disease showed the maximal accumulation of the major glycosphingolipid substrate and Gb3 in the lysosomes of all the cardiac tissues examined; the greatest concentrations were found in the mitral

valve in addition to the LV myocardium (28). The valvular involvements in Fabry disease differed significantly between valves.

Minor structural abnormalities of the mitral valve were found in 57% of patients and the aortic valve was affected in 47% Valvular abnormalities were often associated with minor/mild degrees of regurgitation (14). Weidemann *et al* (29) reported no severe valvular disorders in a cohort of 111 patients with Fabry disease; instead, only a few cases of mild-to-moderate aortic, mitral or tricuspid disorders were noted. In addition, in Fabry cardiomyopathy, echocardiography might reveal very prominent papillary muscle associated with concentric LV hypertrophy (30). The thickening of the papillary muscle and mitral leaflet, along with mild mitral regurgitation, could be found in half of the Fabry disease patients (31). The findings of diffuse ballooning of the mitral valve and massive glycolipid storage in the valve tissue suggested that the abnormal storage process is responsible for the valvular insufficiency (32). Other authors proposed that there was a high frequency of mitral valve prolapse in Fabry disease patients (19, 33). Mitral valve thickening, deformity, or prolapse is often seen in young patients, whereas aortic disorders appear in older patients (17). But, findings in recent reports were not consistent with these arguments (31).

Conduction abnormalities and arrhythmias

Gb3 deposits have been found in the conduction system in addition to the deposit in the myocardium (34). This predisposes to rhythm disturbances resulting in tachy- and mostly bradycardia. The typical electrocardiogram findings of Fabry disease include short P-R intervals (The P-R interval refers to the time from the beginning of the P wave to the beginning of the ventricular wave, representing the time from the beginning of atrial depolarization to the beginning of ventricular depolarization) in the early stage, and P-R interval prolongation, atrioventricular block, electric LV hypertrophy, ST (the ST segment represents the period from the end of the QRS complex (J) to the beginning of the T wave on electrocardiogram) depressions and T-wave inversions at the late stage (14). Fabry disease is often associated with P-R interval shortening, QRS (the QRS complex reflects the changes of left- and right-ventricular depolarization potential and time) interval prolongation, positive Sokolow Lyon index, pseudo-myocardial infarction pattern and repolarization dispersion (35). Cryptogenic ventricular ectopic beats are frequent (36). P-R interval shortening and first-degree atrioventricular block were found in 14% and 1.4% of Fabry disease patients, respectively (37). Electron microscopy of the myocardial biopsy of Fabry cardiomyopathy patients revealed the prominent involvement of cardiac conduction tissue, which was largely occupied by vacuoles (36).

Aortopathy

In patients with Fabry disease, inflammatory and neurohormonal mechanisms were identified in the vascular dysfunction predisposing to tissue ischaemia, hypertrophy and fibrosis (38). The echocardiographic evidence of aortic root dilatation was noted in 30%–56% of male patients with Fabry disease (14, 19, 33, 39). The aortic dilatation at the sinus of Valsalva was found in 32.7% of the male and 5.6% of the female patients; aneurysms were present in 9.6% of the male and 1.9% of the female patients (40). In the advanced stage, with progression of cardiac involvement and LV hypertrophy, marked aortic root dilatation could be seen (41). Additionally, a high prevalence of ascending aorta dilatation and aneurysms in the male patients with Fabry disease compared with the normal population was noted. Females with Fabry disease also developed dilatation of the sinus of Valsalva and ascending aorta, but with a significantly lower rate than males. The dilatation seemed to be independent of cardiovascular risk factors. The lower prevalence and delayed onset of aortic dilatation in the female patients was consistent with the previous arguments of milder female involvements (40).

Coronary artery disease

The true incidence of coronary heart disease in Fabry disease remains unclear, because cardiac catheterization is not routinely performed in such patients (13). Angina was frequent in 13%–23% of the Fabry disease patients, but myocardial infarction is uncommon (42, 43). According to the Fabry Outcome Survey database, the incidence of myocardial infarction was < 2% (13/752) in Fabry disease patients (14). The pathogenesis of angina might be coronary vasospasm due to endothelial infiltrates and dysfunction, decreased coronary reserve, and LV hypertrophy (14). A double-blind, randomized, placebo-controlled trial showed Gb3 deposits in the interstitial capillary endothelial cells in the myocardiocytes, which was considered to be the true mechanism of the coronary lesion in Fabry disease patients (44). There was electrocardiographic evidence of myocardial injury but no evidence of ischaemic myocardial damage (13). Elevated troponin I levels were noted in 46.2% of the patients with Fabry disease with angina pectoris

(13). Coronary and ventricular angiography revealed slow coronary flow and slow runoff of the contrast medium in normal coronary calibres in those presenting with angina (13). Revascularization of stenotic coronary arteries was required in < 1% of the Fabry disease patients (14). The post-mortem examination of the hearts of Fabry disease patients revealed accumulation of Gb3 in the lysosomes of the vascular endothelium in addition to marked accumulation of the major glycosphingolipid substrate Gb3 in the lysosomes of all the cardiac tissues (28).

Isolated cardiac variant

Although Fabry disease may involve many systems, including neurological, metabolic, gastrointestinal and renal, isolated cardiac variants have been described (45). This is because Gb3 deposit occurs almost exclusively in the heart in quite a number of patients (6, 46, 47). The isolated cardiac variant of Fabry disease was present in about 3% of male patients with LV hypertrophy (48). Significantly reduced plasma α-Gal activity, missense mutations in the α-Gal gene and low α-Gal mRNA amounts were noted in at least some of the patients (48).

Diagnosis

The protean clinical manifestations of Fabry disease often lead to delayed diagnosis for many years (49). A known familial history of Fabry disease may lead to an early diagnosis and prompt treatment (50). The diagnosis is primarily biochemical, based on determination of enzymatic activities in different biological tissues (such as plasma, leukocytes, fibroblasts and most recently dried blood spots on filter paper) (51), and on histological studies, i.e., a significant Gb3 deposit in the capillary endothelium of the skin (2). Prenatal diagnosis is possible by measuring the α-Gal A activity in the tissue or the fluid taken from around the foetus. This test may be offered to expectant mothers who have Fabry disease. Diagnosis through DNA testing to identify specific gene mutations is also an option (50). In female patients, α-Gal A mutation is more a reliable indicator than clinical symptoms or laboratory findings (2). The prominent papillary muscle that is positively correlated with LV wall thickness could be an echocardiographic marker for the detection of Fabry patients with concentric LV hypertrophy (52). Electrocardiogram is helpful in the diagnosis of not only the conduction of the abnormalities and arrhythmias, but also the diagnosis of LV hypertrophy by displaying a typical giant negative T wave in leads $V_{2\text{-}5}$ (35).

Treatment

Enzyme replacement therapy with agalsidase α (0.2 mg/kg body weight every 2 weeks); and agalsidase β (1 mg/kg every 2 weeks) has been administered to patients and proved to be effective in the LV structural and functional improvements (11, 53). symptomatic treatments include: analgesics, antihypertensives, antiplatelet agents and anticoagulants where indicated for patients with Fabry disease (54). Symptomatic bradycardia and atrioventricular conduction abnormalities frequently warrant pacemaker implantation. Implant indications included symptomatic bradycardia, non-sustained ventricular tachycardia, conduction abnormalities, palpitations and syncope (55). The patients with proven malignant arrhythmias may benefit from an implantable cardioverter-defibrillator (56).

Only 3/752 (0.4%) valvular disorders in Fabry disease required a surgical operation (14). Fernandez *et al* (57) reported a 59-year-old male patient with Fabry disease with severe mitral regurgitation by echocardiography. He received a successful mitral valve repair with a P_2 resection and ring annuloplasty via a right minthoracotomy. Choi *et al* (58) reported aortic mechanical valvular replacement and heart biopsy in a 31-year-old male patient during enzyme replacement therapy. The surgical indication for aortic valve replacement was a more thickened, severely degenerative aortic valve with severe aortic regurgitation. The histology of the aortic valve showed myxoid degeneration of the valve leaflets. Significant LV outflow tract obstruction caused by asymmetric hypertrophy can be cured by alcohol ablation, which may result in complete relief of the obstruction (59).

For the coronary lesions in Fabry disease, coronary angioplasty and coronary artery bypass might achieve less than satisfactory results. Marcì *et al* (60) reported a Fabry disease patient who had a recurrent angina two years after successful coronary angioplasty when the diagnosis of Fabry disease was overlooked. Chimenti *et al* (61) reported coronary artery bypass performed in a 54-year-old man with untreated Fabry disease. The man's left internal mammary artery graft was occluded while his saphenous vein grafts were patent at 1-year follow-up. They proposed that the vein graft might be free of glycosphingolipid accumulation due to low-pressure load. Septal alcohol ablation may be effective in patients with LV outflow tract obstruction. Kunkala *et al* (62) reported successful septal myectomy in two patients with Fabry disease. Their post-operative echocardiography revealed no or minimal residual LV outflow

tract obstruction and no systolic anterior motion of the mitral valve apparatus. Cardiac transplantation has been recommended and performed for end-stage cardiomyopathy secondary to Fabry disease (63, 64). Furthermore, patients with the advanced stages of heart disease, such as congestive heart failure, may be candidates for heart transplantation, as the intrinsic enzyme production within the graft could prevent its rapid deterioration (63). Concurrent heart and kidney transplantations were successfully performed in a Fabry disease patient who was complicated by end-stage renal disease and severe heart failure that responded poorly to enzyme replacement therapy (65).

Outcomes

The patients' prognoses with enzyme replacement therapy relied on the severity of baseline hypertrophy and fibrosis and on the timing of treatment (66). Plasma Gb3 declined by 50% after 10 weeks of treatment with agalsidase α (67). There was a significant reduction in LV mass, an improvement in myocardial function and a higher exercise capacity in comparison with the baselines (68). The histological analyses of the vascular endothelial cells in the patients receiving enzyme replacement therapy demonstrated intracellular Gb3 clearance following treatment (69). Pathological studies revealed cardiomyocyte Gb3 accumulation in baseline biopsies and clearance of Gb3 from cardiac capillaries after enzyme replacement therapy with recombinant human α-Gal A (44). Similarly, Hughes et al (70) discovered a significant decrease in the myocardial Gb3 content in myocardial biopsies and a remarkably, reduced LV mass as measured by magnetic resonance imaging after a 6-month treatment.

Despite the good early and mid-term results of the surgical intervention in Fabry disease patients with simultaneous enzyme replacement therapy, ongoing follow-up is imperative.

CONCLUSION

Cardiac involvements, typically LV hypertrophy, are frequent in Fabry disease. The protean clinical manifestations often lead to delayed diagnosis. The diagnosis is primarily based on laboratory testing for the determination of enzymatic activities or histological studies. Enzyme replacement therapy with agalsidases α or β is effective for Fabry disease. Very few patients with cardiac involvements warrant cardiac surgical procedures.

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REVIEW

Non-pharmacological Community Intervention, Especially Pain Management, in Rheumatoid Arthritis: A Review of the Literature

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ABSTRACT

Objective: *Rheumatoid arthritis (RA) is a crippling disease with significant impact on a patient's life. The objective of this study is to describe the role of unimodular and multi-modular, non-pharmacological community intervention effectiveness, especially pain management interventions in RA.*

Methods: *This review is built on a preliminary literature search, covering 2009 up to December 2013. Selective review of current literature was produced by searching for the terms 'non-pharmacological intervention', 'self-management programme', 'self-care', and 'rheumatoid arthritis', to capture all spectrums of RA non-pharmacological interventions. Twenty-six reviews were included in this overview.*

Results: *A substantial and remarkable number of studies of non-drug care interventions in RA are available. Twenty-six reviews were included in the present overview, which indicated a beneficial effect of cognitive behavioural therapy and psychotherapeutic intervention, self-management, and physical therapy (exercise), but a few studies indicated a beneficial effect of the multi-disciplinary education programme and specific dietary interventions. The evidence of effectiveness varies among the different non-pharmacological modalities and indicates a need for further investigation into the most clinical and cost-effective strategies to deliver individual, non-pharmacological treatment modalities, as well as comprehensive arthritis service delivery models for patients with RA.*

Conclusion: *This article gives a summary of the available evidence regarding the effectiveness of non-pharmacological treatment modalities which are often prescribed as an adjunct to standard care in RA, but the data require scientific appraisal into the most clinically and cost-effective strategies.*

Keywords: Non-drug therapy, intervention studies, pain management, rheumatoid arthritis.

INTRODUCTION

The spectrum and severity of rheumatoid arthritis (RA) are not very different in developing and developed countries, but in the developing countries inadequate rheumatology services further compounds the burden of the disease (1). The incidence and prevalence of these conditions has been proved, is dynamic, not static, and appears to be influenced by both genetic and environmental factors (2). Ample information has been collected in the Community Oriented Program for the Control of Rheumatic Disease (COPCORD) studies (3), which shows wide differences in the prevalence of RA. The prevalence of clinical RA recently reported by the WHO ILAR COPCORD in urban and rural surveys in India

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varied from 0.45% to 0.68% (4). It was noted that 0.33% of urban population and 0.19% of rural population are affected with RA in Iran (5, 6). In Asia-Pacific countries, it was calculated as 0.33% (7), and in developed populations, it was 0.5% to 1% of the adult population (8).

Despite substantial advances in medical treatment, RA is a disease that continues to affect the lives of individuals considerably (9, 10). The challenge is to find a cost-effective treatment for better disease control (11, 12). Pharmacological treatment has recently seen great advances, but it is associated with increased toxicity and cost, and also the long-term outcome is still unknown. Non-pharmacological treatment is cheap, there is less toxicity and better long-term outcome (4, 9, 10, 13).

The objective of this literature review is to present the most recent evidence related to the non-pharmacological intervention programme for the management of RA to inform the development of evidence-based recommendations for general practitioners working in the healthcare setting.

MATERIALS AND METHODS

This review is built on a preliminary literature search. The literature review was conducted in July 2010 up to 2014. Articles published from 1990 to 2013 were considered. The literature review was done by a thorough search conducted in MEDLINE, PubMed (PubMed Central and PubMed Health), EMBASE, Web of Science, and the Cochrane Library to identify studies for inclusion.

Search strategies were adapted to apply to the other databases. The MESH terms—'rheumatoid arthritis', 'arthritis', 'rheumatic diseases', 'joint', 'complementary therapies', 'nonprescription drugs', 'intervention studies', 'self-care, 'pain management'—were used to capture all spectrums of RA non-pharmacological intervention and self-management practices. Inclusion was limited to English language publications. The final search strategy sought to identify non-pharmacological intervention studies at all levels of evidence. Concurrently, a manual search was carried out to find an article review of reference lists of retrieved papers. In the beginning, the papers were selected for inclusion, based on the title and abstract. Studies providing evidence on the efficacy of an intervention compared to another intervention were included. Initial searches failed to identify many articles related to non-pharmacological intervention programmes for management of RA.

Participants relevant to this literature review were people aged 16 years or over with a diagnosis of RA. The review focused on data in adult populations (above 16 years of age). Intervention in the form of any non-pharmacological intervention used to manage RA was eligible for inclusion. Articles focusing on non-pharmacological interventions in RA, with a community approach, big sample size, with control, randomized control trial (RCT) and having a core measure of pain visual analogue scale (VAS), were selected. Other alternative treatment controversies have arisen over the employment of therapies, such as occupational therapy, podiatry, hydrotherapy, joint protection, ultrasound, acupuncture, laser therapy, use of compression gloves, thermotherapy, use of splints or orthoses, homeopathy, and transcutaneous electrical nerve stimulation, which were not eligible for inclusion.

The search strategy was formulated by Ovid in cooperation with a medical librarian to make it applicable to all the databases. A computerized, broad search strategy was developed. Retrieved hits were assessed by four of the authors (HY, FA, MY, NK), who screened the titles and abstracts to identify relevant studies. If there was doubt about a study's relevance, one of the expert authors (AC) was consulted. The relevant full-text article was read by three authors (AC, HY, RF). The methodological quality of the included review was independently assessed by two reviewers (AC, HY). Data were extracted by two of the authors (HY, NK, EG). If there was doubt, one of the other authors (AC) was consulted. In the search finding, the following statement was used to indicate the direction of reduced pain effect.

RESULTS

The literature search identified 14 362 references, which were first examined on the basis of titles and abstracts. Of these, 13 963 references were not related to the non-pharmacological intervention programme for management of the RA disease. A total of 261 references were not RCT studies; 138 references were retrieved in full text; and 112 reviews were excluded: 49 because of conducted to mixed rheumatic and musculoskeletal disease, and 41 were conducted by other than RA. A total of 19 references were excluded because of no relevant intervention on pain, and 3 because of duplicate publication. Twenty-six reviews were included in this overview (Fig. 1).

Cognitive behavioural therapy and psychotherapeutic intervention

A hospital, based on six-month studies by Sharp *et al*, designed and conducted studies to examine the efficacy of cognitive behavioural therapy (CBT) (Fig. 2)

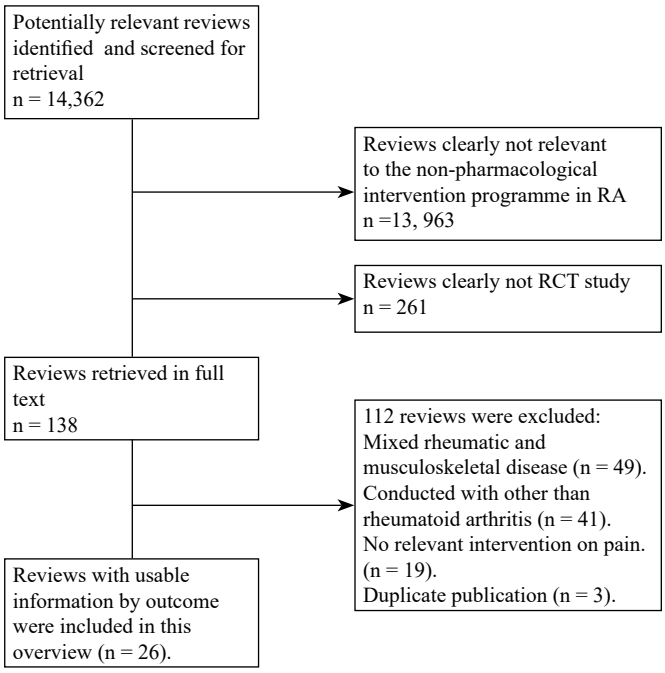

Figure 1: Selection process of eligibility reviews from all identified citations.

CBT: Included 8 individual sessions, each 1 hour per week, developed from standard pain management approaches and self-help educational material developed for patients with arthritis. The programme included an educational component plus the self-management skills of relaxation training, attention diversion, goal-setting, pacing, problem-solving, cognitive restructuring, assertiveness and communication, and management of flare-ups or high-risk situations [14].

LMAP: Included two modules, each with four meetings of 2.5 hours duration and one 2-hour review meeting (one rheumatology OT, one community OT and one rheumatology PT delivered module). Participants could attend two LMAP modules and review meetings over a 3- to 9-month period as convenient to them. Module 1 was developed from a behavioural, joint protection programme. The concepts discussed in meeting 1 were RA, health beliefs, personal impact of arthritis, understanding the multiple factors affecting symptoms, attitudes, personal experiences, self-management methods and motivation for change. Meetings, 2–4, focused on ergonomic approaches to reduce pain, exercises, fatigue management and the benefits of splints. Module 2 focused on participants' exercise beliefs, barriers and problem-solving. Cognitive symptom management included stress management and coping, pain management, distraction and relaxation practice. The review meeting included progress with goals, drug therapy, investigations, communicating with health professionals, team care and topics of participants' choice (eg, diet, complementary therapies, work-support services, Social Security Benefits). Participant workbooks were provided for each module with key points, illustrations and diaries to record practicing joint protection, pacing and exercise [15].

GESO: The programme consisted of 5 weekly, 2-hour group sessions for 8 patients, with or without a significant other. The programme included 3 booster sessions of 2 hours each after 3, 6, and 9 months. Each group had 2 trained leaders (during the 2 days of training): a specialized arthritis nurse and a nurse with experience in working with RA patients. Patients received a programme book with information on the sessions, a self-help guide, various brochures on RA, and an audiotape with relaxation exercises. The programme included contracting, goal-setting, self-management and problem-solving, information on RA and treatment, pain management and relaxation, physical exercises, and coping with depression. In the booster sessions, the accomplishments of goals and problems during the past 3 months were discussed and feedback was given. The assessments were done before, immediately after, and 6 and 12 months after intervention [18].

MSCG: In the programme, patients who participated in 10 sessions, were supported by a manual for patients and led by 2 supervisors. All sessions lasted 2 hours. The first 8 sessions were weekly sessions, the 9th session was 2 weeks after the 8th session, and the 10th session was 3 weeks after the 9th session. At the end of every session (except for the very first session), homework assignments were given. In the CIG, the programme was teaching patients action-directed coping and coping by seeking social support; and 4 problem-solving steps: 1) describe the problem; 2) think about all kinds of possible solutions; 3) choose 1 or more solutions; 4) implement the solution or solutions and evaluate the results. In the MSCG programme, topics of conversation for all sessions were determined by the patients during the first session to exchange information, experiences, feelings, and emotions of the participants. The sessions were led by 2 patients who were trained in supervising mutual support groups [19].

In-patient treatment consisted of a fixed period of 11 days. Each weekly session was performed by the physical therapist, occupational therapist and social worker, with prescribed regimens of bed rest and a daily individual range of motion, muscle-strengthening exercise programme, joint protection, self-care, household and work activities, joint splints, adaptive equipment and coping with the disease. During out-patient care, the prescription of drugs, paramedical treatment and splints was left to the attending physician in the out-patient clinic [21, 22]. The training programme was scheduled for nine sessions within 2 weeks, each group consisted of eight patients, and encompassed a multidisciplinary cooperation between rheumatologists, orthopaedists, physiotherapists, psychologists, and social workers. The following fields were covered: mechanisms of RA, drug therapy, physiotherapy, practical exercise, relieving pain and muscle tension, joint protection devices, joint replacement, coping strategies, stress management and relaxation exercise, dietetics, social assistance, and utilization of public social resources [23].

ASMP: This 6-week series of classes for 2 to 2.5 hours per session (total 12 hours) included information about arthritis, self-management principles, exercise, cognitive symptom management, relaxation, energy-saving techniques, cognitive pain management, dealing with depression, nutrition, communication with family and health professionals, and contracting [24].

SMART: Mailed intervention is a 'tailored, print intervention' which includes a 1-page questionnaire asking questions about pain, disability, exercise levels, and other arthritis-related behaviours. Participants also received a copy of the Arthritis Help book and quarterly follow-up materials. These included a second book, Arthritis: A Comprehensive Guide, a relaxation tape, and a pamphlet on physician/patient communications. The sequence of the questionnaire, letter, and report delivered is repeated every 4 months for 1 year. The result showed that there was an improvement in all baseline variables for SMART and ASMP groups with higher benefit in self-efficacy and doctor visit rate [22].

CDSMP: It is a community-based, a 2.5 hour lecture per week over a 6-week period which included topics such as healthy eating, starting and maintaining exercise, pain and fatigue management, managing sleep, stress management, relaxation techniques, communicating with health providers, managing medications, and planning and problem solving [29].

Figure 2: Uni-modular and multi-modular self-management programme.

in preventing psychological and physical morbidity in patients with RA. The results indicate efficacy in producing reductions in both psychological and physical morbidity (14) (Table 1). Another study, conducted by the same groups over 18 months, revealed that the capacity of coping with pain and depression improved, but no change was observed in other variables (15); see Table 1. A longitudinal study was conducted by Hammond *et al* to develop a modular behavioural group programme—'The Lifestyle Management for Arthritis Programme'

Table 1: Unimodular self-management programme for rheumatoid arthritis

Year	Name of study	Sample size	Design	Duration of study	Duration of RA	Intervention	Key efficacy variable	Key finding	Reference
1993–1994	Vegetarian diet—clinical effect of psychological characteristics	124	RCT 3 arms: vegetarian diet, omnivorous diet and control groups Site: hospital-based rheumatology	13 months	Mean: 13 years intervention and 10 years controls	Vegetarian diet Omnivorous diet	GHQ-20, MHLCS, pain VAS, ESR, TJC, TJS, believe in ordinary and alternative treatment VAS	GHQ (anxiety), internal MHLCS, believe in ordinary and alternative significant improvement and psychological distress decreased	Kjeldsen-Kragh *et al* (1994)[34]
1997–1998	Effects of uncooked vegan diet, rich in lactobacilli, in RA	43	RCT 2 arms: vegetarian diet and control groups Site: hospital-based rheumatology	6 months	Mean: 12.6 ± 12.3 years in intervention and 16.1±13.6 years in control groups	Uncooked vegan diet, rich in lactobacilli	DAS28, TJC, TJS morning stiffness protein (S-CRP), pain VAS, HAQ and global patient	Lost weight, pain VAS, DAS28, HAQ disease activity improved	Nenonen *et al* (1998)[35]
1993–1995	Efficacy of physical therapy	127	Single-blind RCT 2 arms: control wait list; intervention care Site: community-based rheumatology	2 years	Mean 7.6 ± 11 and 7.4 ± 10 in experimental and control group, respectively	Nutrition, exercise, background Std care (RA)	Self-efficacy, pain VAS, disease activity, duration of morning stiffness, tender joint count	Improvement in all variables except pain and disease activity	Bell *et al* (1998)[33]
1994–1996	Cognitive behaviour intervention in preventing psychological and physical morbidity	53	Single blind (assessor) RCT 2 arms: control; intervention care Site: hospital-based clinical psychologist	6 months	Less than 2 years	Cognitive behaviour therapy, background Std care	HADS, HAQ, pain VAS	HADS, depression and anxiety, HAQ showed significant improvement but no benefit in pain	Sharp *et al* (2001)[14]
2001	Effect of patient education programme on adherence to drug treatment	100	Single blind (assessor) RCT 2 arms: control and intervention care Site: hospital-based clinical pharmacology	6 months	Median: 12 years	Patient education program, background Std care (RA)	Articular index, morning stiffness, pain VAS	Improvement in drug adherence but no clinical benefit	Hill *et al* (2001)[19]
2001	A vegan diet free of gluten improves the signs and symptoms of RA	66	RCT 2 arms: vegan diet and non-vegan diet Site: hospital-based rheumatology	1 year	Mean 5.2 ± 2.5 years in intervention and 5.8 ± 2.8 years in control groups	A vegan diet free of gluten and a well-balanced non-vegan diet	IgG, *β*-lactoglobulin, X-ray, TJC, TJS, CRP, PhGA	Significant improvement in clinical parameters, IgG, *β*-lactoglobulin level decreased, no significant differences in X-ray	Hafström *et al* (2001)[36]

Table 1 (*cont'd*)

Year	Name of study	Sample size	Design	Duration of study	Duration of RA	Intervention	Key efficacy variable	Key finding	Reference
1994–1996	Long-term efficacy of cognitive behaviour therapy	53	Single blind (assessor) RCT 2 arms: control and intervention care; Site: hospital-based clinical psychology	18 months	Less than 2 years	Cognitive behaviour programme (CBP), background Std care (RA)	HADS, HAQ, pain, VAS, coping, Ritchie articular index	Coping and depression improved but no change in other variables	Sharp *et al* (2003)[15]
2004–2005	Mediterranean dietary on fat intake and composition of fatty acids in serum phospholipids	51	RCT (assessor blind) 2 arms: control and dietary intervention Site: community-based rheumatology	3 months	NA	Mediterranean dietary: advised to replace high fat dairy products with low fat products	Fat, total saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, n–6 fatty acids, n–3 fatty acids	A lower ratio of n–6 to n–3 fatty acids, better clinical improvement, higher intake of n–3 fatty acids and a lower ratio of n–6 to n–3 fatty acids	Hagfors *et al* (2005)[37]
1997–2002	Cod liver oil (n–3 fatty acids) supplementation in daily NSAID requirement in RA	97	RCT double-blind placebo-controlled 2 arms: vegetarian diet and control groups Site: hospital-based rheumatology	9 months	Mean 13 ± 1.26 years in intervention and 13 ± 1.4 years in control groups	Take either 10 g of cod liver oil containing 2.2 g of n-3 EFAs or air-filled identical placebo capsules	CRP, TJC, TJS, DAS28, pain VAS, HAQ, IgM, EMS, daily NSAID requirement	Significantly reduce daily NSAID requirement no significant differences in the clinical parameters of RA disease activity	Galarraga *et al* (2008)[38]
2007–2008	Vegan diet on blood lipids (oxLDL) and natural atheroprotective (anti-PCs).	66	RCT 2 arms: vegan diet and control non-vegan diet Site: community-based rheumatology	1 years	Mean 5 years vegan group and 5.8 years controls	Vegan diet free of gluten	BMI, DAS28, HAQ, biochemical variables, OxLDL, anti-PC drugs	Decreased LDL and oxLDL levels and raised anti-PC IgM and IgA levels	Elkan *et al* (2008)[39]
2007–2011	Internal family system-based (IFS) psychotherapeutic intervention	79	RCT (assessor blind) 2 arms: control and intervention care Site: hospital-based rheumatology	4 years	Mean ± S.D 18.9 ± 10.8 and 13.9 ± 9.2 in IFC and control groups, respectively	IFS model intervention, background Std care (RA)	DAS28-CRP4, pain VAS, depression, anxiety, physical function, medication usage	Disease activity and medication use unchanged, benefit seen in all other variables	Shadick *et al* (2013)[18]

oxLDL = oxidized low-density lipoprotein; anti-PCs = antibodies against phosphorylcholine; BMI = body mass index; LDL = low-density lipoprotein; IgM = immunoglobulin M; MHLCS = multi-dimensional health locus of control scale; GHQ-20 = General Health Questionnaire; EMS = early morning stiffness; IgG = immunoglobulin G; PhGA = physician global assessment; CRP = C-reactive protein; RA, rheumatoid arthritis; RCT, randomized control trial.

(LMAP); see Fig. 2. It evaluated its longer term effects on pain, physical and psychological status. The study findings indicated that the behavioural group continued to have decreased pain and fatigue; better functional ability, psychological status and self-efficacy scores; and greater use of health behaviours (16); see Table 2.

A recent longitudinal study by Vriezekolk *et al* was conducted to describe the development and feasibility of the integration of a CBT within a multi-modal rehabilitation programme for highly distressed patients with rheumatic diseases. The study concluded that a significant improvement was noticed in physical and psychological functioning, attendance rate and satisfaction (17); see Table 3. A study by Shadick *et al* was conducted for proof of concept of psychotherapeutic intervention on disease activity and psychological status in RA. The study results indicated that the intervention model was feasible and acceptable, provided some sustainable benefits for patients and may complement medical management of the disease (18); see Table

Table 2: Multi-modular self-management programme (SMP) in rheumatoid arthritis

Year	Name of study	Sample size	Design	Duration of study	Duration of RA	Intervention	Key efficacy variable	Key finding	Reference
1992–1993	Intensive, in-patient, multi-disciplinary care *vs* standard care (out-patient)	80	RCT 2 arms: control; intervention care; site: Hospital-based rheumatology	1 year	0.5–33	In-patient training in exercise, coping and occupational therapy in interventional arm, background Std care (RA)	Pain VAS, Ritchie articular index, HAQ, anxiety and depression scale.	Reduced pain, improved indices of function; no benefit for anxiety, depression after 12 weeks	Vlieland *et al* (1996)[24]
1992–1993	Intensive in-patient multidisciplinary care *vs* standard care	80	RCT 2 arms: control; intervention care; site: Hospital-based rheumatology	2 year	0.5–33	In-patient training of exercise, coping and occupational therapy in interventional arm, Background Std care (RA)	Pain VAS, Ritchie articular index, HAQ, patient and physician global assessment.	no significant change in HAQ; rest - significant improvement	Vlieland *et al* (1997)[23]
1999	Long-term benefit of multi-disciplinary arthritis training programme	68	Study 1: Prospective RCT 2 arms: control; intervention care; Site: Community-based internal medicine Study 2: Cross-over, non-controlled observation	Study 1: 1 year; Study 2: 5 years	0.4 to 30 years	Multi-disciplinary arthritis training programme, background Std care (RA)	HAQ, coping, Beck depression, knowledge of drug therapy, physiotherapy, joint protection, relaxation exercises.	Significant improvement in all variables in intervention arm	Scholten *et al* (1999)[25]
2003	Group education in patient of RA and their partner	218	RCT; 3 arms: control ; intervention care; Site: Hospital based communication studies	12 months	Mean 11.7 ± 9.8 Years	Education programme, background Std care (RA)	Self-efficacy pain, exercises, coping, DAS28, fatigue -VAS.	Improvement in fatigue and coping with no change in rest variables	Riemsma *et al* (2003)[20]
2008	Lifestyle management for arthritis programme (LMAP)	167	Parallel-group RCT; 2 arms: control; intervention care; Site: Hospital-based rehabilitation centre	12 months	Mean 7.34 ± 6.9	LMAP *vs* standard self-management programme (SP), Background Std care (RA)	Pain VAS, self-efficacy, fatigue, HAQ, psychological status, exercise, joint protection	Significant improvement in all variables	Hammond *et al.* (2008)[16]

Table 3: Uni-modular self-management programme (SMP) in arthritis

Year	Name of study	Sample size	Design	Duration of study	Duration of RA	Intervention	Key efficacy variable	Key finding	Reference
2001	Effect of coping intervention in rheumatic diseases	168 RA 67%, OA3.6% and RA54.5%, OA9.1% and RA55.4% OA10.7% in CIG and MSCG and WLCG, respectively	Single Blind (assessor) RCT 3 arms: control; intervention care; Site: Hospital-based health education	6 months	Mean were 12.6 ±10.75	CIG programme: *vs* MSCG programme, background Std care	Coping, functional, health status, life satisfaction	CIG showed better improvement in coping and functional state than other arms	Savelkoul *et al.* (2001)[21]

1. These results suggest that CBT can be an effective adjunctive treatment for patients with RA and can help them in both psychological and physical morbidity.

Education

A study by Hill *et al* demonstrated improvement in drug adherence with an education programme (19); see Table 1. Another study by Riemsma *et al* was designed to determine the effects of group education. The study findings indicated that participation of a significant other in psycho-educational programmes does not have only positive effects. Instead of stimulating patients to adopt beneficial health behaviours and increase their self-efficacy expectations, participation of a significant other led to decreases in self-efficacy and increased fatigue, whereas patients participating in group education without partners showed increases in self-efficacy and decreased fatigue (20); see Table 2. A study by Savelkoul *et al* was conducted to assess the effects of a coping intervention group (CIG) and the manual support control group (MSCG), with rheumatic diseases (Fig. 2). The results showed that, at post-intervention, the coping intervention resulted in more action-directed coping than in the mutual support groups (21); see Table 4. A study by Ünsal and Kasikçi was conducted to determine the effects of education on the self-efficacy perception of individuals with arthritis. Study findings indicated that self-efficacy levels after education were significantly improved in the experimental group (22); see Table 3.

Few studies have explored the effect of patient education (PE) in patients with RA, but it seems to be an essential part of the successful management of RA disease.

Table 4: Multi-modular self-management programme (SMP) in arthritis

Year	Name of study	Sample size	Design	Duration of study	Duration of RA	Intervention	Key efficacy variable	Key finding	Reference
1998	Patient education of ASMP - 6 weeks *vs* 3 weeks version	151 (14% RA, 56% OA, Other 19%)	Comparison study 2 arms: control; intervention care; Site: Community-based patient education	4 months	NA	ASMP 6-week module *vs* 3-week module, background Std care	Pain VAS, disability, depression, exercise, physician's visit	6-week ASMP better than 3- week ASMP	Lorige *et al* (1998)[26]
1998	Long-term outcome of ASMP in arthritis	112 (RA 46% OA 44% Other 10%)	Pre-test post-test 1 arms intervention care; Site: Community-based psychological rheumatology	12 months	1–49 years	ASMP, background Std care	Self-efficacy pain, exercise, communication with physician, HAQ, pain VAS, HADS, GP visit	Significant improvement in all variables	Barlow *et al* (1998)[27]
1999	Arthritis self-manager through an adult education programme	89 (RA 45%, OA 48%, Other 42%)	Pre-test, post-test 1 arms intervention care; Site: Health service network, arthritic care network and community-based psychological rheumatology	4 months	0–50	ASMP, background Std care	MHAQ, pain VAS, fatigue VAS, depression, self-efficacy for pain VAS, exercise, communication with physician	Significant improvement in all variables	Barlow *et al.* (1999)[28]
2000	ASMP in arthritis in UK	544 RA 37% *vs* 33% OA 52% *vs* 52% Other11% *vs* 14% in intervention and control groups, respectively	Pragmatic RCT 2 arms: control; intervention care; Site: Community-based psychological rheumatology	16 months	Mean 10.7 ± 11.2 *vs* 11.3 ± 10.9 intervention and control groups	ASMP, background Std care (RA)	Exercises, diet communication with physician, MHAQ, pain VAS, HADS	Significant improvement in all variables	Barlow *et al* (2000)[29]

Multi-disciplinary programme

Two studies by Vlieland *et al* were designed to compare the effects of in-patient, multi-disciplinary treatment with standard out-patient care. The results showed that the percentage of patients responding to the ACR criteria was significantly greater in the in-patient group (23, 24) (Table 2). Scholten *et al* conducted two studies to assess the sustainable benefits of a professional, multi-disciplinary training programme for patients with RA. Results of the one-year study and 5 years after baseline evaluation indicated significant improvements in HAQ, decreased depression, reduced fatigue, increased coping capacity and knowledge of drug therapy, sustained improvement in physiotherapy, and focus on joint protection and relaxation exercises (25); see Table 2. The review of studies demonstrated a rheumatology clinic with multi-disciplinary team care has a beneficial effect with respect to disease activity and emotional status. Therefore, a multi-factorial approach, utilizing medications and self-management techniques, is necessary. Fortunately, with proper counselling, individuals with RA can safely exercise, improve overall physical fitness, enjoy greater ease with daily living activities, and improve a sense of well-being.

Self-management

A longitudinal, community-based study by Lorig *et al* was designed to compare the 3- and 6 Arthritis Self-management Programme (ASMP). The results indicated that the 3-week ASMP intervention (Fig. 2) was not as effective in changing health behaviours, health status or healthcare utilization as the 6-week ASMP (26); see Table 5. Barlow *et al* conducted a study to determine the long-term effect of ASMP on physical and psychological well-being of patients suffering from arthritis. Data were collected via mailed, self-administered questionnaires. The findings of the study had demonstrated that patients with arthritis derive substantial and prolonged benefits in terms of perceived ability to manage arthritis, reduction in pain and improved physical and psychological well-being (27); see Table 5.

Another study was designed by Barlow *et al* to determine the ASMP's effectiveness when delivered in an adult education setting. The finding of the study showed that the ASMP programme was not only acceptable to people with arthritis, but can offer substantial benefits in terms of an enhanced sense of control, a reduction in pain, increased use of cognitive and behavioural techniques, and enabled persons to discuss arthritis in health settings (28); see Table 5. In 2000, Barlow *et al* conducted a study to determine whether the ASMP improves perceptions of control, health behaviours and health status, and changes the use of healthcare resources. Participants were given a copy of the Arthritis Help book. The ASMP had a significant effect on arthritis self-efficacy for other symptoms, pain subscales and health behaviours, resulting in less depression and a greater, positive mood (29); see Table 5. Lorig *et al* tried to examine two studies on the Self-management, Arthritis Relief Therapy (SMART) and compare it with the ASMP (Fig. 2). Participants were recruited from the Arthritis, Rheumatism and Aging Medical Information System (ARAMIS) databank centres. The findings of the study indicated that a mail-delivered SMART programme was similarly effective in the classic ASMP, with slightly better results in the first year and a slightly more rapid attenuation over the next 2 years (30); see Table 3. Lorig *et al* conducted a study to compare the relative effectiveness of the ASMP and the Generic Chronic Disease Self-management Programme (CDSMP) , and background standard care for individuals with arthritis (Fig. 2). The findings of the results showed that both programmes had positive effects, and the CDSMP should be considered a viable alternative (31); see Table 3.

In 2009, Barlow *et al* conducted a study to examine the pattern of scores on self-efficacy, health status and use of self-management techniques among a group of ASMP participants. The results showed that long-term maintenance of self-efficacy, psychological well-being and self-management techniques may be possible following attendance at the ASMP (32); see Table 3. Published literature suggests that patients with RA will need long-term care. The treatment comprises not only drug therapy, but also a self-management programme of educational instruction, guidance and support to cope with the consequences of the disease and manage this persistent, damaging, inflammatory disorder.

Physical therapy (exercise)

An empirical study was conducted by Bell *et al* to evaluate the short-term efficacy of a physical therapy (PT) programme (Fig. 2) for persons with RA. Improvement was noted in the primary variables, such as self-efficacy, disease management knowledge, duration of morning stiffness, and tender joint count, but there was no significant change in the pain VAS and disease status measures (33); see Table 1. Then, the short- and long-term health benefits and risks of physical activity at moderate and vigorous intensity levels had not yet been compared in early or established RA.

Table 5: Multi modular self-management programme (SMP) in arthritis

Year	Name of study	Sample size	Design	Duration of study	Duration of RA	Intervention	Key efficacy variable	Key finding	Reference
1996 to 1997	SMART *vs* Usual care or ASMP in arthritis	2 RCT: 1st—1090 2nd—341 (RA 60% OA 40%)	2 RCT Staff involved in administering was blinded to participant status 2 arms: control; intervention care; Site: Medical information system, (ARAMIS) databank centre, and community-based medicine	18 months and 3 years	NA	SMART *vs* ASMP, background Std care	HAQ index, pain VAS, depression, role function, doctor visits, self-efficacy	Improvement in all baseline variables for SMART and ASMP groups with higher benefit in self- efficacy and doctor visit rate	Lorig *et al.* (2004)[30]
2002 to 2003	ASMP *vs* CDSMP in arthritis	355 RA 18% *vs* 13%, OA 75.7% *vs* 5.1%, Other arthritis 10.5% *vs* 19.8% in ASMP and CDSMP groups, respectively	RCTs 2 arms: control; intervention care; Site: Community-based medicine	1 year	NA	ASMP versus CDSMP, background Std care	Disability, global health, pain, fatigue, exercise, self-efficacy, health care utilization	Lesser disability indices, pain, fatigue and health care utilization with improved self- efficacy seen in ASMP group	Lorig *et al.* (2005)[31]
2009	ASMP in arthritis	124 (RA 59, OA 59, Other arthritis 6)	Cross-sectional Follow up 2 arms: control; intervention care; Site: Community-based health and life sciences	8 years	Mean 19±11 years	ASMP, background Std care	Self-efficacy, exercise, communication with physician, HAQ, HADS, GP visit	Significant improvement, in all variables	Barlow *et al.* (2009)[32]
2005	Effect of education on perceived self efficacy in arthritis	80 OA (24 *vs* 16) RA (9 *vs* 7) Other (7 *vs* 17) in intervention and control group, respectively	Pre-test and post-test equivalent control group 2 arms: control; intervention care; Site: Hospital-based health sciences	6 months	6 months to more than 11 years	Education programme -arthritis, treatment, care, preventing method, exercise. background Std care	Self-efficacy in pain, ASES	Significant improvement, in all variables	Unsal.and Kasikei. (2009)[22]
2008 to 2009	CBT with multimodal rehabilitation in rheumatic disease	25 (Inflammatory rheumatic disease and OA)	Proof-of-concept study 2 arms: control; intervention care; Site: Rheumatology-based clinic	15 months	NA	Cognitive behaviour therapy with multimodal rehabilitation programme. background Std care	Significant improvement in physical and psychological functioning, attendance rate, satisfaction	Significant improvement in all variables.	Vriezekolk *et al* (2012)[17]

Dietary interventions

Several clinical trials and studies were conducted to assess the effect of dietary interventions in RA (34–39); see Table 1. The findings also showed that dietary interventions can assist with the management of disease symptoms that accompany RA, such as pain; tender, swollen joints; stiffness; and associated disability and disease progression. Clinical trials demonstrated that a subset of patients will benefit from following a vegetarian, vegan or Mediterranean-style diet, or by eliminating certain foods from their diet (40). This type of diet was shown to be associated with anti-inflammatory effects (30, 31, 41) which are of desired benefit in RA. Mahan *et al* suggested the dietary changes to promote

an anti-inflammatory diet (42). All studies on diet and RA were carried out on an established and prolonged disease. Dietary therapy is an area of self-help which patients with RA frequently want to explore, typically in the early stages of the disease, but little is known about the extent of dietetic involvement in rheumatology. Good nutrition is an essential part of RA self-care because without it the body, and sometimes medications, do not work as well they should.

DISCUSSION

Lifelong disability, excruciating pain, psychological fatigue, anxiety, and decline in life quality are consequences which have always been associated with RA (43). Aggressive therapies with potent drugs like biologics are very effective but fraught with dangers of serious drug toxicity and life-threatening adverse events (4, 9, 10, 13). It was observed that despite excellent advances in management care, patients suffering from RA continue to develop functional limitations, such as deformities (9, 10). It is against this background that more evidence of the efficacy of adjunct therapy with non-pharmacological methods (exercise, diet, cognitive education) be obtained through well-designed studies in RA.

The concept of early and aggressive treatment of RA has occupied centre stage since 1989, when reversing the pyramid (the step-down bridge concept) was published (44). From the year 1990, there was an increasing awareness about the concept: 'A window of opportunity for the therapeutic consultations/treatment in rheumatoid arthritis' (45, 46). Experimental methods were used to find a solution for how we can meet the patients' needs in the best way (47). Three early-period, experimental approaches demonstrated the path of the required change in non-pharmacological treatment measures. The first among the three was the ASMP—the prototype arthritis education programme. Originally developed by Lorig in 1981 at Stanford University, USA, the programme was adopted by the arthritis foundation in 1981 (48). The next one was based on visits carried out by groups of doctors to their patients, and was created by Dr. John Scott in 1997 (49). The third experimental programme focused on patients who stayed far away from city centres in remote areas, and access for medical attention was enhanced using the telephone or by other electronic means such as the Internet (49–51).

Non-drug therapies are often employed as complementary adjuncts to pharmacological treatment to aid the coping mechanism of patients with RA as they combat the disease (52). Several non-pharmacological, clinical, experimental methods, and/or models such as ASMP or ASHC (28), CBT (14), LMAP (16), SMART (30), and CDSMP (31) were evaluated on patients suffering from arthritis. Tables 2–5 describe the key features of several studies undertaken to evaluate such modalities of treatment. These studies have demonstrated the role of a self-management programme in RA.

Using a multi-modular, self-management programme for patients, Vlieland et al showed improvement in physician global health (PHGH) and patient global health (PTGL) by intensive, in-patient, multi-disciplinary care versus standard care (24). Several studies using a modular multi-programme (Tables 2, 3, 5) made similar observations in different groups of subjects, and noted a significant decrease in pain VAS and physician visit times or healthcare utilization (Tables 3 and 5).

The effectiveness of multi-disciplinary team care in countering established RA is well recognized. The benefits of such non-pharmacological treatments can be gauged from the conclusions drawn from several RCTs and Cochrane Reviews. It is hardly surprising, therefore, to note that patients with RA constitute the high-end spectrum of complementary and alternative practice therapies, given the nature of the disease as particularly chronic and persistent (43). A diverse range of modalities comprising the 'multi-disciplinary rheumatology team', as various health professionals prefer to label it, include exercise therapy, physical modalities, orthoses and assistive devices, self-management, and dietary interventions. Recent years have witnessed the publication of a sizeable number of reviews focused on a broad spectrum of non-pharmacological interventions in RA (53, 54).

Contemporary interventions that supplement pharmacological and surgical interventions include conventional therapies such as PT and occupational therapy; rehabilitation and self-management programmes are also put to use (43). Evidence strongly suggests that joint-specific, dynamic exercises may lead to significant amplification in strength and physical function (55). The beneficial effects of self-management and functional ability through occupational therapy have been shown in recent meta-analyses (56, 57). Similarly, employment of hydrotherapy in RA cases has also reported positive results (58, 59). There have been insufficient studies on the effectiveness of specific diets in managing RA efficacy. Diet modification has been noted by several RCTs; for example, it has been noted that the vegetarian diet group exhibited considerably better effects on pain and

disease activity across most of clinical variables (36, 60, 61). However, long-term compliance and nutritional deficiencies reduced the acceptability of many dietary interventions (Table 1).

The self-management programme is reported to impart psychological courage and the ability to face the lifelong challenge of RA, and it increases the acceptability of medical treatment (62). Management should address both the physical and mental aspects of life (63). Furthermore, the self-management programme provides a major support to the patient (49). It also provides a better awareness of the ailment and thereby enhances the confidence to self-manage health problems with greater courage (15, 64). It also encourages better compliance of the drug management programme, regular assessment and monitoring of the disease and drug-related effects, knowledge of the progress of the disease, and goal-setting for the treatment and achievement of targets at set times (65).

The first aim of a combined strategy with supervised, sustained standard of care, medical management and self-management programme is to obtain an early remission of the disease. The next target is to bring the body to a fully functional status and to resume work with great physical and mental involvement, and all this may also require vocational rehabilitation (65). The RA self-management intervention programmes help people to maximize their abilities; reduce pain, functional limitations, disability, and depression; and increase self-care behaviours (48). A self-management intervention programme to provide the knowledge, skills and confidence to manage RA was devised (66).

The very few rheumatologists available in developing countries do not have the time and the inclination for community and PE. Education should be left to the allied rheumatology health professionals, if available (67). A professional multi-disciplinary approach to educate patients with RA leads to a significant and sustained improvement in the clinical outcome, and it is an approach that should be established as part of conventional therapy (25). The members of a multi-disciplinary team should take particular care to ensure that a common approach to PE is arrived so that the patients receive a consistent health message (68).

In the literature review, studies have shown that a short period of initial, intensive, non-pharmacological therapy (mostly cognitive behaviour change and supervised exercises) is followed by long-term gains in the form of better improvement in RA symptoms and control and better health measures (Tables 1, 2, 3, 5). A number of multi-modular programmes for patients with RA or other forms of arthritis have made similar observations in different groups of subjects (Tables 2, 3, and 5). Physical therapy and exercise showed significant reduction in fatigue and significant improvement in joint protection, communication with physicians and dietary habits. A number of multi-modular intervention programmes (Tables 2, 3, and 5) made similar observations in different groups of subjects in patients with RA or other forms of arthritis.

The literature on the effectiveness of non-pharmacological treatment modalities in RA supports the effectiveness of dynamic exercise and cognitive behavioural interventions, and to a lesser extent, joint protection programmes and foot orthoses, and dietary manipulation. Decreased physical activity levels in patients with RA combined with the symptoms of the disease, for example, pain and fatigue, corroborate to formulate a vicious circle that contributes directly to a detrimental effect on other aspects of skeletal muscle health (69). Patients with RA consistently reported a 70% reduction in strength in comparison to healthy counterparts (70). A 2-year strengthening programme resulted in significant improvements in subjective patient assessments of disability by the Health Assessment Questionnaire (HAQ) (71). Decreased habitual physical activity in patients with RA is generally attributed to joint pain, restricted mobility, fatigue, reduced muscle mass, strength, and endurance (72). A corroboration of aerobic and strength exercise training constitutes an ideal exercise programme for the treatment of patients with RA (73).

Exercise is an important component of several self-management programmes, and several studies are reviewed and described in the above section on self-management progress. Research has validated the beneficial role of exercise in yielding specific health benefits in persons with RA. As demonstrated by previous research, exercise is fundamentally beneficial for patients with RA when comparing the effectiveness of high- and low-intensity exercise training in stable RA. The intervention programme on the improvement of life quality in patients with RA is multifaceted, and there are other modes of non-pharmacological treatment of RA, such as occupational therapy. To the best of our knowledge it is not possible to have RCT study based on decreasing pain with big sample size, especially in only RA until the date in these fields is included.

Patients with RA are often treated aggressively with disease-modifying, anti-rheumatic drugs (DMARDs) (*eg*, methotrexate, hydroxychloroquin, *etc*) along with

steroids, in addition to analgesics and other anti-inflammatory drugs and supportive therapy (4). Such a therapy is fraught with drug-related side effects and toxicity and moreso as patients with RA need long-term treatment (9, 10, 13). There is a need to quickly control the disease and judiciously reduce the medicines to the minimum to sustain control. This is not an easy task and, in real life, it continues to be a major therapeutic challenge. In the last decade or so, biologic DMARDs have emerged as very potent medications, but they are extremely expensive and have the potential risk of several side effects, including proneness to tuberculosis and life-threatening infections (4, 13). Gentler treatment modalities are required to augment the therapeutic efficacy of anti-RA medications. A non-pharmacological treatment could fill up this void and also improve the side effect profile during this period.

CONCLUSION

Epidemiology has taken on new roles in the management of healthcare services. The literature on the effectiveness of non-pharmacological treatment modalities in RA supports the use of dynamic exercise and cognitive behavioural interventions, and to a lesser extent, joint protection programmes and foot orthoses, and dietary manipulation. The effectiveness of multidisciplinary team care in countering established RA is well recognized. It was established that despite excellent advances in management care, patients suffering from RA continued to develop functional limitations, such as deformities. Contemporary computation of the provision and reimbursement of healthcare is based on existing evidence. Policy direction, formulations and purchases are regulated by the requirement and supply of data on the effective parameters of interventions. On a similar note, researchers, healthcare professionals and patients also subscribe to the informational paradigm to identify and define research parameters, and improve upon existing clinical practices and self-management stratification. Self-management arthritis programmes, though found useful by several studies, described above are uncommon in routine clinical practice. Therefore, it is prudent to consider non-pharmacological methods, adjunct to standard care with drugs. At this stage, it may be advisable for patients to also opt for an adjunct, non-drug treatment, like the patients who receives counselling alongside standard care (53). These findings have implications for health policy and allocation of funding for both healthcare and research.

Ethnicity, presumably, may play a major role in the extent of coping with pain and arthritis. Non-pharmacological means to improve the management of RA, as an adjunct therapy to standard care holds a socio-economic appeal for the community. Our results can be exploited further by constructing preventive, instructional, non-pharmaceutical strategies to treat RA that is suited to the community.

Limitation of the literature review

Some databases might not have been covered due to a lack of access to them. Therefore, it is not claimed that this review covers all relevant articles. In some instances, original research articles were cited without a clear account of how the articles were found. At times, personal experience and conventional wisdom are included which may be difficult to distinguish.

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REVIEW

Oral Health in Crack—Cocaine Users and Its Impact on Their Quality of Life: A Literature Review

MA Brown[1], MÂ Naval Machado[2]

ABSTRACT

Background: *Crack is the most addictive and potent derivative of cocaine. There is a scarcity of information regarding the oral health of crack users and also the impact this has on their quality of life. The aim of this literature review was to ascertain information regarding oral health and also its impact on the quality of life of crack users.*

Methods: *The keywords oral health, quality of life, crack cocaine and drug users were applied to the databases PubMed, Google Scholar and Scielo to obtain the articles. Articles used were published between 1992 and 2017.*

Results: *Crack cocaine users present poor oral health and are usually polydrug users or have a history of consuming other substances such as cannabis, alcohol, tobacco and opiates. The use of crack may individually impact oral health or may be attributed to the effect of polydrug usage, henceforth impacting their quality of life. In addition, socio-demographic and behavioural factors may also impact oral health-related quality of life.*

Conclusion: *Crack has an impact on the oral health of crack users, which also affects their quality of life. This demonstrates the importance of dental surgeons being included in multidisciplinary teams responsible for the rehabilitation of crack addicts.*

Keywords: Crack cocaine, drug users, oral health, quality of life

INTRODUCTION

Cocaine is an alkaloid derived from the coca plant (*Erythroxylum coca*) (1). It must be first converted into powder and mixed with sodium bicarbonate to produce a smokable form named crack. Crack is thought to be the most addictive and potent derivative of cocaine (2, 3). Crack cocaine dependence results in euphoria, psychotic effects, cognitive impairment, physical and mental health issues (4).

Globally, 0.3%–0.5% of the world's population aged between 15 and 64 years old are cocaine users. A substantial proportion of which, however imprecisely estimated, are crack-cocaine users (5). Cocaine is the main drug of concern in Latin American and Caribbean countries (6); it is also known that the use of crack is prevalent in the Americas (7). South American countries like Brazil, for example, has been identified as one of the emerging nations where the use of intra-nasal cocaine as a powder or smoked (crack and other related forms) is increasing. Contrary however to the United States of America and the majority of the European countries, cocaine use has declined and stabilized (7). When compared to women, men have three times a greater chance than women to use such substances (6).

Drug addicts have far worse oral health when compared to the general population (8). Addicts tend to give lower priority to their oral hygiene, and their primary concern is to aliment their chemical dependence (9). The most common dental diseases associated with substance dependence are caries, enamel erosion and periodontal disease (10, 11).

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Dental diseases seen in addicts are attributable to local environmental factors combined with the systemic effects of the drug and are not directly related to the effect of the drug itself (12). Other authors mention that the direct physical effects of the substances provoke xerostomia due to an increase in hyposalivation, which causes higher rates of caries (13). Socio-demographic factors such as low access to dental care, poor oral hygiene and smoking also seem to influence oral health complications among addicts (14).

Moderate and high-level users of cocaine and crack have 2.2 times more chance of presenting a worse general quality of life (15). Crack cocaine users also present higher DMFT (decayed, missing, filled teeth) index values (15).

There is a scarcity of information regarding the oral health of crack users and also the impact this has on their quality of life. Therefore, the aim of this literature review was to ascertain information regarding the oral health of crack cocaine users and its impact on their quality of life.

Search method

PubMed, Google scholar and Scielo were the databases used to obtain the articles used in this literature review. The terms used to search for articles were 'oral health' AND 'quality of life' OR 'drug users' AND 'crack cocaine'. A total of 35 articles published between 1992 and 2017 were included in this review.

The impact of crack on oral health

Poor oral health is frequently seen in individuals with substance dependence; however, very little is known about how illicit drugs affect oral health (16). There is even far less information available about the effect of crack on oral health. Notwithstanding, crack is a derivative of cocaine, and it can be hypothesized that both drugs have similar effects on the oral cavity. The use of intra-nasal cocaine may cause nasal septum perforation, palatal perforation, bruxism, cervical abrasion (2), corrosion of gold restorations, occlusal wear, excessive haemorrhage after tooth extraction, increased rate of tooth decay, halitosis and periodontitis (3).

It is possible that these alterations also occur with crack cocaine use; however, the smoke generated from smoking crack may give rise to other alterations (17). Before getting to the lungs, crack smoke comes into contact with the oral mucosa. Crack smoke induced significant cellular alterations in tracheobronchial (17) and oral mucosa smears (18). Chronic smoking of crack may induce inflammatory changes (18) and alterations in the proliferation pattern in the oral mucosa (19). Cocaine use may result in transient chorea, which also manifests itself in the mouth as buccolingual dyskinesia, commonly known as 'crack dancing' or 'twisted mouth' (12).

While some illicit substances cause xerostomia, which leads to an increase in caries (13), crack does not interfere with salivary flow rate nor buffer capacity (20). Though it does significantly decrease saliva pH, this change is not capable of altering the oral environment in favour of caries development and other dental alterations (20). Henceforth, if crack addicts have an increase in DMFT values or periodontitis, it cannot be attributed to salivary factors (20).

Crack cocaine users are usually polydrug users or have a history of consuming other substances such as cannabis, alcohol, tobacco and injection drug use of heroin and other opiates (21). Studies have shown that persistent alcohol abuse increases periodontitis (22). Additionally, crack and cocaine users were shown to have greater periodontal probing depths than non-users of these substances (23). Chronic use of cannabis increases DMFT scores and also causes xerostomia, which may increase the risk of caries (24). One study showed that crack and marijuana smokers smoked up to 18 tobacco cigarettes per day (25). Tobacco smoking has been shown to increase the risk of periodontitis (26) and oral cancer (27) over time. Opiates such as heroin and methamphetamine cause an increase in caries and enamel erosion (13, 28).

Polydrug users of cocaine and other substances showed significantly higher DMFT values, poor oral hygiene habits (9, 10) and a greater risk of developing caries when compared to non-users (10).

It is unclear whether these oral health consequences are caused by the use of specific substances, by substance dependence in general (11) or yet by the compound effect of these substances. Moreover, it is a difficult task to determine the long-term effect of specific drugs in polydrug users (9).

Other factors contributing to the poor oral health of drug addicts, which may also be true for crack addicts, include a cariogenic diet (13, 28); neglect of oral and general health as they are primarily concerned with the acquisition of drugs; low self-esteem due to their general appearance being deemed as unimportant compared to the problem of being substance dependent and low access to dental services (28).

Impact of crack on oral health-related quality of life (OHRQoL)

There is a dearth of investigations on the impact of oral health on the quality of life of users of illicit drugs and even less information regarding users of crack cocaine. One study showed that the use of crack had a statistically significant negative association on self-reported health status (29). When the frequency of crack usage was compared to the use of alcohol and tobacco, only the frequency of crack showed a negative association with self-reported health status (29). To further support this, another study showed that crack users reported poor OHRQoL when adjusted for factors like sex, age, schooling, income, smoking, dental caries and periodontal disease (30).

Oral health-related quality of life was evaluated in HIV-infected women and a similar group of at-risk HIV uninfected women. This study showed that the use of crack was a behavioural risk factor, significantly associated with a poorer OHRQoL (31). Hence if dental professionals were to discourage the use of crack in these patients, OHRQoL could possibly be improved.

Institutionalized juvenile law offenders in Brazil, in which 41% of the sample size were users of crack/cocaine, showed poor oral health conditions with high impact on their quality of life (32). The Oral Health Impact (OHIP-14) instrument was used to measure OHRQoL, in which scores among adolescents with higher DMFT values reflected higher levels of impact in the dimensions of psychological discomfort and disability (32). Subjects with decayed and untreated teeth reported the worst impact on quality of life and had the highest scores in the dimensions of psychological discomfort and physical disability (32).

The OHIP-14 instrument was also used to evaluate the influence of oral health on the quality of life of alcohol and drug addicts, who were being treated at a specialized dental centre in Amsterdam. The participants in this study scored the highest for the dimensions of physical pain, psychological discomfort and disability. Thus, poor oral health of the drug addicts had a relevant impact on daily functioning (33).

The low quality of life of alcoholics and drug addicts is related to high DMFT values, low income and the use of cocaine/crack. Moderate and high-level users of cocaine and crack had 2.2 greater chance of presenting the worse general quality of life than low-level users of these substances (15).

DISCUSSION

Crack users are a distinct and complex population (21). The use of crack cocaine is associated with unemployment, low levels of education, low annual income, history of legal and criminal problems, low levels of family satisfaction (34), gender, sex work and multiple drug use (21). Crack cocaine addicts reported significantly lower subjective health perception than persons without a history of crack use (29, 34). Henceforth, these socio-demographic factors have an impact on the general quality of life of crack addicts. Oral health is an important part of general health and well-being (14); it is therefore likely that these factors also influence OHRQoL.

Lifestyle factors, such as oral health behaviour were found to be associated with socio-economic and educational background factors (14). Unemployed and less educated drug addicts exhibited unfavourable oral health behaviour (14). Similarly, it was shown that low income and use of crack cocaine were related to low quality of life (15). Furthermore, the use of crack is related to socio-economic factors (34). More studies are needed to confirm this and to further confirm if this also applies to OHRQoL.

It is difficult to predict the exact outcomes of crack on oral health, due to polydrug use. In this regard, acute and chronic effects of their drug habits might be even greater than it is for people who use just one type of drug. Not many studies have been able to estimate these potential interactions, but it is likely to be of importance (1). Given the prevalence of crack cocaine use, more studies are needed in this aspect that will help the dental professional to understand the effects of crack cocaine and to better provide treatment.

There is very little information available in the literature about OHRQoL in crack addicts. This is due to the difficulty in martialling study participants. Information available is based on institutionalized drug addicts in rehabilitation (15). More studies are needed that include all segments of the population to facilitate the development of preventative measures and treatment interventions (34). OHRQoL has the potential to better understand and ameliorate clinical practice, dental research, dental education and also populations. OHRQoL data is capable of providing important information necessary for the evaluation of oral healthcare and for the creation of public health policies for users of crack cocaine.

CONCLUSION

Based on the information presented, the use of crack has a negative impact on the oral health and OHRQOL of crack users. This demonstrates the importance of dental surgeons, inserted in multi-disciplinary teams responsible for the rehabilitation of crack users. Dentists will promote oral health, which also influences general health and facilitates social reintegration.

AUTHORS' NOTE

MA Brown was responsible for the conception and design, the research in databases to obtain the articles and for the drafting and critical revision of important intellectual content. MAN Machado was involved in the final revision and approval of the version for publication.

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CASE REPORT

Neurofibromatosis and Atypical Presentation of Tumours

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ABSTRACT

Type 1 neurofibromatosis (NF1) is a common genetic disease that increases a patient's lifetime risk for malignancy. Multiple myeloma (MM) is one malignancy that is associated with the disease less frequently and like other tumours, may be more aggressive as well as have unusual presentations. Therefore, MM must be considered as a differential diagnosis in any NF1 patient presenting with an extremity tumour. The aggressive nature can be assessed with haemoglobin concentration and specific tumour markers. The poor prognostic features of tumours in NF1 patients are often present and should be looked for in assessing this cohort.

Keywords: Malignancy, multiple myeloma, neurofibromatosis

INTRODUCTION

Type I neurofibromatosis (NF1) is an autosomal dominant disease, characterized by benign neurofibromas (1). The disease is common with an incidence of 1:2000 worldwide and 1:1141 in the Caribbean (2–4). Furthermore, there are over 1000 mutations associated with NF1 with the most common transformation to chromosome 17 (5, 6). As a consequence of these mutations, this subgroup of patients has a 2.7- to 5.0-times higher risk of cancer than the general population (7, 8). In addition, these tumours exhibit more aggressive behaviour and may have unique presentations (9).

Malignant tumours typically associated with NF1 tend to affect the nervous and gastrointestinal systems, such as peripheral nerve sheath tumours and gastrointestinal stromal tumours, respectively (9–11). Conversely, multiple myeloma (MM) is one malignancy that has rarely been associated with NF1 with little information available on the association between these two diseases (12–14). The case below will consequently illustrate a unique presentation of MM in a patient with NF1, highlighting the need for clinicians to be aware of rare disease associations in this population.

CASE REPORT

A 47-year-old female who presented with a three-month history of pain and swelling of her right shoulder, after an initial fall. She was diagnosed as a child with type 1 neurofibromatosis (NF1) with multiple plexiform neurofibromas and had a first-degree relative with the disease. For the initial injury, the patient was diagnosed with a ligamentous injury and discharged with analgesia. The shoulder on second presentation had generalized swelling and tenderness. In addition, passive and active ranges of motion were markedly decreased and she had no distal neurovascular deficit. X-ray from the initial fall (Fig. 1) revealed a lytic lesion at the greater tuberosity. The image from presentation (Fig. 2) showed lytic destruction of the metaphysis extending into the diaphysis. Additionally, periosteal calcification was noted, and the lesion was fractured with < 10° of the fracture.

The provisional diagnosis was a pathological fracture, secondary to a bone malignancy. Full clinical examination did not reveal any site for a potential primary lesion. Staging computerized tomography (CT) showed pulmonary lesions that could be a potential malignancy. The admission laboratory findings revealed a normocytic anaemia (Table). The immunoglobulin G (IgG), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels were mildly elevated and were not meeting the criteria for diagnosis of multiple myeloma (MM). A tru-cut needle biopsy was performed with a 22G × 200 mm and showed histological findings consistent with a plasmacytoma fulfilling a major

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criterion for MM. Immunohistochemistry was positive for CD138 and CD20, confirming the diagnosis and Ki-67 was > 80%, suggesting a high mitotic rate. Bone marrow aspirate performed revealed a > 30% plasmacytosis. The diagnosis of MM was made with two major criteria and a minor criterion (the lytic lesion of Fig. 1) being fulfilled. The patient started on a chemotherapy regime and is presently having her fracture managed conservatively.

Table: Showing the blood parameters to diagnose multiple myeloma

Blood parameter	Patient result	Normal range
Presenting haemoglobin concentration/g dL^{-1}	7.5	12.0–15.5
White blood cell count/ $\times 10^9$ L^{-1}	4.5	4.0–10.5
Mean corpuscular volume/fL	93.2	80–98
Platelet count/ $\times 10^9$ L^{-1}	185	140–400
Na concentration/m mol L^{-1}	133	135–145
K concentration/m mol L^{-1}	4.7	3.5–5.0
Ca concentration/mg dL^{-1}	9.3	8.0–10.0
Albumin concentration/g dL^{-1}	3.6	3.5–5.0
IgG concentration/mg dL^{-1}	2250	500–1500
IgA concentration/mg dL^{-1}	54.5	60–130
IgM concentration/mg dL^{-1}	26.5	50–150
B 2 microglobulin concentration/mg dL^{-1}	10	< 11.3

DISCUSSION

Type I neurofibromatosis (NF1) has many phenotypic variability with 1347 known mutations of which 20% are recurrent (15, 16). These mutations increase the incidence and severity of malignancies (17). In addition, multiple myeloma (MM) association with the condition is extremely rare with only three cases documented up to 2007 (12–14). The case, consequently, illustrated a patient with NF1 who had an aggressive case of MM, with a high mitotic rate. The case also highlighted the difficulty in diagnosing MM, with biopsies needed to make the diagnosis and the IgG levels were not meeting the criteria for diagnosing MM (18).

The presentation of a pathological fracture in NF1 patient requires working up the patient as a tumour of unknown origin, as opposed to assuming the lesion is neurological in origin. The clinical examination and computerized tomography (CT) did not reveal a primary source, highlighting the difficulty in diagnosing this subgroup. The presentation of upper limb fractures in MM patients is rare, however, with the presence of NF1 in the patient, atypical presentation of the disease should be expected (19).

The presence of aggressive tumours in NF1 patients is well documented. The case presentation showed only a three-month period from the presentation with a lytic lesion (Fig. 1) and gross bony destruction with a pathological fracture (Fig. 2). Furthermore, the patient was staged as Durie–Salmon staging III for MM, due to the low haemoglobin concentration, highlighting the rapid progression of the disease (20). The Ki-67 tumour marker of > 8% from immunohistochemistry confers decreased survival rates and is correlated to high proliferation (21). Consequently, the rapid progression of MM, high stage at presentation and presence of specific tumour markers confer poor prognosis to the patient, attributable to the presence of NF1 mutations.

Fig. 1: Showing the lytic lesion (arrow) on initial presentation.

Fig. 2: Showing the pathological fracture at the proximal humerus.

NF1 is associated with malignancy that tends to be more aggressive. As illustrated by our case, disease progression in these patients can be rapid and atypical presentation is common. This knowledge of tumour behaviour in NF1 patients should allow early diagnosis and treatment, improving their survivorship.

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CASE REPORT

Serious Gastrointestinal Form of Henoch-Schönlein Purpura Induced by *Helicobacter pylori* Infection and Complicated by Bradycardia and Euthyroid Sick Syndrome

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ABSTRACT

Association between Henoch-Schönlein purpura and Helicobacter pylori *infection is rarely reported in the literature. We present a case of Henoch-Schönlein purpura with severe gastrointestinal manifestations, bradycardia and euthyroid sick syndrome, which resolved only after the eradication of* Helicobacter pylori *infection.*

Keywords: Bradycardia, euthyroid sick syndrome, *Helicobacter pylori*, purpura

INTRODUCTION

Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis in children (10–30 cases per 100 000 children under 17 years) and usually occurs in children younger than 10 years (1). Henoch-Schönlein purpura is non-granulomatous, small-vessel vasculitis, which presents with palpable purpura on the lower extremities and buttocks with possible joint, gastrointestinal and renal involvement (1). In 75% of patients, an infection precedes HSP (2). *Helicobacter pylori* (HP) infection is rarely associated with HSP.

We present a case of HSP with severe gastrointestinal manifestations, bradycardia and euthyroid sick syndrome, which resolved after the eradication of *Helicobacter pylori* infection.

CASE REPORT

A five-year-old boy was hospitalized due to palpable purpura, abdominal pain and vomiting. The disease began four days earlier with petechial rash on the legs, followed by episodes of abdominal pain and vomiting. He was previously healthy.

On admission, he had palpable purpura on the legs and gluteus, and feet oedema. The abdomen was slightly meteoristic and sensitive in the paraumbilical region. Other findings were normal, like C-reactive protein 24.3 mg/L (0–5 mg/L), ESR 10 mm/h, WBC 20.5×10^9/L (78% granulocytes and 16% lymphocytes), ERC 5.49×10^{12}/L, HGB 133 g/L, HTC 43% and PLT 305×10^9/L. Coagulation profile, electrolytes, renal and liver function, immunoglobulins (Ig) A, M and G, complement components C3 and C4, anti-streptolysin O titre were normal. Viral serology was negative. Anti-nuclear antibodies (ANA), lupus anti-coagulant, anti-cardiolipin antibodies (ACLA) IgG and IgM, anti-ß2 glycoproteins IgM and IgG were negative. Urine showed proteinuria 2+, 15 erythrocytes; 24-hour proteinuria was 0.154 g/day. Throat swab was negative. Occult blood in the stool was positive. Copro-culture and clostridium difficile toxin were negative. Ultrasonography of the abdomen showed oedematous walls of the distal part of the terminal ileum (wall thickness: 5.3 mm) with intense regional blood flow (Power Doppler) and a moderate amount of free fluid in the abdomen (Fig. 1).

Our diagnosis was HSP, so we started therapy with methylprednisolone (1 mg/kg per day) and proton pump inhibitor. On the third day, palpable purpura re-emerged, now affecting all four extremities. This was accompanied by intense abdominal pain, colic, diarrhoea and haematochezia. Ultrasound examination of the abdomen showed advanced thickening of intestinal walls. Due to exacerbation of the disease, we administered

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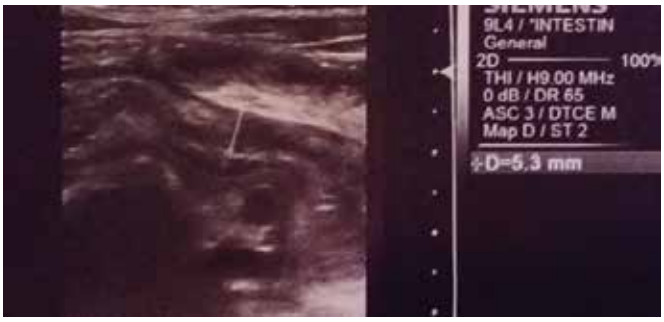

Fig. 1: Ultrasonography of the abdomen showing oedematous walls of the distal part of the terminal ileum.

methylprednisolone pulse therapy (30 mg/kg per day) for three days, and then proceeded with methylprednisolone at the standard dose of 1 mg/kg per day. Oral intake was suspended and total parenteral nutrition initiated. All these therapeutic measures gave only short-term effect.

On the ninth day, previous symptoms relapsed. Ultrasonography revealed further thickening of the intestinal walls. Intravenous immunoglobulins (IVIG) of 2 g/kg were given. This was followed by a significant clinical improvement, however, in attempts to reduce the doses of corticosteroids, abdominal pain and skin lesions relapsed.

During the third week of illness, the boy become bradycardic (heart rate: 44 per minute) and constipated.

Standard ECG showed sinus bradycardia. 24-hour ECG Holter monitoring showed persistent bradycardia with a mean heart rate of 55 per minute, minimal heart rate of 39 per minute, without significant sinus pauses and conduction disorders (Fig. 2). Echocardiography was normal.

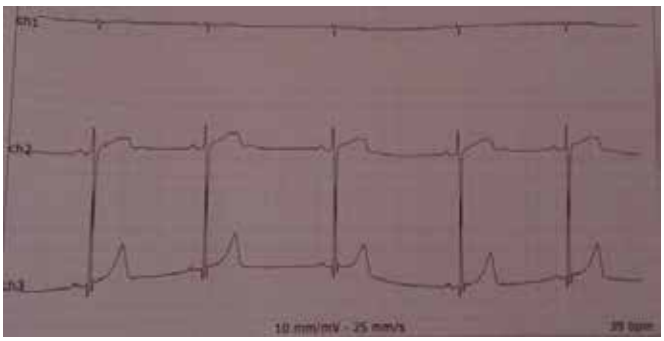

Fig 2. 24-hour ECG Holter monitoring showing bradycardia with heart rate of 39 per minute.

Thyroid function tests were indicative of euthyroid sick syndrome: (tri-iodothyronine [T3] – 0.72 nmol/L [reference range: 1.42–3.8 nmol/L], normal levels of thyroxine [T4] and thyroid-stimulating hormone [TSH]). Levothyroxine was introduced in the therapy and gradual normalization of the heart rate and hormones levels occurred.

Due to relapsing gastrointestinal symptoms, anti-*Helicobacter pylori* IgG and IgA antibodies were determined; and the results were positive for IgG antibodies (90.1 RJ/ml, reference < 22 RJ/ml), so a seven-day course of amoxicillin and metronidazole was administered. After the eradication of HP, there was no further re-occurrence of abdominal pain; findings of occult blood in the stool became and remained negative; abdominal ultrasound findings normalized and skin lesions permanently resolved. The corticosteroids were gradually reduced and discontinued after two months. Levothyroxine therapy has been discontinued after one month.

DISCUSSION

Gastrointestinal symptoms occur in 51%–74% of children with HSP and usually manifest as diffuse abdominal pain or colic, associated with nausea, vomiting and diarrhoea (3, 4). There is no consensus on the treatment of severe gastrointestinal manifestations of HSP and recommendations are based on small studies and case reports. The most commonly administered therapy are methylprednisolone pulses and IVIG, and sporadically—plasmapheresis, cyclophosphamide, methotrexate, mycophenolate mofetil, azathioprine, rituximab, factor XIII concentrate replacement therapy, *etc*. (5, 6). In our patient, relapsing episodes of gastrointestinal symptoms required complete cessation of oral intake and introduction of parenteral nutrition.

Several smaller studies and case reports that indicate an association between HSP and HP infection were recently published. In those cases, the eradication of HP led to a prompt resolution of HSP symptoms (7). In children, HP infections may be asymptomatic, as was the case with our patient. Increased IgA levels, decreased C3 levels, increased cryoglobulins and elevated levels of pro-inflammatory mediators caused by HP infection may have some role in the course of HSP (8). Previous studies indicate that the eradication of HP may lead to resolution and decreased recurrence of HSP. However, there is not enough evidence to substantiate the claim that HP infection may trigger HSP (8). In our case, resolution of all symptoms after the eradication of HP suggests an association between HP infection and HSP.

In our patient, the course of disease was complicated by persistent bradycardia. There are few described cases of adult patients treated with methylprednisolone, in whom bradycardia emerged within a few hours to

several days after the start of the therapy. Also, in the patients treated with conventional lower doses of corticosteroids, episodes of bradycardia were reported, but were extremely rare (9). The mechanisms by which corticosteroids may cause bradycardia have not been fully elucidated; however, there is speculation that corticosteroids may directly affect cardiomyocytes, modulating their sensitivity to catecholamines, or cause rapid electrolyte shifts across cell membranes, or indirectly—by inducing arterial hypertension. However, in our patient, the likely cause of bradycardia was decreased T3 levels. Possible mechanisms of decreased T3 availability may be corticosteroid-induced block of peripheral conversion of T4 to T3 or competition between corticosteroids and thyroid hormones for albumin-binding sites that decreases T3 levels despite normal T4 levels (10).

AUTHORS' NOTE

All the authors have participated in the concept and design, analysis, drafting and revising of the manuscript. Each author listed has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. The authors of this paper do not have any potential conflict of interest.

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CASE REPORT

A Case of Pulsatile Tinnitus Associated with Internal Jugular Vein Stenosis Diagnosed by Multidetector-computerized Tomography Angiography

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ABSTRACT

Tinnitus is a discomforting condition associated with a sound in one or both ears that occurs without an external stimulus and can be either pulsatile or continuous. Vascular and non-vascular factors are involved in the aetiology of pulsatile tinnitus (PT), requiring a careful physical examination and evaluation with proper and sophisticated imaging techniques to identify the cause(s). It is known that turning the neck towards the affected ear decreases PT, whereas turning the neck towards the unaffected side increases PT from venous hum, due to bending of the internal jugular vein over the transverse process of the atlas leading to increased blood flow. In this report, we present a rare PT case caused directly by jugular vein stenosis, in which clinical characteristics were in disagreement with the literature. In our case, PT markedly decreased, instead of being aggravated, when turning the neck to the unaffected side in a 35-year-old woman. There was axial maximal intensity above the left jugular bulb and about 85% stenosis in 3-D volume rendering images. We discuss the differential diagnosis by multidetector-computed tomography angiography with respect to its advantages over other imaging techniques such as CT, MR, MR angiography and conventional angiography.

Keywords: Jugular vein stenosis, multidetector-computed tomography-angiography, pulsatile tinnitus.

INTRODUCTION

Tinnitus is a discomforting condition associated with a sound in one or both ears such as ringing, whistling, clicking, or buzzing that occurs without an external stimulus and can be either pulsatile or continuous (1). Underlying factors causing pulsatile tinnitus (PT) can be considered in two groups: non-vascular and vascular causes. The cause of PT may be the turbulence of blood flow, which depends on increased flow volume or stenosis of vessel lumen (1). PT cases resulting from venous factors are reported to be mostly due to benign intracranial hypertension (BIH), followed by jugular bulb abnormality, and dural sinus stenosis (1), whereas those resulting from arterial factors are mostly linked to carotid atherosclerotic disease and glomus tumours (2).

Pulsatile tinnitus requires careful physical examination and evaluation with proper and sophisticated imaging techniques to identify the origin of the symptoms. The differentiation of venous PT and arterial PT can be provided by pressing on the internal jugular vein (IJV). In patients with PT caused by venous factors, this application ends up with a pause of PT (1). It is known that turning the neck towards the affected ear decreases tinnitus, whereas turning the neck towards the unaffected side increases tinnitus from venous hum, due to the bending of IJV over the transverse process of the atlas leading to increased blood flow (3).

External structures pressing on the jugular vein may lead to PT. However, to our knowledge, no report on PT caused directly by jugular vein stenosis has been documented. In this report, we present a unique PT case associated with jugular venous stenosis diagnosed by multidetector-computed tomography angiography

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(CTA) and discuss its clinical characteristics which are in disagreement with current literature.

CASE REPORT

A 35-year-old female presented with a 3-year history of non-progressive PT in the left ear. There was no history of hearing loss, trauma of head or neck, ototoxicity, or cardiovascular disease. The physical examination, except for auscultation, was normal. The noise was abolished by occluding the left IJV. Pure tone audiometry and tympanometry were normal. Opposite to common experience, PT markedly decreased,, instead of being aggravated, when she turned her neck to the unaffected side. Tinnitus completely disappeared after digital pressure on the left side of her neck.

The patient was subjected to multidetector CTA (Aquillon, Toshiba Medical Systems, Tokyo, Japan). In addition to the traditional axial images, all the other available techniques (multiplanar reconstructions and 3D volume-rendering images) were used to assess the arterial and venous structures. There was axial maximal intensity above the left jugular bulb and about 85% stenosis in 3D volume rendering images (Figure).

DISCUSSION

Pulsatile tinnitus is a common disorder and results from a variety of otologic and vascular lesions, including primary venous anomalies as well as conditions causing increased intracranial pressure and transmission of arterial pulsation to the dural venous sinuses (4). Pulsatile tinnitus may originate from vascular diseases and tumours. The most common tumoural causes are glomus jugulare and glomus tympanicum. In a review involving 107 patients with PT or vascular retrotympanic mass, it was reported that 25% had objective tinnitus and 25% had acquired vascular lesions and that a vascular tympanic membrane was present in 35%, whereas normal vascular variants were present in 21% (5).

Unilateral objective tinnitus caused by IJV is a mystery. Movement of the neck to the contrary side causes the IJV to bend over the transverse process of the atlas giving rise to turbulence in blood flow, with this maneuver; the effective lumen of the vein is being opened up because of the contraction of ipsilateral SKM, thereby increasing the venous return. Movement of the neck to the affected side has the contrary effect, resulting in decrease of the tinnitus (1). The neck movement rearranges turbulent flow in the IJV in association with BIH and/or external compression on the IJV because the IJV curves around the lateral process of the atlas (6).

Nehru *et al* reported a reduction in tinnitus when turning the neck to the affected ear and aggravation of tinnitus when turning neck to the unaffected ear in patients with venous hum, also known as idiopathic or essential PT when aetiology is unclear (3). Our patient has 85% stenosis in IJV, which was located above the transverse process of the atlas. In contrast with the literature, the PT significantly deceased when the neck was turned to the unaffected ear in our case. This reduction was probably related to blocking of blood flow further due to squeezing of IJV by the transverse process of the atlas at the time of turning neck to the unaffected ear. In addition to the involvement of IJV in the PT, this is the first case, to our knowledge, showing this phenomenon.

Various imaging modalities, including CT, MR imaging (MRI), and MR angiography (MRA), and conventional angiography, are used for the PT diagnosis. However, the selection of the most appropriate imaging method is essential for determining underlying causes. Krishnan *et al* evaluated PT using CT arteriography and venography (CTA/V) and reported their comprehensiveness and high reliability (7). The CT angiography was employed in the diagnosis of the PT cases caused by an aberrant internal carotid artery (8) and high-homolateral jugular bulb and aplasia of the contralateral transverse and sigmoid sinuses (9). Various diagnostic imaging methods have been suggested. In the absence of objective PT, use of MRI/MRA is recommended (5), whereas in the presence of PT, use of high-resolution CT (HRCT) followed by Doppler ultrasonography or HRCT followed by temporal MRI and carotid Doppler may be an appropriate initial diagnostic step (10). These suggest that imaging for the initial diagnostic step can be complicated and time consuming. However, the clinician may choose directly angiography to be certain about the involvement of vascular factors (11). CTA spatial resolution is higher than MRA and CTA image can be obtained while running CT without necessitating an extra investigation, especially in claustrophobic patients and patients with aneurysm clips and pacemakers. Despite digital subtraction angiography being a standard reference for the evaluation of aneurysms, stenosis, and vascular malformations, CTA is a new, cost-effective and minimally invasive alternative (12).

Using 3D-CTA for the entire head from the skull base to the vertex, Matsumoto *et al* showed that this modality provided information on detailed vasculature of tumours and cerebral haemodynamics (13). in the diagnosis and preoperative evaluation, 3D-CTA may replace conventional angiography' which is an invasive method with

less ability to demonstrate images of the lesion, arteries, veins and bony structures, and their relationships. In this case study, we were able to detect IJV stenosis and its location using multidetector CTA (Figure).

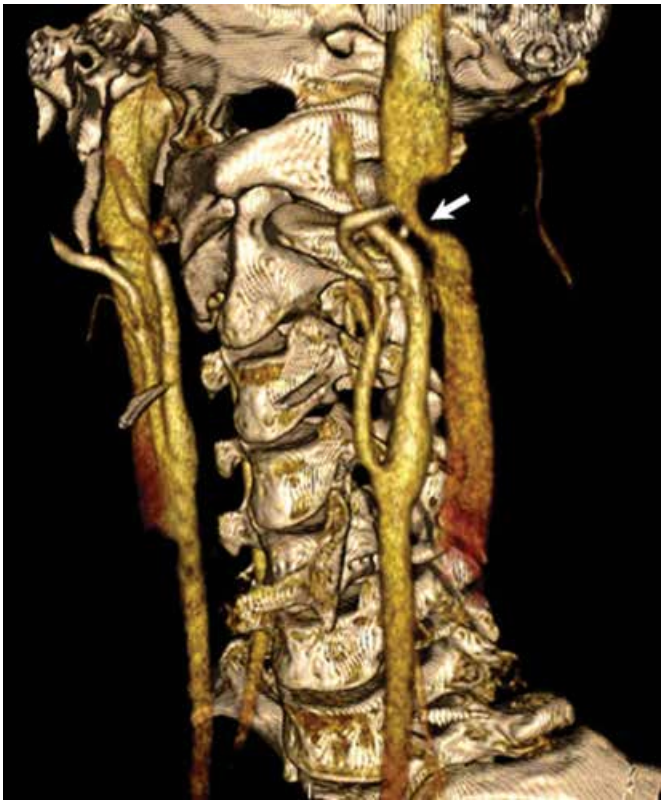

Figure: Appearance of the left jugular bulb and stenosis in multidetector-computed tomography angiography.

CONCLUSION

A unique PT case resulting from IJV stenosis and clinically reduced by turning the neck to the unaffected side, in contrast with the literature, was presented. Employing CTA directly as a first initial diagnostic step allowed us not only to save time by eliminating multiple radiological examinations, but also to view middle and inner ear, arterial, and venous structures.

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LETTER TO THE EDITOR

Primary Cutaneous Marginal Zone Lymphoma

The Editor,

Sir,

A 64-year-old male was referred to the haematology outpatient clinic with multiple irregular plaques with central necrosis ranging from 0.5 to 5 cm on the medial surface of both legs. Lesions appeared gradually and progressed over 2 months (Figure). He also complained of fatigue; but his history of presenting complaint was otherwise unremarkable. He had a past medical history of type 2 diabetes mellitus, hypertension, coronary artery disease, chronic obstructive pulmonary disease and hyperlipidaemia. He was taking an angiotensin-converting enzyme inhibitor and thiazide diuretic combination, a statin, 300 mg acetylsalicylate daily, 2 g of metformin and acarbose with meals. Physical examination revealed moderate pretibial oedema apart from plaques. He had no hepatosplenomegaly or lymphadenopathy. Routine blood tests were normal. Peripheral blood smear was negative for atypical cells.

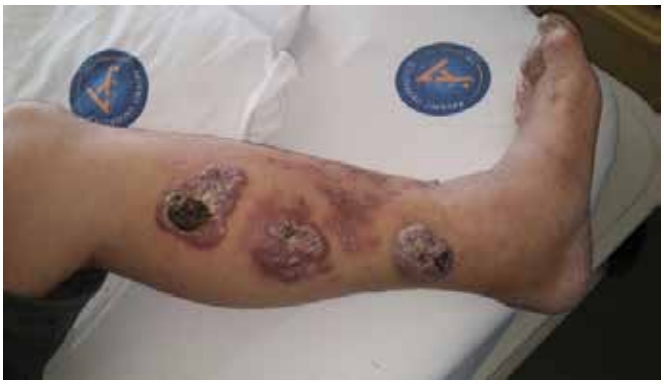

Figure: Patient's leg shows multiple irregular plaques with central necrosis ranging from 0.5 to 5 cm on the medial surface.

A punch biopsy of the lesion showed CD20, CD79a and Pax-5 positive atypical B-cells producing kappa light chains; findings were consistent with marginal zone lymphoma. Ki-67 index was 40%. A full-body CT scan did not reveal any pathological lymph nodes or splenomegaly. Bone marrow biopsy was negative for lymphoma infiltration; bone marrow aspiration, flow cytometric analysis, conventional cytogenetic and FISH analysis were negative as well. Both serum and urine immunofixation electrophoresis revealed no monoclonal bands. The patient was diagnosed as primary cutaneous marginal zone lymphoma and is being followed up for therapy.

Primary cutaneous B-cell lymphoma is a rare lymphoproliferative disorder manifested by cutaneous infiltration of monoclonal B cells without evidence of extracutaneous involvement. The aetiology and pathogenesis of primary cutaneous B-cell lymphoma remains poorly understood.

Primary cutaneous lymphoma presents in the skin with no evidence of extracutaneous disease at the time of diagnosis. Among the various types of lymphomas, primary cutaneous marginal zone lymphoma is an indolent lymphoma composed of small B cells. They must be distinguished from systemic lymphomas, which may involve the skin secondarily and have a completely different clinical behaviour and prognosis. Therapeutic mainstays for primary cutaneous marginal zone lymphoma have primarily included radiotherapy and surgery.

Keywords: Cutaneous lymphoma, marginal zone lymphoma, Turkey.

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