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EDITORIAL

The Clinical Translational Research Unit (CTRU): The New Core of the Faculty of Medical Sciences Research Enterprise

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The Faculty of Medical Sciences (FMS) has a long history of producing seminal work across a wide range of clinical and scientific disciplines. This work has contributed to the research enterprise of the University of the West Indies (UWI) as a premier higher education institution with strong roots in the Caribbean and expanding globally. With 76 years of service to the Caribbean community, the FMS has an impressive group of multi-disciplinary stakeholders in health research who consistently guide decision-making which informs clinical practice and public health policy across local, regional, and international landscapes (1–3).

The global disruption caused by the COVID-19 pandemic during the 2019–2020 academic year presented an unprecedented challenge to universities worldwide, including the UWI. The importance of the leadership of medical faculties in exploring systems to strengthen research capacity has been highlighted in recent post-pandemic studies from both developed and developing countries (4–9). During this period, the FMS experienced a decrease in research output, both in the number of publications and clinical trial registration (Figure 1A and B). In response, the faculty had to swiftly adapt, recalibrate and transform its research systems. However, this period of upheaval also presented an opportunity for self-reflection, organizational restructuring and the identification of new research directions. It allowed the FMS to strengthen existing partnerships, explore emerging areas of research, and reimagine the future of the faculty. This culminated in the Clinical Translational Research Unit (CTRU) of the Dean's Office of FMS; an initiative that marked a new era of research collaboration and innovation. The CTRU evolved from the Health Research Resource Unit, initially created to provide methodological and data analytical support for faculty research, the Clinical Trials Centre which coordinated and implemented clinical trials, as well as the Translational Innovative Entity which provided entrepreneurial support to faculty and students.

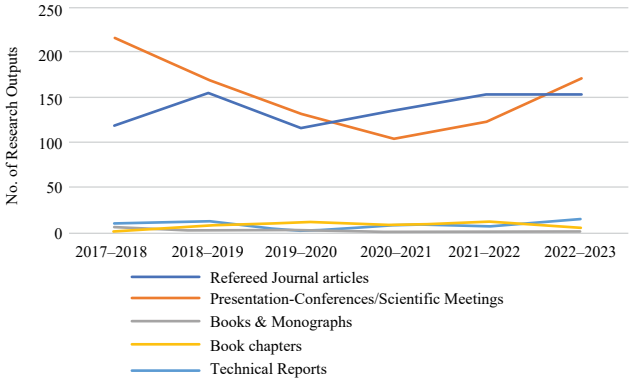

Figure 1A. Trend in FMS research outputs for academic years 2017/18–2022/23.

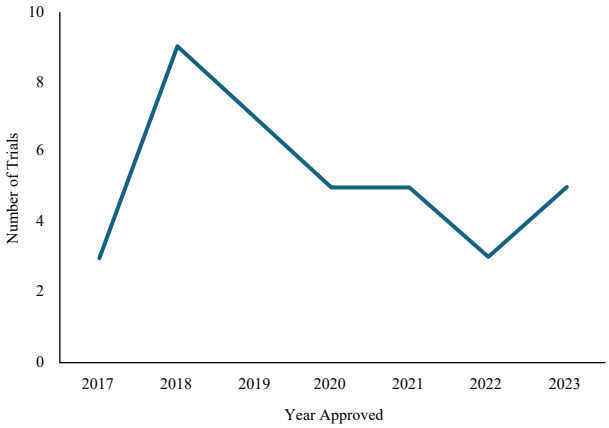

Figure 1B. Clinical trials register by FMS on Clinicaltrials.gov between 2017 and 2023.

CTRU Organizational Structure

The CTRU structure, which reports to the Dean, includes a full time Research Manager, Deputy Dean of Research, Biostatistician/Epidemiologist support, Librarian assigned to the faculty, Faculty multimedia/ information technology support, and administrator assistant support. The Unit introduced Research Liaison

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Officers within all clinical and non-clinical departments. Nominated by the Heads of Departments, these officers serve as the critical link between their respective departments and the CTRU. Working closely with the heads of departments, these representatives facilitate research development across departments and are given the task of ensuring that departmental research activities align with the faculty research goals. Additional expertise is invited as needed for special activities such as for the mounting of training workshops and research conference activities. Through the concerted efforts of the CTRU, the research publication and clinical trial registration output for 2022–2023 reflected a trajectory toward pre-pandemic levels.

CTRU Mission and Strategic Goals

The mission of CTRU is to enhance the research capacity of FMS, positioning it as a key driver of scientific advancement. The unit operates under primary objectives designed to foster a robust research ecosystem and the strategies employed focus on research capacity training, consultations, supporting access to research resources and ensuring that research outputs are effectively communicated (Table 1).

CTRU offers a wide range of services to support the primary objectives, including:

1. **Training Workshops/Seminars/Webinars/Journal Club Support:** The CTRU provides targeted training for faculty members, and post-graduate students. Training workshops, webinars and seminars are conducted throughout the academic year to enhance research competencies. A key initiative of the CTRU is the revitalization of journal clubs, which will serve as central hubs for academic engagement and research exchange.
2. **Resource Repository Development:** Since the inception of CTRU, continuous training activities have been organized and delivered. These include the FMS Research Toolkit, *Design to Publication—A Practical Guide*, which was launched in 2023 in celebration of the 75th anniversary of the UWI. This comprehensive resource, grounded in translational science principles, guides users through seven key stages of the research process—from conceptualization to publication. It includes a range of supplementary materials, such as a video masterclass series and a Research Conceptualization Template designed to assist researchers in developing strong research proposals. These resources are housed on the UWI online learning platform which is accessible to all faculty and registered students. The resources are also available on the FMS YouTube channel. Complementing the resources developed by the unit are the resources on the UWI online learning platform provided by our Library partners which include training material on engaging with library services, avoiding plagiarism, proper use of citation managers and expert navigation of the publication landscape.
3. **Research Liaison Officers Support:** The CTRU, in partnership with these officers, ensures

Table 1. Primary objectives and strategies of the CTRU

Primary objectives	Strategies of CTRU
1. **Capacity Building for Researchers in the Health Sciences:** The CTRU aims to cultivate a cadre of researchers who can generate reproducible, responsible, and high-impact research within a culturally informed and ethical framework. The research generated should tackle problems of national and international significance, yielding competitive research grants, high-quality journal publications and cogent evidence-based policy and practice guidelines.	**Research Capacity Training:** Developing the skills of faculty members and students to improve research design, execution, and dissemination.
2. **Development of Academic Leaders:** The CTRU strives to produce future academic leaders proficient in communicating biomedical science and contributing meaningfully to global research discussions.	**Consultations and Technical Reviews:** Providing expert guidance to strengthen research proposals and methodologies.
3. **Promoting Multi-disciplinary Collaboration:** A cornerstone of the CTRU's vision is the fostering of a multi-disciplinary approach to problem-solving, allowing for innovative and comprehensive solutions to complex scientific and health challenges.	**Research Platforms:** Supporting access to tools and resources to aid in research development.
4. **Facilitating Translation into Practice and Policy:** The CTRU seeks to bridge the gap between research and practice, ensuring that scientific findings are translated into actionable policies and interventions.	**Knowledge Management and Dissemination** Ensuring that research outputs are effectively communicated and shared within and beyond the faculty.
5. **Establishing Research Repositories:** A key focus is the creation and maintenance of well-characterized information and biorepositories, ensuring that these resources facilitate efficient data sharing and future collaborations.	

continuous research development at the department level with the inclusion of both staff and students. The initiatives encouraged include regular journal club meetings, research project discussion forums, ethical review consultations, basic biostatistics support, assisting with clinical trial registration, and formation of paper writing groups to increase publication output. CTRU holds regular meetings with these officers to gather information on best practices and the specific needs of each department.

4. **Clinical Trial Support for Startup and Monitoring:** The CTRU provides oversight for all clinical trials of the faculty. By supporting researchers, the established UWI protocol for registration and monitoring are ensured. The unit also supports patient safety monitoring and adverse event reporting needs.
5. **Research Output Analysis:** The CTRU is developing systems to monitor and track departmental research activities, providing a clear overview of progress in relation to the FMS research agenda. These systems will allow for real-time reporting on research outputs. The CTRU also provides robust publication support, ensuring that prospective authors have the resources they need to publish in high-impact journals.
6. **Consultation and Communication:** In addition to the business meetings with Research Liaison Officers, updates and resources are disseminated to the full faculty through the FMS email platform and during regular departmental meetings. Information shared includes internal and external collaboration opportunities, grant funding opportunities and postgraduate training opportunities. The unit is accessible to the faculty for support with grant applications, project management guidance and facilitating research innovations. Other initiatives include continuous needs assessment systems to identify gaps in skills, resources, and the creation of research data repositories.

In conclusion, the vision of the leadership of the FMS, including the Dean and the Heads of Departments, the capacity building through the CTRU is positively impacting the research output of FMS. Through strategic next steps focusing on maintaining a collaborative, inclusive approach with our Research Liaison Officers, research supervisors, students, technical and administrative support, the CTRU will continue to elevate the research enterprise of the FMS.

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ORIGINAL ARTICLE

Relationship between *Helicobacter pylori* Infection and Gastrointestinal Symptoms in Children

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ABSTRACT

Objective: *To examine the relationship between Helicobacter pylori* (H. pylori) *infection and gastrointestinal symptoms, and the efficacy of eradication treatment.*

Methods: *A retrospective chart review was carried for children (5–18 years old), who underwent a ^{14}C-urea breath test (^{14}C-UBT) for* H. pylori *infection. Pre- and post-treatment ^{14}C-UBT results, gastrointestinal symptoms,* H. pylori *eradication protocol and treatment consistency were noted.*

Results: *At presentation, out of 537 patients (65.2% girls), 43.9% had ^{14}C-UBT positivity. The frequency of heartburn, acid regurgitation and halitosis (*$p = 0.001$, $p = 0.006$ *and* $p = 0.03$, *respectively) were significantly high in the ^{14}C-UBT (+) patients; the frequency of epigastric pain (*$p < 0.0001$*) was significantly high in the ^{14}C-UBT (–) patients at presentation. The ^{14}C-UBT (+) patients were treated with amoxicillin + lansoprazole + clarithromycin (66.1%)/ metranidazole (33.9%). After the eradication treatment, control ^{14}C-UBT was negative in 62.5% of patients treated with metranidazole compared with 47.4% of patients treated with clarithromycin protocol (*$p = 0.03$*). After the eradication treatment, the frequency of gastrointestinal symptoms (except the feeling of hunger) were significantly decreased regardless of treatment success (*$p < 0.0001$*). The frequency of total gastrointestinal symptoms (*$p < 0.0001$*), epigastric pain (*$p < 0.0001$*), epigastric burning (*$p = 0.003$*), heartburn (*$p = 0.002$*), acid regurgitation (*$p = 0.006$*), nausea (*$p = 0.001$*), halitosis (*$p = 0.02$*) and early satiety (*$p = 0.02$*) were significantly reduced in patients with control ^{14}C-UBT (–).*

Conclusion: H. pylori *eradication, or the attempt to eliminate* H. pylori*, reduces gastrointestinal symptoms in* H. pylori*-infected children.*

Keywords: Children, dyspepsia, *Helicobacter pylori*, treatment

INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most common bacterial pathogens in humans and is acquired mainly during childhood. The prevalence of *H. pylori* infection is still common in developing countries. It can persist for a life time, and chronic infection is nearly always accompanied by chronic active gastritis. The *H. pylori* infection is usually asymptomatic particularly in children, however, may cause serious diseases, such as peptic ulcer disease, non-cardiac gastric adenocarcinomas and the gastric mucosa-associated lymphoid tissue lymphomas, especially in adults (1, 2). There have been conflicting reports on the relationship between *H. pylori* infection and gastrointestinal symptoms in children and

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adults. The resolution of dyspeptic symptoms after a successful *H. pylori* eradication remains controversial. Also, relation of healing of mucosa after the eradication or suppression of acid-related symptoms by proton pump inhibitors (PPIs) is debatable (2–11). We aimed to examine the relationship between gastrointestinal symptoms and *H. pylori* infection at presentation and after eradication treatment.

SUBJECTS AND METHODS

A retrospective chart review was carried out in 1850 patients who underwent a ^{14}C-urea breath test (^{14}C-UBT) for the detection of *H. pylori* infection. These patients were either primarily admitted or referred to our paediatric gastroenterology outpatient clinic after ^{14}C-UBT performed between January 2011 and January 2013. Age, gender, symptomatology and ^{14}C-UBT results at diagnosis were noted by the same observer. The records of the ^{14}C-UBT-positive patients were reviewed for the given randomized empirical treatment protocol, treatment consistency, symptomatology and post-treatment ^{14}C-UBT results by the same observer. Epigastric pain, epigastric burning, heartburn, acid regurgitation, nausea, vomiting, recurrent abdominal pain (RAP), early satiety, halitosis and a frequent feeling of hunger were considered in the symptomatology. Localized pain sensation in the epigastric region was considered as epigastric pain. Localized burning sensation in the epigastric region, not radiating up towards the throat was considered as epigastric burning. If the burning sensation was in the chest, radiated up towards the throat, it was considered heartburn.

A sudden regurgitation of acid gastric content was considered as an acid regurgitation. Inability to finish a normal meal was considered as early satiety (12). Halitosis was determined if patients complained of an unpleasant or offensive odour emanating from the oral cavity (6). Recurrent abdominal pain was defined if abdominal pain was present for at least three months, with at least three episodes, severe enough to affect child's activity (13). The 'improvement' of a symptom was defined, if only there was a complete resolution of the symptom after the eradication treatment. The ^{14}C-UBT was performed with Heliprobe® system (Kibion, Upsala, Sweden).

The study was approved by the Ethics Committee of the Turkish Republic Health Ministry, Ankara Child Health Diseases, Haematology Oncology Training and Research Hospital (2014/023 protocol number), Ankara, Turkey. Of the 1850 patient records, 537 patients (350 girls, 65.2%) met the following criteria for inclusion in the study: (a) 5–18 years of age; (b) if at least one of the above gastrointestinal symptoms was present for at least two months; (c) not treated with antimicrobial drugs or acid-suppressive drugs for at least one month prior to the ^{14}C-UBT; (d) naïve for *H. pylori* eradication treatment; (e) if treatment protocol consisted of lansoprazole (1–2 mg/kg per day, maximum: 2 × 30 mg/day) + amoxicillin (50 mg/kg per day, maximum: 2 g/day) + metranidazole (15 mg/kg per day, maximum: 1 g/day) or clarithromycin (15–20 mg/kg per day, maximum: 1 g/day) for 14 days, twice daily; (f) if the symptomatology was noted after treatment; (g) if the control ^{14}C-UBT was performed at least one month after completing the eradication treatment. Children were excluded from the study if: (a) they had a previously known peptic ulcer disease, or no gastrointestinal complaints at the presentation; (b) the treatment protocol did not include the drugs above; (c) the eradication treatment was discontinued or improperly used; (d) after the eradication treatment, a control ^{14}C-UBT was not performed; (e) the control ^{14}C-UBT was performed less than one month or more than two months after completing the eradication treatment.

Statistical analyses

Statistical analyses were performed using SPSS software (ver. 17.0, SPSS. Inc., Chicago, IL, USA). The results are presented as means ± SDs with descriptive statistics. The Student's unpaired *t*-test was used as appropriate. When the variances were unequal or the distributions not normal, the Mann–Whitney *U*-test was used. The significance level was set at $p < 0.05$.

RESULTS

Mean age of 537 patients (65.2% girls), who underwent the ^{14}C-UBT, was 11.6 ± 3.3 (range: 5–18) years old. Among 537 patients, 236 (43.9%) were ^{14}C-UBT (+) at the presentation. There were 159 (67.4%) girls among the ^{14}C-UBT (+) patients and 191 (63.5%) girls among the ^{14}C-UBT (–) patients. There was no gender difference between ^{14}C-UBT (+) and ^{14}C-UBT (–) patients at the presentation ($p > 0.05$). The ^{14}C-UBT (+) patients (12 ± 3.3 [range: 5–17.5] years) were older than the ^{14}C-UBT (–) patients (11.4 ± 3.4 [range: 5–18] years) at the presentation ($p = 0.03$).

In Table 1, the gastrointestinal symptoms of patients are given based on the ^{14}CUBT results at the presentation. Epigastric pain were more frequently observed in the ^{14}C-UBT (–) patients as compared with the ^{14}C-UBT (+) patients ($p < 0.0001$). Heartburn, acid regurgitation

and halitosis were more frequently observed in the ^{14}C-UBT (+) patients as compared with the ^{14}C-UBT (–) patients ($p = 0.001$, $p = 0.006$, $p = 0.03$, respectively). Nausea, vomiting, epigastric burning, early satiety, RAP and a frequent feeling of hunger did not differ between the ^{14}C-UBT (–) and ^{14}C-UBT (+) patients ($p > 0.05$; Table 1).

Table 1: Symptoms of patients at diagnosis with respect to the ^{14}C-urea breath test (UBT)

Gastrointestinal symptoms (n: 537)	Number of patients (%)		
	^{14}C-UBT (–) (301 patients)	^{14}C-UBT (+) (236 patients)	*p*-value
Epigastric pain	236 (78.4)	144 (61)	< 0.0001
Nausea	145 (48.1)	101 (42.8)	N.S.*
Acid regurgitation	79 (26.2)	88 (37.3)	0.006
Epigastric burning	46 (15.2)	46 (19.4)	N.S.
Heartburn	23 (7.6)	39 (16.5)	0.001
Vomiting	43 (14.2)	29 (12.3)	N.S.
Halitosis	41 (13.6)	49 (20.8)	0.03
Early satiety	28 (9.3)	27 (11.4)	N.S.
Recurrent abdominal pain	23 (7.6)	22 (9.3)	N.S.
Feeling of hunger	14 (4.6)	11 (4.7)	N.S.

*N.S. = non-significant.

All ^{14}C-UBT (+) patients (n = 236) were administered an eradication protocol: 156 (66.1%) patients were treated with amoxicillin + clarithromycin + lansoprazole and 80 (33.9%) patients with amoxicillin + metranidazole + lansoprazole. No difference was found in age or gender between treatment protocols at the presentation ($p = 0.34$ and 0.25, respectively).

Regardless of the protocol, 124 of 236 (52.5%) patients were ^{14}C-UBT (–) after the treatment. Treatment success did not differ by age and gender ($p = 0.07$ and 0.5, respectively). Fifty (62.5%) patients treated with the metranidazole protocol had a negative control ^{14}C-UBT after the eradication treatment, compared with 74 (47.4%) patients treated with the clarithromycin protocol ($p = 0.03$).

All gastrointestinal symptoms were compared before and after the eradication treatments, as shown in Table 2. After the eradication treatment, regardless of treatment success, 117 (49.5%) patients were still symptomatic, however, the frequency of total gastrointestinal symptoms were significantly decreased ($p < 0.0001$). The frequency of epigastric pain, epigastric burning, heartburn, acid regurgitation, nausea, vomiting, RAP, early satiety and halitosis were reduced significantly as shown in Table 2.

Table 2: Gastrointestinal symptoms of the ^{14}C-urea breath test (UBT)-positive patients at the presentation and after the eradication treatment independent of the control ^{14}C-UBT results

Gastrointestinal symptoms	Number of patients (%)		
	At presentation	Post-treatment	*p*-value
Total gastrointestinal symptoms	236 (89.1)	117 (49.5)	< 0.0001
Epigastric pain	144 (61)	72 (61.5)	< 0.0001
Nausea	101 (42.8)	42 (35.9)	< 0.0001
Epigastric burning	46 (19.4)	28 (11.8)	< 0.0001
Acid regurgitation	88 (37.3)	38 (32.4)	< 0.0001
Halitosis	49 (20.8)	27 (23)	< 0.0001
Heartburn	39 (16.5)	10 (4.2)	< 0.0001
Vomiting	29 (12.3)	3 (2.5)	< 0.0001
Early satiety	27 (11.4)	13 (11.1)	< 0.0001
Recurrent abdominal pain	22 (9.3)	8 (6.8)	< 0.0001
Feeling of hunger	11 (4.6)	7 (5.9)	N.S.*

*N.S. = non-significant.

After the eradication treatment, the frequency of total gastrointestinal symptoms were decreased significantly in the ^{14}C-UBT (–) patients compared with the ^{14}C-UBT (+) patients ($p < 0.0001$). The frequency of epigastric pain, epigastric burning, heartburn, acid regurgitation, early satiety, halitosis and nausea were significantly reduced in the ^{14}C-UBT (–) patients as shown in Table 3.

Table 3: Gastrointestinal symptoms of patients with respect to control the ^{14}C-urea breath test (UBT) results after the eradication treatment

Gastrointestinal symptoms	Number of patients (%)		
	^{14}C-UBT (+) (n: 112)	^{14}C-UBT (–) (n: 124)	*p*-value
Total gastrointestinal symptoms	78 (85.7)	39 (26.8)	**< 0.0001**
Epigastric pain	48 (52.7)	24 (16.5)	**< 0.0001**
Nausea	30 (33)	12 (8.2)	**0.001**
Epigastric burning	20 (22)	8 (5.5)	**0.003**
Acid regurgitation	25 (27.4)	13 (8.9)	**0.006**
Halitosis	18 (19.7)	9 (7.6)	**0.02**
Heartburn	7 (7.7)	3 (2)	**0.002**
Vomiting	2 (2.1)	1 (0.6)	N.S.*
Early satiety	10 (11)	3 (2)	**0.02**
Recurrent abdominal pain	6 (6.6)	2 (1.3)	N.S.*
Feeling of hunger	4 (4.4)	3 (2)	N.S.*

*N.S. = non-significant.

DISCUSSION

In our study, *H. pylori* infection was found in 43.9% of the children who had gastrointestinal symptoms. After the eradication treatment, the frequency of gastrointestinal symptoms were reduced significantly regardless of the treatment success. Nearly half of the infected children were resistant to the given eradication treatment.

The frequency of gastrointestinal symptoms were significantly reduced with a successful eradication.

Chronic *H. pylori*-associated gastritis is generally asymptomatic, particularly in children (2, 14). Symptomatic diseases associated with the *H. pylori* infection generally arise mainly in adults from long-term infection (14). *H. pylori* infection may cause dyspeptic symptoms through several mechanisms, such as increased gastric acid secretion, persistent and active inflammation of the gastric mucosa, and post-infective motility changes in the gastrointestinal tract, elevated fasting and post-prandial levels of serum gastrin, and decreases in somatostatin secretion (14).

There is conflicting evidence for an association between the gastrointestinal symptoms and *H. pylori* infection in both children and adults (2–11, 15–17). Carvalho *et al* (10) reported no differences among the rates of symptoms between *H. pylori*-infected and non-infected children. Also, Ozen *et al* (18) reported that *H. pylori*-infected children did not complain much more than others of abdominal pain or dyspepsia. Spee *et al* (8) found no evidence of any relationship of RAP, nausea, halitosis, dyspepsia, regurgitation with the *H. pylori* infection in children in a meta-analysis of 38 studies. However, Daugule *et al* (11) reported a higher prevalence of the *H. pylori* infection in children with gastrointestinal symptoms compared with asymptomatic children. In the meta-analysis of Spee *et al* (8), an association between the *H. pylori* infection and both vomiting and upper abdominal pain was found in referred children (but not in children who were seen in primary care). In our study, halitosis, acid regurgitation and heartburn were more prevalent among *H. pylori*-infected patients at the presentation, however, epigastric pain was more prevalent in the ^{14}C-UBT (–) patients. There was no difference in RAP, nausea, vomiting, early satiety or the frequent feeling of hungry prevalence between the ^{14}C-UBT (–) and (+) patients at presentation.

The resolution of dyspeptic symptoms due to a successful *H. pylori* eradication also remains controversial in both children and adults (16, 17). It has been reported that the 'active' component (polymorphonuclear leucocyte infiltration) of gastritis recovers quickly and completely following bacterial eradication, however, lymphocytic infiltrate in the gastric mucosa may persist for several months or even years (19). It has been suggested that these cells can cause alterations in the gastric mucosal function by production of different cytokines. After bacterial eradication, it may take at least 6–12 months for the gastric mucosa to normalize (20). Ashon *et al* (7) reported bacterial eradication had no effect on gastrointestinal symptoms, such as abdominal pain, heartburn and regurgitation, hunger pain, nausea, sensation of fullness, burping or bloating in children. On the other hand, Uc and Chang (9) reported a clear improvement in dyspeptic symptoms after a successful eradication in children. Ozcay *et al* (3) reported that abdominal pain and dyspeptic symptoms were reduced or completely resolved in 75.7% of children after a successful eradication.

A relationship between gastric acid output and improvement of dyspeptic symptoms following *H. pylori* treatment has been reported (17). Also, increased gastric acid secretion associated with the *H. pylori* infection may be suppressed by PPIs, and acid-related dyspeptic symptoms may be relieved in attempts to eliminate *H. pylori* (17).

In our study, the frequency of total gastrointestinal symptoms (except the feeling of frequent hunger) were significantly decreased after the eradication treatment regardless of treatment success. This may be related to the improvement of acid-related dyspeptic symptoms due to PPI treatment. Also, the frequency of total gastrointestinal symptoms were found to be reduced significantly in patients who underwent a successful *H. pylori* eradication. Epigastric pain and burning, nausea, acid regurgitation, halitosis, heartburn and an early feeling of satiety were significantly improved with a successful eradication.

No relationship has been reported previously between the *H. pylori* infection and RAP, and screening for *H. pylori* is not recommended in children with RAP (1, 8). In our study, RAP was not related to the *H. pylori* infection at the presentation, and also after a successful eradication, no significant improvement was seen in RAP. Regardless of treatment success, the frequency of patients with RAP reduced after the eradication treatment, this may be due to use of PPIs or antibiotics.

The relationship between *H. pylori* infection and gastro-oesophageal reflux disease (GERD) remains a matter of controversy. Both aggravation and recovery of oesophagitis after *H. pylori* treatment have been reported in adults (21–24). In children, any association between the *H. pylori* infection and GERD also remains controversial. No association, a positive correlation and protection against GERD have all been reported (22–24). In our study, we found that the frequency of acid regurgitation and heartburn were significantly higher in *H. pylori* (+) patients, and both were reduced after the eradication treatment and also after a successful eradication.

Unfortunately to establish a precise relationship between GERD and *H. pylori* due to these results would not be appropriate, because endoscopic, histopathological and pH monitarization findings were not included to the study.

In previous reports, a possible link between the *H. pylori* infection and halitosis has been postulated. Especially after a successful *H. pylori* eradication, an improvement of halitosis has been reported (6, 25, 26). In our study, halitosis found to be related with the *H. pylori* infection and improved with *H. pylori* eradication. However, defining of halitosis due to patients' complaints, in spite of an objective method as gas chromatography which evaluates volatile sulphur compounds in breath was a limiting factor in our study.

In the developing countries, the prevalence of *H. pylori* infection is still common. In Turkey, the *H. pylori* infection was diagnosed in 50%–56% of 'healthy' children by using the ^{13}C-UBT (18). Also, eradication rates remain low in the developing countries (approximately 50%) (1, 17). Regardless of the treatment protocol, treatment success was 52.5% in our study similar to the previous reports. Eradication rates may differ with the given treatment protocol due to antibiotic resistance. A recent review of primary antimicrobial resistance in *H. pylori* in Turkey demonstrated resistance rates to amoxicillin, clarithromycin and metranidazole of 0.97%, 24.8% and 33.7%, respectively (27). In the previous years, a clarithromycin resistance rate was reported to be 18%–22% in children (3, 28), however, recent studies demonstrated the increased clarithromycin resistance rates (42%–53%) in our country (29, 30). In our study, primary clarithromycin resistance rate was 52.6% similar to the recent reports. The high resistance rates to clarithromycin in our country may be due to the common and uncontrolled use of clarithromycin in children. Primary metranidazole resistance rate of 37.5%, and we found that metranidazole was more effective than clarithromycin in eradication of *H. pylori*.

The study limitations were the following: (a) being a retrospective study; (b) upper gastrointestinal endoscopy, histopathologic examination, *H. pylori* culture were not included in the study; (c) a symptom rating scale to compare the severity of pre- and post-treatment symptoms was not used because of reviewing the records. However, we tried to minimize these limitations as follows: (a) we considered the 'improvement' of any symptom to be complete resolution of the symptom. If the symptom was merely reduced, or reduced immediately after treatment but again relapse, it was not defined as resolution; (b) the symptomatology was reviewed by the same observer.

CONCLUSION

In our study, nearly half of the children with gastrointestinal complaints had the *H. pylori* infection and nearly half of the infected children were resistant to the eradication treatment. Not only a successful eradication but also attempt to eliminate *H. pylori* resulted in a significant reduction of gastrointestinal symptoms.

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ORIGINAL ARTICLE

Degenerative Disc Pathology in Patients with Ankylosing Spondylitis: Frequency and Association with Disease Activity

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ABSTRACT

Objective: *To determine the frequency of degenerative disc pathology in patients with ankylosing spondylitis (AS) and explore its association with parameters of disease activity.*

Methods: *Patients between 15 and 65 years of age diagnosed with AS whose lumbar magnetic resonance imaging records were available in the registry database were enrolled. A total of 88 patients and 440 discs were evaluated. Modic classification was used for endplate degeneration, and the Pfirrmann scale, and the degree of disc herniation were analysed for disc degeneration. Aforementioned parameters were evaluated to determine whether they were associated with erythrocyte sedimentation rate, serum C-reactive protein (CRP) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Values were expressed as frequencies and percentages for categorical variables. Spearman's test was used for correlation analysis.*

Results: *Among 440 discs examined, Modic changes were detected in 13% (person count [PC]: 30.7%) and Modic type 2 changes were the most common (disc count [DC]: 8.9%, PC: 25%). The most frequent Pfirrmann change was grade 1 degeneration (DC: 57.7%, 254 discs), and the most common form of disc herniation was bulging disc (DC: 21.7%, PC: 67%). A positive correlation was found between L1-L2 disc herniation and BASDAI activity and between L2-L3 disc herniation and CRP level (*$p < 0.05$*).*

Conclusion: *A high prevalence of Modic type 2 changes and bulging herniation was found. While this study may provide some insight for degenerative disc disease in AS, further studies involving a larger number of patients and a control group are needed.*

Keywords: Ankylosing spondylitis, disc degeneration, disc herniation, Modic changes.

INTRODUCTION

Ankylosing spondylitis (AS) is a member and also a prototype of the spondyloarthropathy (SPA) family of inflammatory disorders (1). The most common involvement is the involvement of the axial skeleton (2). The main clinical symptom is low back pain associated with the sacroiliac joint and spinal involvement (3). In AS, disease-specific vertebral changes include Romanus lesions, squaring of the vertebral bodies, syndesmophyte, 'bamboo spine' appearance, ankylosis, and Andersson lesions. In addition to these changes, disc degeneration and damage and destruction of vertebral endplates occur in patients with AS. These changes resemble those seen in severe degenerative disc disease (4, 5). Intervertebral disc degeneration is thought to be the first step in degenerative spinal changes. Furthermore, disc degeneration is considered to be one of the causes of several symptoms (neck pain or low back pain) (6).

Disc involvement plays a crucial role in the degenerative process that occurs in the axial spine. In AS, intervertebral disc involvement has been overshadowed by disease-specific pathologies, and in the present study, disc involvement in AS will be examined extensively. Usually, Andersson lesions, causing discovertebral erosion, has been the primary focus of studies in AS patients (7–13). There are few studies that explored the incidence

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of degenerative disc disease in AS, and these studies investigated solely endplate degeneration (14, 15). In a separate study that examined the SPA group of diseases as a whole, both endplate degeneration and disc degeneration were evaluated (16). However, as a result of our literature search, we did not identify any studies that investigated endplate degeneration, disc degeneration and disc herniation collectively in AS patients.

The purpose of the current study was to determine the frequency of degenerative disc pathology in AS patients and explore its association with parameters of disease activity.

SUBJECTS AND METHODS

The study was conducted retrospectively by examining the patient registry database. Before initiation of the study, approval was obtained from the Education Planning Committee and the Ethics Committee of Kayseri Research and Training Hospital. Patients between 15 and 65 years of age were enrolled. Study patients were selected from outpatients with examinations performed in the Kayseri Research and Training Hospital from December 2013 to January 2015. Patients diagnosed with AS according to the 1984 modified New York classification criteria and/or the 2009 Assessment of SpondyloArthritis international Society (ASAS) axial spondyloarthropathy classification criteria were studied (17, 18). Among those patients, patients with lumbar spine magnetic resonance imaging (MRI) records were included in the study.

Patients with other forms of spondyloarthropathy as well as AS, a past history of a surgical operation to the lumbar region, metallic implants that could impair image quality, a previous trauma or fracture to the lumbar region, spondylitis due to infectious diseases, or a metabolic bone disease affecting the degenerative process were excluded from the study. A flowchart diagram is provided in Fig. 1.

Magnetic resonance imaging evaluation

Lumbar MRI scans of patients were examined by three radiologists with an expertise in the musculoskeletal system. A total of 440 discs including L1-2, L2-3, L3-4, L4-5, and L5-S1 levels were examined at axial and sagittal T1 and T2 sequences. All images were evaluated using 21-inch high-resolution screens. For lumbar MRI scans, Modic classification was used for endplate degeneration, and Pfirrmann scale and the degree of disc herniation were analysed for disc degeneration.

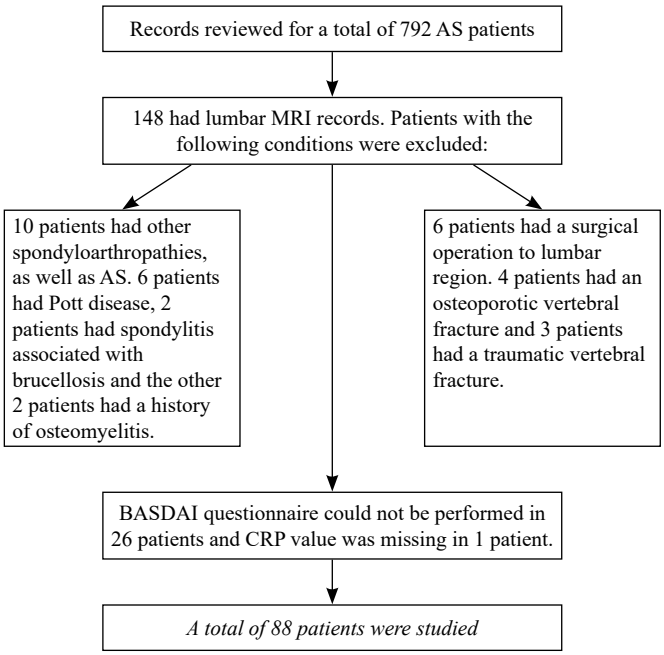

Fig. 1: Flowchart diagram. AS = ankylosing spondylitis; BASDAI= Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein; MRI = magnetic resonance imaging.

Modic changes

A formal classification was first provided by Modic *et al* in 1988 (19). Type 1 changes were hypointense on T1-weighted imaging (T1WI) and hyperintense on T2-weighted imaging (T2WI) and were shown to represent bone marrow oedema and inflammation (Fig. 2). Type 2 changes were hyperintense on T1WI and isointense or slightly hyperintense on T2WI and were associated with conversion of normal red haematopoietic bone marrow into yellow fatty marrow as a result of marrow ischaemia. Modic type 3 changes were

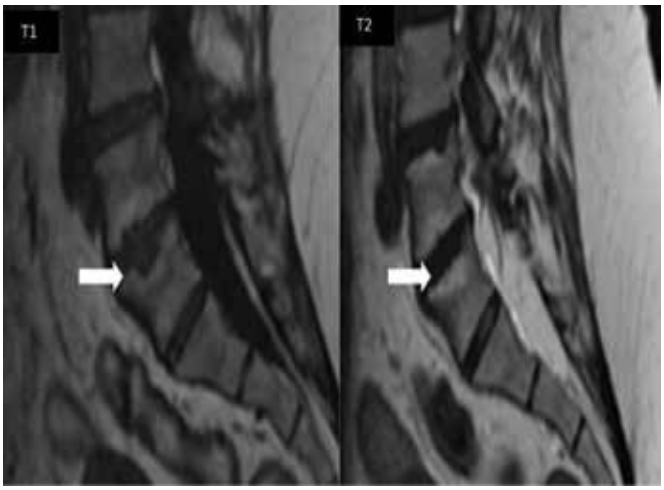

Fig. 2: Modic type 1 change observed in sagittal T1 and T2 sections.

subsequently described as hypointense on both T1WI and T2WI and were thought to represent subchondral bone sclerosis. Mixed-type 1/2 and 2/3 Modic changes have also been reported, suggesting that these changes can convert from one type to another and that they all represent different stages of the same pathologic process. The absence of Modic changes, a normal anatomic appearance, has often been designated as Modic type 0 (20). In the present study, oedema caused by a Romanus lesion or a Schmorl nodule was not included in the Modic classification.

Degree of disc herniation

The herniated disc was subdivided into bulging, subligamentous herniation and extrusion. Bulging was defined as displacement of the disc material greater than 50% of the disc circumference. When disc displacement was less than 50% of the disc circumference, the herniation was regarded as either protrusion (subligamentous herniation) or extrusion. The disc was defined as protrusion if the greatest distance between the edges of the disc material beyond the disc place was less than the distance between the edges of the base in any of the same planes. The extrusion was characterized as a greater diameter of the extruded fragment than of its base in any one plane (21).

Pfirrmann grading system

The degree of disc degeneration was graded on T2-weighted images with a modified Pfirrmann (22) scale as grade 1 (normal shape, no horizontal bands, distinction of nucleus and anulus is clear), grade 2 (non-homogeneous shape with horizontal bands, some blurring between nucleus and anulus), grade 3 (non-homogeneous shape with blurring between nucleus and anulus, anulus shape still recognizable), grade 4 (non-homogeneous shape with hypointensity, anulus shape not intact and distinction between nucleus and anulus impossible, disc height usually decreased; see Fig. 3), and grade 5 (same as grade 4, but collapsed disc space).

Laboratory parameters and disease activity

In order to assess the relationship between disc pathologies observed in lumbar MRI scans and laboratory parameters of patients, average erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values obtained in the previous year were analysed. To explore the association between disease activity and disc degeneration, patients were contacted via phone calls and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) questionnaire was administered to patients during the calls.

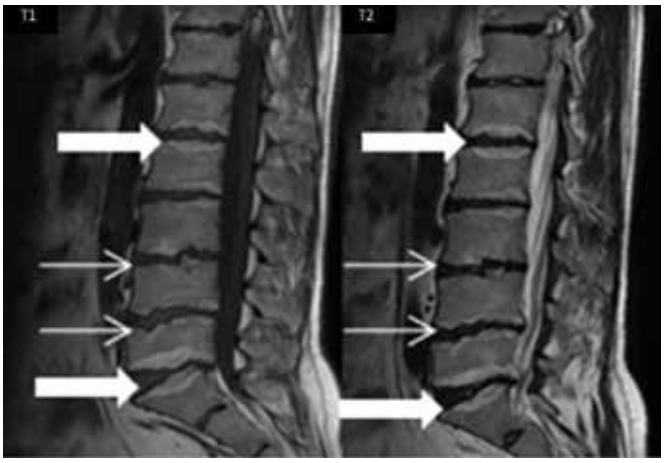

Fig. 3: Pfirrmann grade 4 degeneration (thin arrows) and Modic type 2 change (thick arrows) seen in sagittal T1 and T2 sequences.

Analysis of the prevalence of abnormal findings

The prevalence of the various abnormalities was calculated by disc count (DC) and person count (PC). Disc count is the number of discs, irrespective of the subjects (0–440), and PC is the number of subjects with disc degeneration (0–88).

Statistical analysis

Histogram and q–q plots were examined, and Shapiro–Wilk's test was performed to assess data normality. Values were expressed as frequencies and percentages for categorical variables, and mean and standard deviation or median and minimum–maximum statistics for continuous variables. Spearman's test was used for correlation analysis. Analysis was conducted using R 3.1.1 (www.r-project.org) software. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Of 88 patients enrolled in the study, 38 (43.2%) were females and 50 (56.8%) were males. The mean (±SD) age of study patients was 40.34 ± 9.67 years. Clinical and demographic characteristics of patients are shown in Table 1. Table 2 summarizes the prevalence of Modic changes, disc bulging, protrusion, extrusion and disc degeneration levels in the MR studies. Table 3 shows the association of degenerative disc findings with ESR, CRP and BASDAI score.

Table 1: Patient characteristics

Variable	Statistics
Age (years)	40.34 ± 9.67
Gender	
Male	50 (56.8)
Female	38 (43.2)
Sacroiliac screening	
MRI sacroiliitis	66 (75.0)
Radiographic grade III sacroiliitis	14 (15.9)
Radiographic grade IV sacroiliitis	8 (9.1)
Laboratory values	
ESR	10.25 (2.00–58.00)
CRP	4.80 (3.30–46.40)
BASDAI	5.23 ± 2.12

Values are expressed as n (%), mean ± SD or median (min–max).
MRI = magnetic resonance imaging; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index.

Modic changes

Among 440 discs examined, Modic changes were detected in 13% (PC: 30.7%) but absent in 87% (PC: 64.7%). Modic type 1 change was observed in 13.6% of patients (DC: 3.6%). Modic type 2 was the most common pathologic Modic type affecting 25% of patients (DC: 8.9%). Both Modic type 1 and type 2 changes were observed in 5.7% of patients (DC: 1.1%), whereas Modic type 3 change was present in only 2 out of 440 discs. Modic changes were most commonly detected at L5-S1 disc (DC: 26.1%, 23 discs) with decreasing frequency towards the proximal disc. There was a significant association between Modic changes in L1-L2 and L3-L4 with CRP elevation ($p < 0.05$). Also, a significant relation was observed between Modic changes in L1-L2 disc and BASDAI ($p < 0.05$).

Table 2: Summary of the prevalence of disc bulging, protrusion, extrusion, disc degeneration levels and Modic changes in the MRI studies

Variable	Disc distance					
	L1-L2	L2-L3	L3-L4	L4-L5	L5-S1	Total
Modic						
Normal	82 (93.2)	83 (94.3)	80 (90.9)	73 (83.0)	65 (73.9)	383 (87)
Modic-I	2 (2.3)	1 (1.1)	2 (2.3)	3 (3.4)	8 (9.1)	16 (3.6)
Modic-II	4 (4.5)	4 (4.5)	5 (5.7)	12 (13.6)	14 (15.9)	39 (8.9)
Modic-III	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.1)	2 (0.5)
Pfirrmann						
Pfirrmann-I	70 (79.5)	64 (72.7)	51 (58.0)	34 (38.6)	35 (39.8)	254 (57.7)
Pfirrmann-II	9 (10.2)	15 (17.0)	26 (29.5)	36 (40.9)	26 (29.5)	112 (25.5)
Pfirrmann-III	3 (3.4)	8 (9.1)	8 (9.1)	16 (18.2)	21 (23.9)	56 (12.7)
Pfirrmann-IV	6 (6.8)	1 (1.1)	3 (3.4)	2 (2.3)	6 (6.8)	18 (4.1)
Disc prolapsus						
Normal	84 (95.8)	74 (84.1)	68 (77.3)	41 (46.6)	36 (40.9)	303 (68.9)
Bulging	4 (4.5)	12 (13.6)	17 (19.3)	35 (39.8)	27 (30.7)	95 (21.6)
Protrusion	0 (0.0)	1 (1.1)	3 (3.4)	12 (13.6)	25 (28.4)	41 (9.3)
Extrusion	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Values are expressed as n (%).

Table 3: Spearman correlation coefficients among Modic changes, Pfirrmann scale, disc herniation and ESR, CRP and BASDAI

Variable	Disc distance				
	L1-L2	L2-L3	L3-L4	L4-L5	L5-S1
Modic					
ESR	–0.171	–0.170	–0.074	–0.002	0.086
CRP	0.034	–0.086	0.010	0.149	0.155
Basdai	0.025	0.131	0.141	0.064	0.100
Pfirrmann					
ESR	–0.191	–0.123	–0.119	–0.112	–0.010
CRP	–0.057	–0.099	–0.052	0.063	0.030
BasdaI	0.117	0.219	–0.025	0.343	0.072
Disc prolapsus					
ESR	–0.262	0.082	–0.134	–0.007	–0.018
CRP	–0.129	0.023	–0.001	0.058	–0.128
Basdai	0.022	0.203	0.120	0.264	0.105

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index.

Pfirrmann classification

The most common Pfirrmann change was grade 1 degeneration (DC: 57.7%, 254 discs), followed by grades 2, 3 and 4. None of the patients had grade 5 disc degeneration. Grades 2, 3 and 4 Pfirrmann changes were most frequently detected in L4-L5 and L5-S1 discs with decreasing frequency towards the proximal disc. Pfirrmann grade 4 disc degeneration was greater at L1-L2 and L5-S1 levels compared to other disc levels. L5-S1 disc degeneration showed a significant association with CRP ($p < 0.05$). At other disc levels, Pfirrmann scale did not show any association with ESR, CRP and BASDAI.

Disc herniation

Disc herniation was present in 137 discs out of 440 discs studied (DC: 31.1%, PC: 85.2%). Bulging was the most common form of disc herniation (DC: 21.7%, PC: 67%). Only one patient had disc extrusion, and sequestered discs were not found in any patient. Disc herniation mostly affected L4-L5 and L5-S1 discs with decreasing frequency towards the proximal disc. A positive correlation was found between L1-L2 disc herniation and BASDAI and between L2-L3 disc herniation and CRP ($p < 0.05$).

DISCUSSION

Modic changes

Substantial vertebral pathologies occur in the early and later stages of the disease in AS. This manifests itself clinically as low back pain. We think that degenerative disc disease affects AS patients to a greater extent and has some significance in contributing to low back pain in these patients.

There are several studies in literature that investigated Modic changes in asymptomatic subjects, the general population and patients with degenerative disc disease. A review of these studies revealed that Weishaupt *et al* found Modic type 1 changes in 2% of asymptomatic subjects, Modic type 2 in 7% and all types of Modic changes in 11% (23). In a separate study conducted with an asymptomatic population, Modic type 1 changes were found in 1.35% of the discs and Modic type 2 changes in 6.4% (24). A study on the general population showed that Modic changes were present in 6% of individuals 40 years of age and 9% of individuals 44 years of age (25).

Modic changes were studied more extensively in patients with degenerative disc disease or low back pain in comparison to asymptomatic patients. Modic *et al* studied patients with degenerative disc disease and found that Modic type 1 and 2 changes were present in 4% and 16% of patients, respectively (19). In a degenerative disc disease study by Toyone *et al*, the authors suggested that Modic type 1 changes could coexist with low back pain, whereas Modic type 2 changes could concurrently occur with stable degenerative disc disease (26). Kuisma *et al* showed Modic type 2 changes in 21% of discs in degenerative disc disease and found that Modic changes are a common phenomenon in degenerative disc disease (27). Kjaer *et al* reported a greater incidence of low back pain in a group of patients with both lumbar degenerative disc disease and Modic changes in comparison to the patient group with only degenerative disc disease without any Modic changes (28). This suggests that Modic changes might have a role in the development of low back pain. Although Jarvik *et al* did not identify an association between low back pain and Modic changes (29), other studies suggested that Modic changes might actually be associated with low back pain (27, 30–32). Additionally, in a review of 33 studies involving patients with low back pain, Modic type 2 changes were most commonly detected and a positive correlation between Modic changes and low back pain was demonstrated (33).

Only few studies are available which explored Modic changes in AS. In a 2009 study conducted by Nguyen *et al* that examined endplate degeneration in AS patients, 40 patients with a diagnosis of AS were evaluated for Modic changes. In that study, 15 out of 40 patients were found to have Modic 1 changes (PC: 37%). However, the same study focused specifically on Modic type 1 changes rather than examining other Modic changes individually (14). In the current study, all types of Modic changes (1, 2 and 3) were studied separately, and overall Modic changes were observed in 30.7% of patients. Of these changes, Modic type 1 changes were found in 13.6% (DC: 3.6%, 16 discs) and Modic type 2 in 25% (DC: 8.9%, 39 discs) of study patients. Similar to other study populations, Modic changes were most commonly observed in L4-5 and L5-S1 discs in the present study (27, 34–36).

In our study, the observed prevalence of Modic changes was greater in comparison to the prevalence in studies with asymptomatic patients or general population and similar to studies in patients with low back pain. Previous studies have shown a positive correlation between Modic changes and low back pain. We believe that the high prevalence of Modic changes that we observed in the present study might have significance in contributing to low back pain encountered in AS.

A significant association was found in the present study between Modic changes in L1-L2 and L3-L4 discs with elevated CRP ($p < 0.05$). Also, there was a significant association between Modic changes in L1-L2 disc with BASDAI ($p < 0.05$). This finding led us to think that Modic changes in upper lumbar levels might be correlated with parameters of disease activity. Thus, studies involving thoracic and thoracolumbar regions might be of value to assess the association of Modic changes with disease activity parameters.

Disc herniation

Many studies are available in the literature which examined disc herniation in asymptomatic subjects. Jensen *et al* found bulging in 52% and protrusion in 27% of patients without low back pain (37). Boden *et al* reported bulging and other types of hernia in 20% of patients younger than 60 years of age without low back pain (38). In Weinreb *et al*'s study, the corresponding rate was 54% among asymptomatic female patients (39). In the present study, it was 85.2% (DC: 31.1%). Bulging was identified in 67% (DC 21.7%) and protrusion in 35.2% (DC 9.4%) of our patients. Distribution of disc herniation by disc level was as follows: 4.5% for L1-L2, 15.9% for L2-L3 disc, 22.7% for L3-L4 disc, 52.3% for L4-L5 disc, and 59% for L5-S1 disc. In a study with 200 healthy volunteers, the corresponding rates were 0.5%, 3.5%, 6.5%, 25%, and 35%, respectively (40). Consistent with other studies, disc herniation most commonly affected L4-5 and L5-S1 disc levels in the current study (34, 41).

We did not identify a study that focused on disc herniation in AS patients. In the current study, we found an increased prevalence of disc herniation and specifically bulging in AS patients. We suggest that additional disc pathologies such as Modic changes might aggravate low back pain in AS. Similarly, Albert *et al* stated that disc herniation commonly occurs together with Modic changes and suggested that such coexistence might be closely associated with low back pain (30).

In the current study, a positive correlation was found between L1-L2 disc herniation and BASDAI and between L2-L3 disc herniation and CRP ($p < 0.05$). As with Modic changes, the association between disc herniation and parameters of disease activity was significant at upper lumbar levels. Thus, examination of upper vertebral segments would provide further insight while exploring an association between disc herniation and disease activity parameters.

Pfirrmann disc degeneration

There are few studies in the literature that assessed Pfirrmann disc degeneration. Frequency of disc degeneration varies across these studies. Pfirrmann *et al* evaluated 300 intervertebral discs in order to perform magnetic resonance classification of intervertebral disc degeneration. In that study, grade 1 Pfirrman degeneration was found in 4.6%, grade 2 in 27.3%, grade 3 in 24%, grade 4 in 22.6%, and grade 5 in 21.3% of the discs (22). Corresponding rates were 57.7%, 25.5%, 12.7%, 4.1%, and 0%, respectively, in our study. Takatalo *et al* found grade 3–5 disc degeneration in 13.4% of the discs in young patients with mechanical low back pain (34). We did not identify a study that specifically explored Pfirrmann disc degeneration in AS. We believe that further studies are needed to have a clear understanding of the link between AS and Pfirrmann disc degeneration.

CONCLUSION

In the present study, we observed a high prevalence of Modic type 2 changes and bulging herniation in AS patients. We think that this might contribute to low back pain observed in AS. Also, Modic changes and disc herniation in upper lumbar levels were positively correlated with parameters of disease activity. Thus, studies involving the thoracic spine would be of value to assess the association of degenerative disc disease with disease activity parameters. In conclusion, the present study might provide some insight for degenerative disc disease in AS. However, there is a need for studies involving the entire spine with a larger number of patients and a control group.

LIMITATION TO THE STUDY

The major limitation of the present study is the absence of a control group.

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ORIGINAL ARTICLE

Investigation of Post-operative Recovery State of Lumbar Spinal Stenosis Patients: A Single Centre Experience

F Altinel[1], ÖA Öztürkeri[2], GÖ Söylev[3], C Altin[4]

ABSTRACT

Objective: *To investigate the changes and improvement in neurological symptoms of post-operative period lumbar spinal stenosis (LSS) and lumbar disc herniation (LDH) patients and discover pathognomonic radiological features.*

Methods: *Forty-four LSS and 37 LDH patients with mean age of 58.70 ± 14.58 (24–81) that have undergone decompressive laminectomy, posterior lumbar stabilization or lumbar micro-discectomy were enrolled. Patients' demographic data and pre- and post-operative neurological symptoms analysed with the Japanese Orthopaedic Association (JOA) scale were recorded and compared with the magnetic resonance imaging (MRI) results. We have measured from the patients' MRI images of axial sections before a decision of surgery. We have also evaluated and graded the protrusion degrees of herniated discs in the sagittal plane of MRI. The transverse interpedicular diameter (TIP), midline antero-posterior (M-AP), interfacet (IF) values and JOA scale were compared between LDH and LSS.*

Results: *All measured osteal body diameter mean values (TIP, M-AP, IF) in LSS were less than the LDH group. Only IF mean values were shown to be statistically significant (*$p < 0.004$*). Sagittal disc section measurements were not statistically significant for LSS and LDH (*$p < 0.182$*). The pre- and post-surgery JOA score mean values of the LDH were higher than the LSS group (*$p < 0.005$*). The lumbar microsurgery discectomy recovery rate was higher than the posterior segmental instrumentation.*

Conclusion: *The TIP, M-AP, IF diameters decreased with age, which was the main pathological mechanism of LSS development. This suggests that the degenerative process of the narrowing spinal canal, which increases with age, is responsible for LSS presentation. Lumbar spinal stenosis (LSS) has a relationship with facet arthropathy over other parameters.*

Keywords: Decompressive laminectomy, lumbar discectomy, lumbar spinal stenosis

INTRODUCTION

Lumbar spinal stenosis (LSS) and lumbar disc herniation (LDH) patients have a broad spectrum of clinical symptoms, such as back pain, lower extremity paraesthesia, numbness, motor disability, bladder and rectum dysfunction. The main pathology of LSS is the irreversible degenerative changes in lumbosacral nerve roots due to compression of the neural and foraminal canals. On the other hand, patients with lumbar disc herniation can also present similar clinical symptoms. The pathology predominantly is the protrusion of a herniated disc to the spinal canal. The signs and symptoms of central canal stenosis resemble cauda equina syndrome. Lateral recess stenosis can be presented by unilateral or bilateral radiculopathy, which suggests herniated disc syndrome. Lumbar spinal stenosis is one of the most frequent indications for spinal surgery of people over 60 years old, and this is due to the degeneration of the spinal structure. Lumbar spinal stenosis (LSS) can be caused mainly by degenerative or congenital factors separately or together (5). Although

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congenital (developmental) stenosis is rare, degenerative (acquired) stenosis is very frequent. In the latest literature, Abbas *et al* (1) reported that in LSS patients, the vertebral objects and canals have smaller diameters than normal; therefore stenosis can be characterized by short pedicles and narrowing of the spinal canal dimensions. They also mentioned that both genetic factors and degenerative changes play a role in the LSS development (1).

There are many studies focused on the mechanisms for the development of LSS and LDH. Ligamentum flavum hypertrophy, degenerative changes in the intervertebral discs and decrease of the antero-posterior diameter of the spinal canal have been suspected so far. In this study, we investigate the diameters of the posterior bone structure (transverse interpedicular diameter [TIP], interfacet [IF], midline antero-posterior [M-AP]). Normal and abnormal values of spinal canal diameter and diameters of its pathologies have been established by various anatomical, radiological, surgical observations. Although measurements can differ between computed tomography (CT) and magnetic resonance imaging (MRI) techniques, a specific range to determine normal and borderline values has been used. The ranges used in this study on axial section of lumbar MRI are: 20–30 mm transverse interpedicular diameter (TIP), 15–25 mm midline antero-posterior (M-AP), 10–20 mm interfacet (IF), 3–5 mm pedicular height (PH) and 5–8 mm superior facet height (SFH). The posterior protrusion into the spinal canal at the sagittal sections can be defined as normal range (1 mm), slight protrusion (2 mm), mild protrusion (3 mm), moderate protrusion (5 mm) and severe protrusion (6 mm). This is used for the grading system in order to evaluate LSS using CT and MRI measurement techniques (Fig. 1).

In LSS patients, pedicle and lamina is short and thick, which makes the facet slide into the midline and base of the spinal canal. Posterior bony structure has a triangular shape rather than circular and its diameter is smaller than normal. In these patients, midline antero-posterior diameter is smaller than 12 mm and also lateral recess and foraminal diameter is smaller than 4 mm (15) (Fig. 2).

Figure 2 shows angular-edged LSS deformity at spinal canal L4-5 level.

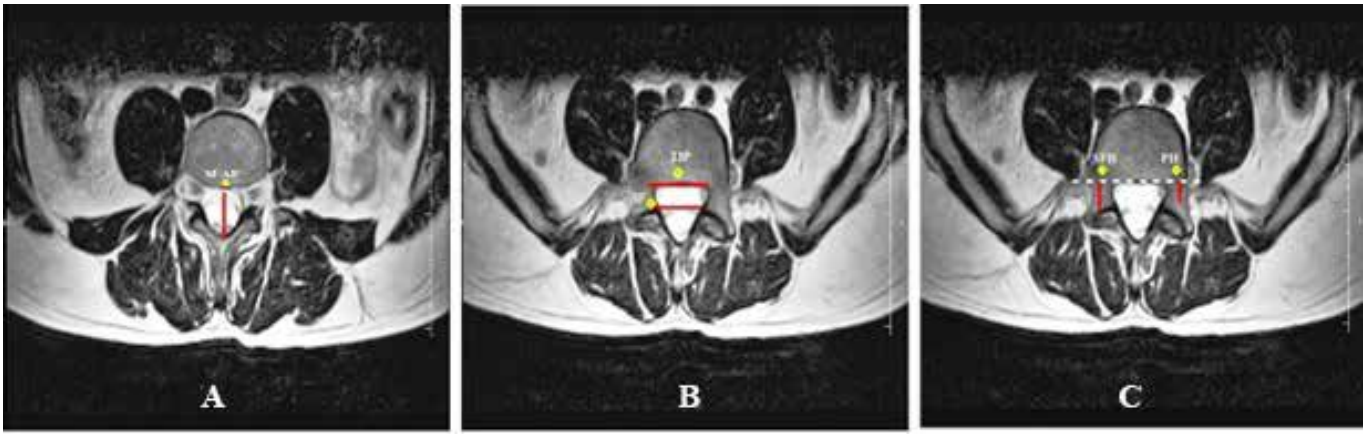

Fig. 1: Measurements of axial sections of spinal canal.
(A) M-AP = midline A-P diameter. (B) TIP = transverse interpedicular diameter; IF = interfacet diameter. (C) SFH = superior facet height; PH, pedicle height.

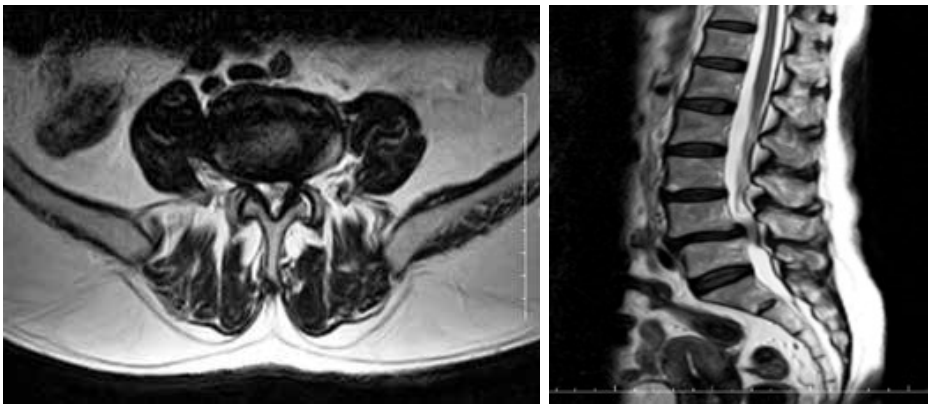

Fig. 2: Axial and sagittal sections of stenotic neural canal at L4-5 level.

Zheng *et al* (21) and Singh *et al* (12) evaluated the AP diameter of congenital and degenerative LSS compared with a control group. They thought that the pedicle length and vertebral body width in LSS was decreased, in the meanwhile, AP diameter of vertebral body and body height did not differ when it was compared with the controls. Therefore, we mainly focussed on the spinal canal diameter measurements in our study.

SUBJECTS AND METHODS

This study was performed on 81 patients that were treated in the Zubeyde Hanim Hospital's Neurosurgery, Physical Therapy and Rehabilitation and Neurology Clinics, Baskent University between the years 2011 and 2013. After a cardiological examination, operations were performed on ASAPS category I-III patients. Medical histories of all patients were taken, and they were subjected to a neurological examination before and after surgery. The results were evaluated and compared by the Japanese Orthopaedic Association (JOA) scale and post-operative recovery rates were determined as percentages. Images were reviewed by the two independent investigators (radiologist and neurosurgeon).

Demographic parameters such as age and gender were recorded. Antero-posterior radiographs of all patients were taken before and after the surgery, lateral hyperflexion and hyperextension positions. PACS software and PACS workstation were used for measurements of posterior protrusion values of herniated disc levels in sagittal sections of lumbar vertebra and also measurements of TIP, M-AP, IF in axial sections.

In our trial, 44 patients have undergone decompressive laminectomy, posterior segmental instrumentation surgery or unilateral laminotomy bilateral decompression. Thirty-seven patients have undergone lumbar microdiscectomy surgery.

Statistical analysis

SPSS for windows version 17.0 (SPSS. Inc., Chicago, IL, USA) was used for all analyses. The Student *t*-test was used to compare age, JOA scores and bone canal measurements data between the groups. Pearson's correlation was used to determine pre- and post-surgery JOA scores between the groups. p-value < 0.05 was considered statistically significant.

The factors of age, gender ratio, initial and 6–12 months JOA score were compared between the two groups LSS and LDH, using the Student *t*-test. The TIP, M-AP and IF values of LSS and LDH were compared with the *t*-test.

RESULTS

Baseline clinical symptoms of patients in our study group are reported in Table 1.

Table 1: Baseline clinical symptoms of patients

Patient group (%)	LDH (n = 37)	LSS (n = 44)
Back pain	97	82
Leg pain	91	79
Lower extremity motor disability	8	18
Numbness	5	14
Urinary dysfunction	2	9
Gait disturbance	2	14
Neurogenic claudication	16	52

LDH = lumbar disc herniation; LSS = lumbar spinal stenosis.

All measured osteal body diameter mean values (TIP, M-AP, IF) in LSS were less than the LDH group. The TIP, M-AP, IF values on both the LDH and LSS were compared. The IF mean values were shown to be statistically significant ($p < 0.004$). Sagittal disc section measurements were not statistically significant for LSS and LDH ($p < 0.182$). The pre- and post-surgery JOA score mean values of the LDH was higher than the LSS group ($p < 0.005$). The recovery ratio of 6–12 months after the surgery and JOA score were higher in the LDH group ($p < 0.001$). According to the surgical procedures, the lumbar microsurgery discectomy recovery rate was higher than the posterior segmental instrumentation. Surgical recovery rates in LDH and LSS patients were not statistically significant according to the gender parameter ($p < 0.93$) (Table 2 and Fig. 3).

Table 2: Characteristics of 81 patients with JOA scores and spinal canal diameters

Variable	LDH group n = 37	LSS group n = 44	*p*-value
Age	50.1 ± 14.7	66.0 ± 9.8	0.005
TIP (mm)	20.2 ± 4.0	16.4 ± 3.7	0.787
M-AP (mm)	14.5 ± 2.8	12.9 ± 2.9	0.442
IF (mm)	16.5 ± 4.1	12.6 ± 2.9	0.004
Sagittal disc plane	6.6 ± 1.8	6.2 ± 1.2	0.182
JOA (Pre-op)	7.0 ± 1.7	6.2 ± 2.9	0.005
JOA (6–12 months)	14.5 ± 1.0	13.1 ± 2.1	0.004
JOA recovery rate (%)	93.4 ± 12.1	77.7 ± 23.0	0.001

IF = interfacet; LDH = lumbar disc herniation; LSS = lumbar spinal stenosis; M-AP = midline antero-posterior; TIP = transverse interpedicular diameter.

Comparison of age and bony structure diameter (Pearson correlation: −0.547, $p < 0.001$) showed that MIP, TIP,

IF values decreased as the age increased. According to these data, the spinal canal diameter was narrower in the LSS compared to the LDH (TIP: −0.513; M-AP: −0.352; IF: −0.573). It was noticed that LSS was seen more frequently in older age compared to LDH, which suggests that a degenerative process is the main factor in LSS.

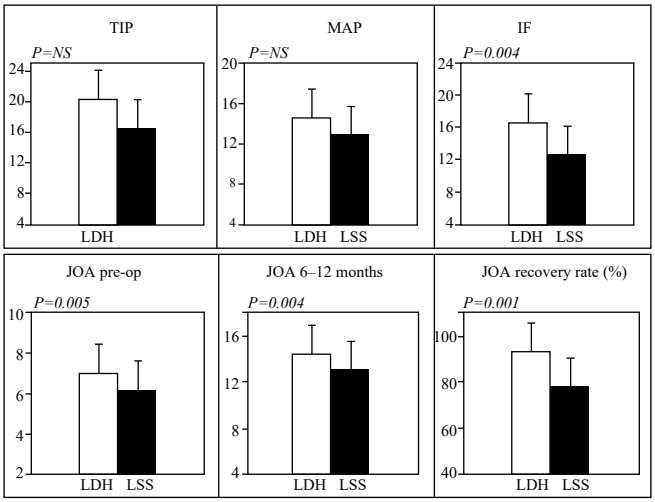

Fig. 3: Comparison of spinal canal diameters and JOA scores between the LDH and the LSS group patients.

DISCUSSION

Lumbar spinal stenosis is a condition that has different presentations due to the reduction of the total area of spinal canal, lateral recess or neural foramina (3, 7). Stenosis develops due to disc degeneration in intervertebral connection points, facet arthropathy, ligamentum flavum hypertrophy, spondylosis and sometimes due to the complex process of spondylolisthesis (9, 11). Neurological claudication is the most frequent indication for the spinal surgery in individuals diagnosed with lumbar spinal stenosis over 60 years (2, 6, 13).

The degenerative form of LSS is often limited to a single level of spine, particularly L4-5 (4, 10). In contrast, the developmental form can be seen in several levels of the spine. In our study, the MRI sections showed that the pathological narrowing of spinal canal is seen mostly at L4-5 in the symptomatic patients.

Previous researches indicate that the rate of lumbar spinal stenosis does not change with gender or race. On the other hand, there is the literature that shows degenerative LSS is seen at a higher rate with people over 60 and the rate increases with older age (11). Our study also showed no correlation with gender and there was an increase in the LSS rate with age. Disc degeneration develops by age and the main factor in degenerative LSS is the combination of other pathologies with disc degeneration. Kirkaldy-Willis *et al* (8) defined the triple joint complex that occurs in the vertebral disc, upper and lower vertebral body and facet joints.

Any change that occurs between the components of this complex affects one another by time. If these changes are severe, they will result in a narrowing of the canal followed by the presentation of clinical symptoms of spinal stenosis. In the current study, we observed that the mean values of TIP, M-AP and IF were less than the LDH with LSS. However, only the IF values were significant to distinguish LDH and LSS ($p < 0.04$); TIP and M-AP values were not statistically significant. These data suggest us that degenerative LSS has a preferential relationship with facet arthropathy over other parameters. The deformity of spinal canal from ovoid to angular-edged formed by degeneration of facet basis and ligamentum flavum hypertrophy can be explained by the decrease in interfacet diameter, which is the main predictor of degenerative LSS in our study.

Neurological symptoms due to compression of dural sac have appeared gradually by the time. Similarly, although lumbar disc herniation and the presence of spondylolisthesis seem like causing the development of lumbar spinal stenosis, clinically and radiologically. Sagittal disc section and protruded disc measurements were not statistically significant ($p < 0.182$) in the current study.

In many studies including Abbas *et al* (1), spinal canal measurements were made by the computerized tomography. However, in our study, ligamentum flavum hypertrophy in narrow spinal canal was also taken under consideration for that reason MRI was used for all measurements (1). Currently, MRI has a better spatial resolution and capacity to show soft tissue changes such as ligamentum flavum, disc herniation, *etc*. Pre-operative MRI variables and surgical outcomes of patients were compared in a study in which two groups had no difference, according to the degree of disc degeneration, foraminal stenosis, facet arthrosis and presence of listhesis ($p < 0.05$) (2). We also considered the proposal regarding correlation between the surgical outcome and post-operative imaging (MRI or CT scans) of surgically treated LSS patients, however, in our study, post-operative imaging was based on the radiography. It would be better for future research to consider comparisons between the parameters of post-operative surgical, clinic and imaging changes.

In our study, there were 18 patients with L4-5 level, 14 patients with L5-S1 level, 4 patients with L3-4 level

and 1 patient with L2-3 level disc hernia and also 30 of the total 81 patients had listhesis. Six patients were diagnosed with LSS with listhesis at L2-3, L3-4; 18 patients at L4-5; 6 patients at L5-S1. Thirty-seven of these patients had undergone lumbar microdiscectomy and 36 of 44 patients had decompressive laminectomy posterior segmental instrumentation performed and 8 of them had unilateral laminotomy bilateral decompression by the microsurgical technique. In LSS surgery, positive results are reported at 80% (16, 17). However, in many studies, early- and mid-term results are good, however, in long-term follow-up, results deteriorate and re-stenosis can develop over time (18, 20, 22). In our study, observations on improvement were made during the post-operative 12 months. We believe that further studies should collect data over a longer term. Turner *et al* (14) investigated long-term results after decompression surgery and reported 64% positive results. They also reported that the presence of a degenerative spondylolisthesis improves the positive result of the surgery to 85%. It was shown in our study that clinical outcomes of LDH were better than LSS statistically. Also, we have a 37% existence of spondylolisthesis which supports that degenerative listhesis is a factor in the LSS development.

In Yamashita *et al*'s study (19), older and younger patients had similar clinical courses during their observation after the surgery. However, older patients got worse to a significant extent after 6 months of follow-up (19). This study shows us that degenerative processes and neuroischaemic changes in advanced age are a predictive factor for prognosis.

Investigating the morphometric characteristics of the lumbar vertebrae in degenerative lumbar spinal stenosis patients can help to establish a more complete model for the degenerative LSS pathophysiology and aetiology. This can further help in developing useful treatments and improvement of surgery. Furthermore, the detection of specific features in an asymptomatic population can be important in prevention or the delay of the symptoms.

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ORIGINAL ARTICLE

2:1 Block with Wenckebach Mechanism in Children due to Different Etiologies

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ABSTRACT

Objective: *In children, 2:1 atrioventricular block (AVB) with Wenckebach mechanism is a rare entity.*

Methods: *In seven children, 2:1 AVB with Wenckebach mechanism was detected. The clinical features of these children were retrospectively evaluated.*

Results: *All the patients were asymptomatic. In all, concomitant first-degree atrioventricular (AV) block and/or periodic AV Wenckebach block suggested the presence of 2:1 block with Wenckebach mechanism. In three patients, this conclusion was supported by the demonstration of improved AV conduction with enhanced sinus rates during treadmill test or atropine administration. In two of the patients, intracardiac electrophysiological was performed and showed a prolonged atrium-His interval. Four patients had congenital or acquired heart disease. During a median follow-up duration of 14.4 months, no significant event was observed.*

Conclusion: *In children, 2:1 AV block with Wenckebach mechanism seems a relatively benign process.*

Keywords: 2:1 Atrioventricular block, bradycardia, children, Wenckebach.

INTRODUCTION

In 2:1 atrioventricular block (AVB), a ventricular complex follows every second atrial complex. The atrial rate (the time between the onset of consecutive P waves interval) and the P wave to R wave interval interval of the conducted beat are normal. It is usually due to Mobitz I mechanism (block in the atrioventricular [AV] node) (1). Although the occurrence of 2:1 block due to Mobitz I mechanism had been reported in adults (2), no study on children had been reported. In this paper, we reported our experiences with seven children with 2:1 AVB due to Mobitz I mechanism.

SUBJECTS AND METHODS

The databases of the division of Pediatric Cardiology were analysed and the list of the children with a diagnosis of 2:1 AVB due to Mobitz I mechanism was found. The clinical characteristics of the children were analysed retrospectively in terms of their demographic features, present diseases, clinical presentations, diagnostic methods and follow-up results.

RESULTS

A total of seven children were found to be diagnosed as having 2:1 AVB due to Mobitz I mechanism. Their median age at diagnosis was 2.5 ± 4.8 years (range 2.5–15 years). All but one was female. The individual clinical characteristics of the patients are given in Table 1. In two of the patients, electrophysiological study was performed (Table 2).

Four patients were referred to our clinic for different reasons: evaluation for low heart rate detected during examination (n = 2), easy fatigability (n = 1), Mobitz type II AVB in Holter recording (n = 1), and first attack of acute rheumatic fever (ARF) (n = 1). Two patients were diagnosed on follow-up evaluations for rheumatic heart disease (n = 1) and previous cardiac surgery (n = 1), and 2:1 AV block was detected on the first admission in six patients, on the postoperative sixth month control in one

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Table 1: Individual clinical characteristics of the patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age at diagnosis (Y)	3	7	15	13	2, 5	5	7
Gender	F	M	F	F	F	F	F
Clinical presentation	Low heart rate	Routine control for operated VSD + ASD	Arthritis	Routine control for RHD	Fatigue, murmur	2:1AVB in ECG	Low heart rate
Echocardiography	Normal	Operated VSD + ASD	ARF, aortic and mitral regurgitation	RHD, aortic and mitral regurgitation	Normal	Mild valvular pulmonary stenosis	Normal
Electrocardiography	FDAVB	RBBB	FDAVB	FDAVB	2:1AVB	FDAVB	WB + 2:1 AVB
24-hour ECG monitorisation	FDAVB + WB + 2:1 AVB	WB + 2:1 AVB	FDAVB + WB + 2:1 AVB	FDAVB + WB + 2:1 AVB	FDAVB + WB+ 2:1 AVB	FDAVB + WB+ 2:1 AVB	FDAVB + WB + 2:1 AVB
Follow-up duration (Mo = months)	9.7	14.4	38.1	66.8	No follow-up	No follow-up	11.7
Electrophysiological study	Available	Available	NA	NA	NA	NA	NA

Y = years; F = female; M = male; VSD = ventricular septal defect; ASD = atrial septal defect; RHD = rheumatic heart disease; AVB = atrioventricular block; ECG = electrocardiography; ARF = acute rheumatic fever; FDAVB = first-degree atrioventricular block; RBBB = right bundle branch block; WB = Wenckebach block; NA=not available.

Table 2: Electrophysiological study's results in two patients

Patient no.	AV node Wenckebach point (ms)	AH interval (ms)	HV interval (ms)
1	300	156	30
2	570	128	50

AV = atrioventricular; AH = atrial-His; HV = His-ventricular.

(Pt 2) and on the sixth month control after the first attack of ARF in one (Pt 4) patient.

Electrocardiography and Holter findings at the diagnosis of 2:1 AVB are given in Table 3. 2:1 AVB was present in the surface ECG in two patients and in Holter recordings in all the patients. In one patient (Pt 3), non-sustained 2:1 AVB episode was detected on Holter recording that was applied for a study (3). In all the remaining patients, longer periods of 2:1 AVB episodes were present in Holter recordings. No pauses longer than 2 seconds were detected.

In three patients, 1:1 AV conduction was observed during the advanced stages of treadmill test (with narrow QRS in two, and with wide QRS due to postoperative right bundle branch block in one). In one patient with sustained 2:1 block, AV conduction returned to 1:1 conduction after atropine administration. In the remaining three patients, any test for the evaluation of AV conduction during increased heart rate was not available (due to the short attack of 2:1 AVB in one, and very short investigation period in two patients).

In two patients, control follow-up visits were not available. In the remaining five patients, the median follow-up period was 14.4 months. During this period, no

Table 3: Electrocardiography and Holter findings from the diagnosis of 2:1 atrioventricular block

Patient no.	Surface electrocardiography		Holter	
		Rhythm	SDNN	Longest RR
1	FDAVB	FDAVB, Wenckebach block, 2:1 AVB	67	1429
2	NSR, RBBB	Wenckebach block, 2:1 AVB	278	2000
3	NORMAL	Wenckebach block, 2:1 AVB	57	1070
4	FDAVB	FDAVB, Wenckebach block, 2:1 AVB	101	1640
5	2:1 AVB	FDAVB, Wenckebach block, 2:1 AVB	115	1671
6	FDAVB	FDAVB, Wenckebach block, 2:1 AVB	100	1500
7	Wenckebach block, 2:1 AVB	FDAVB, Wenckebach block, 2:1 AVB	306	1980

SDNN = standard deviation of NN intervals; FDAVB = first degree atrioventricular block; AVB = atrioventricular block; NSR = normal sinus rhythm; RBBB = right bundle branch block.

new 2:1 AVB episodes were observed in repeated Holter recordings in two patients. In one, only first degree AVB and Wenckebach block episodes were observed. In two patients, sustained 2:1 AVB episodes were continued. None of the patients had new and significant symptoms.

DISCUSSION

Mobitz Type I second degree AVB (Wenckebach block or phenomenon) is generally a benign AV conduction problem, and there is a progressive lengthening of the PR interval culminating in a dropped ventricular beat (1).

Mobitz Type II second degree AVB is usually caused by the conduction block within the His-Purkinje system. This conduction abnormality is shown on the ECG as a sudden failure of a P wave to conduct to the ventricle, with no change in the PR interval either before or after the non-conducted P wave (4).

In 2:1 AVB, a ventricular complex follows every second atrial complex. The atrial rate and the PR interval of the conducted beat are normal. These are usually due to Mobitz I mechanism (block in AV node), particularly when associated with normal QRS complexes, but His bundle recording may be necessary to determine whether the block occurs in the upper AV node or at the level of His bundle, in occasional cases (1). Diagnostic clues to the site of block include the following: concomitant first-degree AV block, periodic AV Wenckebach, or improved conduction (1:1) with enhanced sinus rates of sympathetic input suggesting a more proximal interruption of conduction (*ie*, Mobitz type I mechanism); concomitant bundle-branch block, fascicular block, worsened conduction (3:1, 4:1, *etc*) with enhanced sympathetic input localized the site of the block more distally (Mobitz type II mechanism) (5).

In all of our patients, concomitant first-degree AV block and/or periodic AV Wenckebach block suggested the presence of 2:1 block with Wenckebach mechanism. In three patients, this conclusion was supported by the demonstration of improved AV conduction (1:1) with enhanced sinus rates during the treadmill test or atropine administration.

In two of our patients, the 2:1 AVB was sustained, and one had a previous cardiac surgery with complete RBBB. In these patients, the intracardiac electrophysiological study suggested the presence of a suprahisian conduction delay. In the electrophysiological study, normal atrial-His (AH) interval values in children ranged from 50 to 120 milliseconds, and normal His-ventricular (HV) interval values ranged from 25 to 50 milliseconds. A prolonged AH interval indicated a conduction delay in the AV node, and a prolonged HV interval suggested a conduction delay in the His-Purkinje system (6). In our patients, AH intervals were 150 and 128 milliseconds. We could not find any information about the prognosis of 2:1 AVB with Wenckebach mechanism in children. Our limited data suggested a good prognosis for these patients at least during the mid-term follow-up.

CONCLUSION

The findings of the study suggested that the clues indicating a Wenckebach mechanism in children with 2:1 AVB could be obtained by noninvasive techniques. In children with sustained 2:1 AVB intracardiac electrophysiological study could help the differentiation, and the prognosis seemed good.

AUTHORS' NOTE

Concept—NC, HO; design—HK, FL; supervision—NC; materials—HO; data collection and/or processing—HK, FL; analysis and/or interpretation—NC; literature search—NC; writing manuscript—NC; critical reviews—NC, HO.

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ORIGINAL ARTICLE

Epidemiology and Factors Associated with Mortality among Haitian Children and Adolescents Treated for Cancer at a Paediatric Hospital from 2010 to 2014

JG Lucien, JJ Bernard

ABSTRACT

Objective: *Paediatric cancers represent about 1% of all diagnosed cancers around the world (1). This study aimed to describe the epidemiology and to determine the factors associated with mortality of paediatric cancers managed at a Haitian Paediatric Hospital.*

Methods: *This was a cross-sectional study on the cases of paediatric cancers admitted in the St Damien Hospital (SDH) in Haiti from 2010 to 2014. The cancers were studied according to the age (0–17 years old), the gender, the geographic origin, the cancer type, the type of treatment and the therapeutic outcome. The study evaluated whether gender, age group, department of origin, type of cancer, type of treatment, occurrence of relapse or a complication was significantly associated with mortality among this population.*

Results: *One hundred and thirty-nine cases of paediatric cancers (77 males and 62 females) were admitted. The prevalence of cancers was 0.76% (95% CI: 0.64%, 0.89%). Eleven different types of cancers were diagnosed, and the most common ones were the leukaemias (30.93%), renal tumours/Wilms tumour (30.93%), retinoblastoma (15.11%), sarcomas (6.47%) and lymphomas (5.04%). More than 50% of the children with cancer were less than 5 years of age. The cure rate was 74.1%, the relapse rate was 15.1% and the overall mortality rate was 25.9%. The odds of dying were significantly higher in children with blood cancers (Odds Ratio [OR] = 2.2;* $p = 0.04$*), with relapse (OR = 127.5;* $p < 0.01$*) or a complication (OR = 5.5;* $p < 0.01$*).*

Conclusion: *Paediatric cancer care needs to be improved in Haiti, especially for blood cancers, in order to reduce relapse, complications and mortality.*

Keywords: Epidemiology, Haiti, mortality, paediatric cancer, risk factors

INTRODUCTION

Paediatric cancers are rare and represent about 1% of all cancers diagnosed worldwide (1). Several types of childhood cancers have been reported worldwide varying by age, gender, ethnicity and geographic location. Numerous studies have provided important insights in the epidemiology and aetiology of childhood cancers (2, 4, 8). Contrarily to adult cancers that are classified by topography (site) according to the International Classification of Disease for Oncology (ICDO), neoplasms in children are classified by morphology (histology) according to the International Classification of Childhood Cancer (ICCC) (2).

The exact cause of most paediatric cancers are unknown. Oncogenic mutations, lifestyle and environmental factors involved in the development of many adult cancers are probably not responsible for childhood malignancies, as these factors require a long period of time to provoke sufficient DNA damage and trigger oncogenesis (3, 4). Childhood malignancies have, however, been associated with constitutional molecular defects found in diseases such as Beckwith-Wiedemann syndrome and Down syndrome and hereditary conditions such as Li-Fraumeni syndrome. They were indeed shown to be involved in the development of embryonic

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cancers, leukaemias, brain tumours, osteosarcoma and rhabdomyosarcoma (4–6).

The leukaemias and the central nervous system (CNS) tumours are the most common diagnosed cancers among the children around the world (2, 4, 7). According to the North American Association of Central Cancer Registries (NAACCR), the death rates for all childhood and adolescent cancers combined have considerably declined in the last 30 years (1). In the United States, cancer is the second cause of all cause-related deaths in children, and it is the first cause of disease-related deaths. The diagnosis and management of cancer pose an even greater burden on developing countries than for the industrialized countries (7). Resource-limited countries like Haiti cannot afford the modern techniques of diagnostics and treatment.

Haiti is the only low-income country in the American hemisphere with an overwhelmed medical system. Although childhood cancer is a public health issue around the world, its current status in Haiti is not well known. There are very few physicians who are trained in the management of paediatric cancers, and no national cancer registry is available. This study aimed to evaluate the epidemiology of childhood cancers in Haiti, and to determine the factors associated with mortality among the cases diagnosed and managed at a Haitian Paediatric Hospital.

SUBJECTS AND METHODS

This was a cross-sectional study on the cases of paediatric cancers admitted and managed in the Oncology Department of St Damien Hospital (SDH), in Port-au Prince, Haiti, from January 2010 to December 2014. The study included all children and adolescents with a clinically or histologically confirmed diagnosis of malignancy, while those diagnosed with benign tumors were excluded. The cases were divided into blood cancers and solid cancers. Following approval from the Medical Director of the SDH and the Head of the Oncology Department, a comprehensive review of medical charts was conducted. Relevant data were extracted on key variables, including age, gender, geographic region, cancer type, type of treatment, and therapeutic outcomes. The number of diagnosed cases, relapses and deaths related to cancer were evaluated for each year of the study period. A Statistical analysis was conducted using Epi Info version 7.1.0. The study assessed whether variables such as gender, age group, geographical region, type of treatment received, cancer type (solid vs blood tumour), and the occurrence of complications or relapse were associated with mortality in the study population, using odds ratios (OR) as the measure of association. The Mantel-Haenszel chi-square test was employed to evaluate the statistical significance of these associations. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Overall study

The chart review found 139 cases of cancer out of 18,376 admissions during the study period, which gave a cancer prevalence of 0.76% (95% CI: 0.64%, 0.89%). Table 1 presents the descriptive characteristics of the study sample (N = 139). Males comprised 55.4% of the participants, and the largest age group was 1–4 years, representing 47.5% of the sample. The mean age was 5.14 years. The majority of participants (77.1%) originated from the West region and over half of the diagnosed children were under the age of five.

Types of paediatric cancers

Figure 1 summarizes the types of paediatric cancers diagnosed during the study period. Solid cancers (64.03%) and blood cancers (35.97%) accounted for the diagnosed cancer cases. The five most common ones were leukaemias (30.93%), renal tumours/Wilms tumour (30.93%), retinoblastoma (15.10%), sarcomas (6.47%) and lymphomas (5.04%). Renal tumours/Wilms tumour, retinoblastoma and sarcomas were the most common solid cancers diagnosed. Among the blood cancers, acute lymphoblastic leukaemia (ALL) was the most common followed by acute myeloid leukaemia (AML), Hodgkin's lymphoma (HL) and Burkitt's lymphoma (BL).

Management and outcome

All diagnosed patients received at least one or a combination of the three types of treatments such as chemotherapy, surgery and radiotherapy. The solid cancers were responsible for 52.0% of all recorded relapses and 50.0% of all diagnosed deaths. The overall relapse rate was 15.1%, and it was by far dominated by the leukaemias (38.1%), renal tumours/Wilms tumour (28.6%), retinoblastoma (19%) and lymphomas (10%). Twenty of the Twenty-one relapse cases died during the study period. Children under 10 years of age experienced higher mortality rates. A total of 36 children died during the study period, resulting in an overall mortality rate of 25.9%. The highest mortality was observed among patients with leukemia (44.4%) and those with renal

Table 1: Baseline characteristics of the children and adolescents treated for cancer at the St Damien Hospital from 2010 to 2014 (N = 139)

Variables	Frequencies	Proportions (%)	95% CI
Gender	Male (77)	55.4%	46.7%, 63.8%
	Female (62)	44.6%	36.2%, 53.3%
Age	< 1 year old (8)	5.8%	2.5%, 11.0%
	1–4 years old (66)	47.5%	39%, 56.1%
	5–9 years old (41)	29.5%	22.1%, 37.9%
	10–17 years old (24)	17.3%	11.4%, 24.6%
Department of origin	West (99)	71.2%	63.5%, 79.1%
	Artibonite (8)	5.8%	2.5%, 11.1%
	North (6)	4.3%	1.6%, 9.2%
	Southeast (6)	4.3%	1.6%, 9.2%
	Nippes (5)	3.6%	1.2%, 8.3%
	Northwest (5)	3.6%	1.2%, 8.3%
	Center (3)	2.2%	0.5%, 6.2%
	South (3)	2.2%	0.5%, 6.2%
	Grand-Anse (2)	1.4%	0.2%, 5.1%
	Northeast (1)	0.7%	0%, 4%
Type of treatment	**Solid cancers (89):**		
	Chemotherapy only (29)	20.9%	14.4%, 28.2%
	Surgery only (6)	4.3%	1.6%, 9.2%
	Chemotherapy + surgery (35)	25.2%	18.2%, 33.2%
	Chemotherapy + radiation (4)	2.9%	0.8%, 7.2%
	Chemotherapy + surgery + radiation (15)	10.8%	6.2%, 17.2%
	Blood cell cancers (50):		
	Chemotherapy only (43)	30.9%	23.4%, 39.3%
	Chemotherapy + radiation (4)	2.9%	0.8%, 7.2%
	Chemotherapy + surgery (3)	2.2%	0.4%, 6.2%
Relapse	Yes (21)	15.1%	9.6%, 22.7%
	No (118)	84.9%	77.8%, 90.4%
Complications	Yes (68)	48.9%	40.4%, 57.5%
	No (71)	51.1%	42.5%, 59.7%
Death	Yes (36)	25.9%	18.9%, 34.0%
	No (103)	74.1%	66%, 81.2%

tumors/Wilms tumor (27.8%). Complications occurred in 48% of cases, with infection being the most common, affecting 27.34% of patients. Among the 36 deceased patients, 28 (77.8%) had at least one complication (Figure 1).

Factors associated with mortality

Cancer type, gender, age group, type of treatment, department of origin, and the occurrence of relapse or complications were evaluated to determine whether they were significantly associated with mortality (Table 2). The odds of mortality were significantly higher among children and adolescents with blood cancers compared to those with solid cancers (OR = 2.2; $p = 0.04$); A significantly increased risk of death was also observed among patients who experienced complications (OR = 5.5; $p < 0.01$) and those who relapsed (OR = 127.5; $p < 0.01$). Although male patients represented the majority of the sample, their odds of mortality were not significantly different from those of female patients (OR = 1.2; $p = 0.71$).

DISCUSSION

This study included a total of 139 paediatric cancer cases. The age at diagnosis and the predominance of male patients were consistent with findings reported in previous studies (4, 7, 14). According to the literature, paediatric cancers were more prevalent in male patients in almost all types of cancer; however, there was no scientific explanation on the cause of male pre-dominance in childhood cancers (15). The prevalence of paediatric

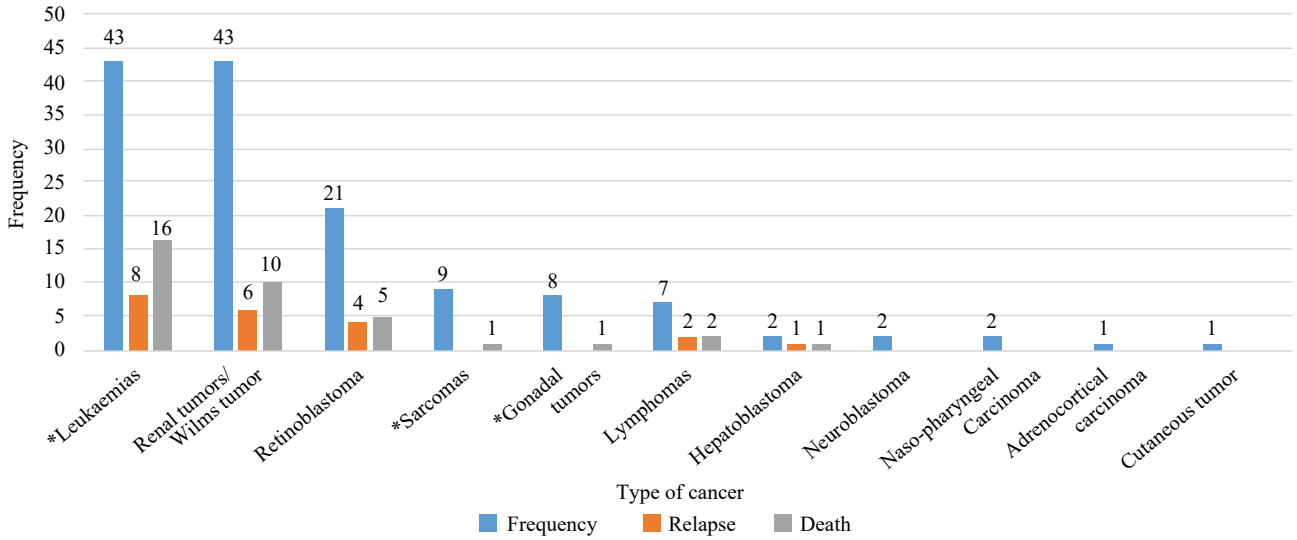

Figure 1: Frequency, relapse and death per cancer type.

Types of paediatric cancers diagnosed from 2010 and 2014 (N = 139):
*Leukaemias: acute lymphoblastic leukaemia (28) + acute myeloid leukaemia (14) + chronic myeloid leukaemia (1) = 43 cases;
*Sarcomas: rhabdomyosarcoma (7) + osteosarcoma (2) = 9 cases;
*Lymphomas: Hodgkin lymphoma (4) + Burkitt lymphoma (3) = 7 cases;
*Gonadal tumours: yolk sac tumour (6) + germ cell tumour (1) + ovarian tumour (1) = 8 cases.

Cancer-related deaths in Haitian children and adolescents from 2010 and 2014 (N = 36):
*Leukaemias: acute lymphoblastic leukaemia (7) + acute myeloid leukaemia (9) = 16;
*Lymphomas: Burkitt lymphoma (2);
*Sarcomas: osteosarcoma (1);
*Gonadal tumours: yolk sac tumour (1).

Relapse cases among Haitian children and adolescents from 2010 to 2014 (N = 21):
*Leukaemias: acute lymphoblastic leukaemia (5) + acute myeloid leukaemia (3) = 8;
*Lymphomas: Burkitt lymphoma (2).

Table 2: Factors associated with mortality among the children and adolescents managed for cancers at the St Damien Hospital from 2010 to 2014

Predictor variables	**N**	**Odds ratio (OR)**	**95% CI**	***p*-value**
Gender (female *vs* male)	139	1.15	0.54, 2.47	0.71
Age (< 5 years old *vs* ≥ 5 years old)	139	1.80	0.83, 3.94	0.14
Department of origin (West *vs* the others)	138	0.72	0.32, 1.64	0.43
Type of cancer (blood cancers *vs* solid cancers)	139	2.22	1.02, 4.82	0.04
Type of treatment for solid cancers (combined *vs* non-combined)	89	2.00	0.72, 5.57	0.18
Type of treatment for blood cell cancers	50	1.34	0.23, 7.75	0.75
Relapse (yes *vs* no)	139	127.5	15.99, 2016.90	< 0.01
Complications (yes *vs* no)	139	5.51	2.29, 13.29	< 0.01

cancers during the study period was below 1%. This prevalence was, however, hospital-based and thus did not reflect the cancer burden among children and adolescents in Haiti. There was nonetheless a possible lack of referral or underdiagnosis of cancer cases because of the poor availability and accessibility to cancer care. It was highly probable that children and adolescents with acute symptoms seen, for example, in acute leukaemia could have died before seeking healthcare. Those with symptoms seen in lymphomas could have been misdiagnosed for tuberculosis, which is endemic in Haiti. Children presenting with masses may have undergone surgical intervention without pathological analysis, potentially leading to death from recurrence or during the intervention. Furthermore, as SDH is located in the capital, it cannot provide cancer care for the entire country. The absence of cancer specialists in other regions hinders referral pathways, particularly for patients residing in rural areas or cities far from the capital.

In our study, children under 9 years old were the most affected, which aligns with existing literature that reports that incidence rates of cancer were higher among children in this age group (15). The reasons for the predominance of cancer in younger children remains poorly understood. However, some gene defects, hereditary conditions, exposure to infectious agents and radiation have been highly hypothesized in the development of cancers in children at an early age (4–6, 15). Although likely, it was impossible to determine whether patients less than 15 years old were more affected than older children as it is proven in some studies (13, 15) because the latter are rerely admitted or managed in the Oncologic Department of St Damien Hospital.

The haematological malignancies and the CNS tumours are the most prevalent cancers among children worldwide (2, 7, 9, 15). This was not the case in our study for the CNS tumours since the suspected cases seen in SDH were mostly referred to another hospital for surgery or further diagnostic work-up. The absence of radiation therapy in Haiti is a major barrier to the optimal management of CNS tumours.

Racial and ethnic disparities persist in both incidence and outcome of blood cancers. According to the literature, blood cancers (particularly ALL) were more prevalent among White children and are less likely to develop among Black children (16–19). Haiti has a predominantly Black population. As previously mentioned, this setting is likely influenced by underdiagnosis, resulting from limited diagnostic capabilities and restricted access to healthcare services, which could attribute to the low incidence of blood cancers.

Although renal tumours/Wilms tumour were among the most prevalent cancers in our study, it was not listed in the top three cancers diagnosed in children particularly in other Caribbean countries (17). Previous studies suggested that race, more than geography or nationality, was a greater risk factor for the development of Wilms tumour, and Black children appeared to be more susceptible than White ones (20, 21). Despite of the probability of an underdiagnosis of blood cancers in Haiti, the predominance of renal tumours/Wilms tumour could be due to a possible existence of some gene mutations among the Haitian population. However, Haitian genetic studies are far from being performed to confirm this hypothesis.

The significant factors associated with mortality related to paediatric cancers in our study were the occurrence of blood cancers, relapse and complication. These findings were most likely related to a delay in the diagnosis of cancers due to late presentation, and a lack of material and human resources at SDH. Also, poor adherence to treatment could negatively influence cancer treatment outcomes and could be detrimental for the treatment of childhood blood cancers which requires prolonged, daily oral or periodic parenteral administration of antimetabolites for up to two years in the maintenance phase (8, 16). This could increase the occurrence of relapse and complication and thus increase the risk of mortality. Even though African Americans are less likely to develop blood cancers (particularly ALL), numerous studies revealed that when compared with White children they fare worse with therapy than other ethnic groups (16–18). Infection, the most common complication, is most likely due to neutropenia related to the use of cytotoxic drugs, well known for this adverse event and the state of immune suppression that characterizes neoplasms, possibly worsened by a poor nutritional status.

Although the aims of the study were reached, there were some unavoidable limitations. This study was unable evaluate the burden of CNS tumours, which alongside with ALL, the two most common cancers diagnosed in the children worldwide. Also, the absence of molecular biology and cytogenetic testing in Haiti limited this study from establishing some key factors associated with prognosis, particularly in leukaemias, Wilms tumour, retinoblastoma and lymphomas. The results of this study were exclusively based on data collected from the only paediatric oncology hospital serving mainly one of the ten departments of Haiti; thus, the study population was not representative of the real cancer burden in Haiti's paediatric population and therefore the results are not generalizable.

CONCLUSION

This study evaluated the clinical epidemiology of cancer among the children and adolescents in Haiti; identified the variables associated with the negative outcomes in those managed for cancer at SDH. The predominance of renal tumours/Wilms tumour are of interest and should be followed closely to determine whether this pattern persists in Haitian children living with cancer countrywide. Although the early diagnosis and treatment are important for the management of cancers, especially in children, the social and economic situation in Haiti is an immense factor that could delay the diagnosis and the initiation of treatment. The lack of human and material resources hinders the capacity to manage cancers properly in Haiti and could be one of the causes of poor outcomes. Nonetheless, the results of this study proved that rigorous actions should be taken to improve the

availability and accessibility of paediatric cancer care in Haiti to reduce relapse, complications and overall mortality.

AUTHORS' NOTE

JG Lucien and JJ Bernard worked together to conceive this study. They both participated in its design and the interpretation of the results.

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ORIGINAL ARTICLE

Health-related Quality of Life and Risk of Malnutrition among Persons on Maintenance Haemodialysis

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ABSTRACT

Objective: *The purpose of this study was to determine health-related quality of life and the risk of malnutrition among persons with chronic kidney disease on maintenance haemodialysis (MHD).*

Methods: *A mixed-methods approach consisting of a case-control study followed by detailed interviews was employed. Cases (MHD) received haemodialysis three times per week. Controls (non-MHD) were persons diagnosed with hypertension and/or diabetes mellitus attending clinics at the same healthcare facility. Face-to-face interviews were conducted using a standardized questionnaire consisting of the 12-Item Short Form Survey and mini-nutritional assessment questionnaire as well as socio-demographic, health-related symptoms, food frequency and physical activity. Anthropometry was assessed using standard procedures. Sixty participants completed the questionnaires on two occasions, 8-weeks apart. The study was approved by The University of the West Indies Ethics Committee.*

Results: *Four hundred and seventy-three persons (MHD = 150; non-MHD =323) participated in the study. The test–retest reliabilities differed by sex and treatment status. Mental component summary score (MCS) and physical component score (PCS) test–retest reliabilities (Cronbach's alpha) for female MHD were 0.75 and 0.68, respectively, while they were 0.5 and 0.53, respectively, for male MHD. There were no significant differences in age, body mass index and sex between MHD and non-MHD. Maintenance haemodialysis participants were more likely than non-MHD to be at increased risk for poorer HRQOL and malnutrition. Mini-nutritional assessment tool scores were positively associated with PCS (*p *= 0.025) and MCS (*p *= 0.002) scores in multivariate regression analyses controlling for age, gender, ethnicity, education, employment, income and comorbidities.*

Conclusion: *Maintenance haemodialysis participants had poorer health-related quality-of-life and were at higher risk of malnutrition than non-MHD.*

Keywords: Chronic kidney disease, haemodialysis, health-related quality of life, malnutrition.

INTRODUCTION

Chronic kidney disease (CKD), a progressive decline in glomerular filtration rate, is a major cause of illness and death globally (1, 2). With an incidence of 29.2 per 100 000, Trinidad and Tobago has one of the highest incidences of CKD in Latin America and the Caribbean. Diabetes mellitus and hypertension are the two most important risk factors for CKD locally (3, 4). With progression, CKD ultimately leads to end stage renal disease (renal failure) requiring dialysis or transplantation. Dialysis is associated with poor health-related quality of life (HRQOL) (5, 6). Furthermore, subjective HRQOL is a well-known predictor of disease outcome. Renal failure is associated with declines in nutritional status due to altered metabolism, fatigue, psychological dysfunction and poor appetite. Dialysis exacerbates nutritional issues with CKD as dietary restrictions are required for patient management (7, 8). Despite the large number of persons

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with CKD on dialysis, there is a paucity of relevant studies on HRQOL and associated issues in this population regionally (4). The purpose of this study was to determine HRQOL and risk of malnutrition among persons with CKD on maintenance haemodialysis (MHD).

SUBJECTS AND METHODS

This study employed a mixed-methods approach; a case–control study followed by detailed interviews of participants was used. Cases were persons with CKD receiving haemodialysis three times per week. Controls were persons diagnosed with hypertension or diabetes mellitus attending clinics at the same institution. To observe an odds ratio of at least 2.0 in the prevalence of poor HRQOL with a case to control ratio of 1:2 with 90% power at the 95% significance level, assuming 30% of controls experience poor HRQOL, we needed at least 473 participants (cases = 150; controls = 323) (9, 10).

Participants were recruited during the period of September 1–December 31 2016. Prior to enrolment, they were informed of the nature of the study. All consents were witnessed by members of the various health-care teams. Ethical approval was obtained from the Ethics Committee, The University of The West Indies. On the day of interview, participants filled out a questionnaire consisting of socio-demographic, dietary behaviours, physical activity, HRQOL, mini-nutritional assessment tool (MNA) and food security items. Health-related quality of life was evaluated using the 12-Item Short Form Survey (SF-12). Sixty participants completed the questionnaires on two occasions 8-weeks apart. The validity and reliability of the SF-12 in assessing HRQOL has been demonstrated in a variety of settings (11).

The SF-12 measures eight domains of health. These are physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE) and mental health (MH). These are summarized into physical component scores (PCS) and mental component summary scores (MCS) (12). Poor HRQOL summary scores determined by this instrument have been shown to be predictive of disease outcomes (12). Risk of malnutrition was assessed with the MNA questionnaire. The MNA has been validated for use in a variety of settings including clinics, institutions and community (12). Participants had anthropometry measured using standard procedures (13). In addition, detailed interviews on HRQOL were conducted on 60 participants (MHD = 20; non-MHD = 40). These were put into themes and important issues categorized.

Statistics

Data were analysed using SPSS version 23 (Chicago, IL, USA). Prior to analyses, data were inspected for errors and required changes made. Physical component and mental component summary scores less than 40 and 45, respectively, were categorized as increased risk of poor HRQOL in these domains (14, 15). Participants with MNA scores less than 8 were considered to be at increased risk for malnutrition. Similarly, qualitative data were coded and categorized by themes relevant to HRQOL issues. Differences in means of continuous variables between MHD groups were analysed using the *t*-tests and its non-parametric equivalent, the Mann–Whitney *U* test. Chi-squared test was used to determine between ordered categorical data. The results were presented as percentages, means ± standard errors/deviation (SE/SD) and odds ratios. Test–retest reliabilities were analysed using Cronbach's alpha (16). Cronbach's alpha values greater than 0.7 were considered acceptable. Finally, p-values < 0.05 were considered statistically significant.

RESULTS

The test–retest reliabilities differed by sex among MHD status. Mental component and physical component summary scores' test–retest reliabilities were 0.75 and 0.68, respectively, among females and 0.50 and 0.53, respectively, among males. For controls, MCS and PCS test–retest reliabilities were 0.93 and 0.75, respectively. Table 1 shows the characteristics of participants by MHD status. There were no significant differences in age, sex, ethnicity, education and anthropometry between MHD and non-MHD. Maintenance haemodialysis participants were more likely to be persons of East Indian descent, while non-MHD participants were more likely to be persons of African descent. Non-MHD participants were significantly heavier and more active than MHD. They were also at lower risk for undernutrition. Overall, males were more likely than females to have a PF (54.9% vs. 45.1%; $p = 0.002$) and PCS (71.6% vs. 62.5%; $p = 0.034$) scores <40. Among persons with CKD, males were significantly more likely than females to have RE (54.2% vs. 45.8%; $p = 0.024$) and RP (55.3% vs. 44.7%; $p = 0.003$) scores < 40. Maintenance haemodialysis participants were significantly more likely than non-MHD to be at increased risk of malnutrition (62.0% vs. 38.0%; p

Table 1: Socio-demographic, anthropometric and lifestyle behaviours of participants by haemodialysis status

Variables	Haemodialysis n = 150 Mean ± SD	Non-haemodialysis n = 323 Mean ± SD	*p*-Value
Age (years)	58.2 ± 16.9	59.8 ± 18.4	0.35
Male/Female (%)	50.7/49.3	50.2/49.8	0.92
Ethnicity (%)			
Indo-Trinidadian	42.7	30.3	
Afro-Trinidadian	41.2	51.1	
Mixed	15.4	18.6	0.04
Years of schooling (%)			
< 8 years	32.7	38.4	
> 8 years	67.3	61.6	0.11
Employment (%)			
No	88.7	67.5	
Yes	11.3	32.5	< 0.001
Income (%)			
< 4000	92.0	70.0	
> 4000–6999	8.0	30.0	< 0.001
Weight (kg)	67.7 ± 12.1	71.7 ± 12.2	0.001
Height (cm)	171.8 ± 14.6	173.9 ± 17.3	0.18
Waist circumference (in)	36.01 ± 5.2	37.6 ± 5.1	0.71
Waist-to-height ratio	0.5 ± 0.07	0.5 ± 0.07	0.79
BMI (kg/m^2)	23.2 ± 4.8	24.0 ± 4.9	0.90
MNA score	7.3 ± 2.3	8.9 ± 2.0	< 0.001
MNA < 8 (%)	62.0	38.0	< 0.001
Physical activity level ≥ 90 minutes/week (%)	19.3	46.1	< 0.001

SD = standard deviation; BMI = body mass index; MNA = Mini-Nutrition Assessment.

= < 0.001). In multivariate regression analyses controlling for age, gender, ethnicity, education, employment, income and comorbidities, MNA scores were positively associated with PCS (p = 0.025) and MCS (p = 0.002) scores.

Table 2. SF-12 subscales and summary scores among participants by maintenance haemodialysis status

Variables	Haemodialysis n = 150 (Mean ± SE)	Non-haemodialysis n = 323 (Mean ± SE)	*p*-Value
Role limitation due to physical problems (RP)	13.3 ± 2.5	61.0 ± 2.6	< 0.001
Bodily pain (BP)	85.2 ± 1.4	94.4 ± 0.7	< 0.001
Social functioning (SF)	56.0 ± 3.4	87.2 ± 1.7	< 0.001
General health (GH)	40.8 ± 2.8	53.8 ± 1.2	< 0.001
Role limitation due to emotional problems (RE)	14.4 ± 2.6	62.2 ± 2.5	< 0.001
Vitality (VT)	50.7 ± 3.0	49.5 ± 1.3	0.69
Mental health (MH)	52.6 ± 1.7	57.7 ± 1.0	0.007
Physical functioning (PF)	12.2 ± 2.2	30.0 ± 2.1	< 0.001
Physical Component Summary score (Mean ± SD)	39.4 ± 5.7	43.5 ± 6.8	< 0.001
Mental Component Summary score (Mean ± SD)	38.4 ± 6.8	43.1 ± 8.0	< 0.001

SD = standard deviation; SE= standard error.

Table 2 shows SF-12 subscales and summary scores among participants by MHD status. With the exception of VT scores, persons receiving MHD had significantly lower subscales and summary scores than non-MHD.

Table 3 shows the proportion of participants having SF-12 subscales and summary scores indicative of poor HRQOL by MHD status. With the exception of MH and BP, MHD participants were significantly more likely than non-MHD to have SF-12 summary and subscale scores indicative of poorer HRQOL in the relevant domains. These were independent of age, sex, ethnicity, education levels and comorbidities.

Table 3. The proportion of participants having SF-12 subscales and summary scores indicative of poor HRQOL by haemodialysis status

Variables	Haemodialysis n = 150 (Mean ± SE)	Non-haemodialysis n = 323 (Mean ± SE)	Odds-ratio (95% CI) Referent = Case	*p*-Value
Role limitation due to physical problems (RP)	82.0 ± 3.1	34.3 ± 2.6	8.7 (5.4, 14.0)	< 0.001
Bodily pain (BP)	10.0 ± 2.5	5.3 ± 1.2	2.0 (1.0, 4.1)	0.087
Social functioning (SF)	42.6 ± 4.1	13.3 ± 1.8	4.8 (3.1, 7.6)	< 0.001
General health (GH)	41.3 ± 4.1	16.1 ± 2.0	3.7 (2.4, 5.7)	< 0.001
Role limitation due to emotional problems (RE)	80.0 ± 3.3	30.3 ± 2.6	9.2 (5.8, 14.6)	<0.001
Vitality (VT)	32.0 ± 3.8	14.5 ± 1.9	2.8 (1.7, 4.4)	< 0.001
Mental health (MH)	23.3 ± 3.5	18.8 ± 2.1	1.3 (0.8, 2.1)	0.264
Physical functioning (PF)	83.3 ± 3.1	58.8 ± 2.7	3.5 (2.2, 5.7)	< 0.001
Physical Component Summary Score (PCS)	84.8 ± 2.7	58.8 ± 3.	3.9 (2.4, 6.3)	<0.001
Mental Component Summary Score (MCS)	90.6 ± 2.4	66.8 ± 2.6	4.8 (2.6, 8.7)	< 0.001

HRQOL = health-related quality of life; SE = standard error; CI = confidence interval.

Results of qualitative analyses indicate the MHD participants were significantly more likely than non-MHD to report psychological/emotional stress related to: routine daily tasks (60% vs. 33%; $p = 0.04$), death of peers (60% vs. 15%; $p = 0.001$), disease complications (94% vs. 26%; $p < 0.001$), medical concerns about their condition (62% vs. 5.6%; $p < 0.001$) and post-treatment symptoms (81% vs. 7%; $p < 0.001$).

DISCUSSION

Our results indicate that persons with CKD on haemodialysis experienced poorer HRQOL than their counterparts with hypertension or diabetes mellitus, the predominant causes of kidney failure in this population (3, 4, 17). This finding is consistent with studies conducted in a variety of settings and suggests that kidney failure leading to haemodialysis may be an additional contributor to poorer HRQOL among participants independent of underlining comorbidities, diabetes mellitus and hypertension (18, 19). This is important as poor HRQOL is an important predictor of disease outcomes among persons receiving MHD (20). Factors leading to poor HRQOL among persons on MHD include fatigue, frailty, impaired mobility and rapid physical decline (21). In our study, cases were more likely than controls to report impaired mobility due to physical disabilities. This reduced their ability to perform routine non-occupational activities (21).

Mental HRQOL among persons on haemodialysis is a diverse and complex issue. Negative emotional states (depression and anxiety) are important predictors of poor physical and mental HRQOL (22). Challenges faced by persons on MHD that created anxiety included inability to effectively manage their condition, death of peers, their illness and its co-morbid conditions and the cost related to treatment, especially in the absence of family support. This cost may be as high as $100 US per week (23). These are important considerations as the majority of participants were unemployed and earned incomes less than $600 US per month. Additionally, 98% of them took ≥ 5 medications per day. Such drugs are expensive to purchase when not available at government-sponsored pharmacies. Thus, socioeconomic issues that affect financial security were important sources of anxiety and poor mental health among MHD (24).

Although there were no statistically significant differences in anthropometry between MHD and non-MHD, nutrition is known to play an important role in the management of persons on dialysis. Declines in mental and physical component scores are most often coupled with poor nutritional status among renal patients (24). Dietary restrictions form a common part of management protocols for such persons and increase the risk of nutrient deficiencies (25). In fact, our results suggest that participants on MHD were at greater risk of malnutrition compared to their non-MHD counterparts. This may have been exacerbated by poor appetite associated with depression, difficulty chewing and mandatory dietary restrictions (21–23).

Limitation

We did not evaluate biochemical data and therefore could not identify specific nutrient deficiencies among participants. The level of depression and anxiety were not measured. This limits our interpretation of many issues surrounding psychological HRQOL among participants. The non-randomized sampling of participants reduces generalization of these findings to local and regional populations of persons receiving haemodialysis (22). The lower Cronbach's alpha values among males may reflect a progressive worsening of their PF. In fact, males formed the majority of deaths in this cohort over the past 2 years.

CONCLUSION

Chronic kidney disease patients on MHD were at increased risk of poorer HRQOL and malnutrition. Additionally, risk of malnutrition was associated with poorer HRQOL.

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ORIGINAL ARTICLE

Obesity and Quality of Life in Kidney Transplant Recipients

MC José María[1], R Artacho[2], MJ Aguilar Cordero[1], J Bravo Soto[3], RF Castillo[1]

ABSTRACT

Objective: *The objective of this research was to analyse the effects of overweight and obesity in relation to markers of chronic graft dysfunction (ie, dyslipidaemia, high blood pressure and proteinuria), and study their impact on the quality of life of kidney graft recipients in the first year after transplantation.*

Methods: *This study monitored 1500 kidney transplant recipients of both genders. One year after receiving the graft, all of the patients had blood tests to measure their biochemical parameters. Their weight and height were also measured. Furthermore, data regarding graft loss and delayed renal function were also evaluated.*

Results: *The results showed an increased prevalence of overweight and high body mass index (BMI) among the graft recipients, participating in the study. Furthermore, there was a direct relation between these parameters and those of health status perception, graft rejection and reduced renal function.*

Conclusion: *A high BMI, proteinuria, and high blood pressure in the first year after transplantation can lead to chronic graft dysfunction and significantly reduce the patient's quality of life. Renal dysfunction markers along with obesity and a high BMI contributed to a decrease in the glomerular filtration rate (GFR) and ensuing complications in the first year after transplantation. This affected the quality of life of these patients who, as a result, suffered from chronic kidney disease. Consequently, their physical condition was negatively affected, which increased the rates of morbidity and mortality.*

Keywords: Kidney transplantation, lipid alterations, obesity anthropometry, quality of life

INTRODUCTION

Within the context of public health and medicine, in general, quality of life is an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns (1). Health professionals often use health-related quality of life to measure the effects of a chronic illness in the patients in order to gain a better understanding of how an illness can affect their daily life (2, 3). Currently, there is a growing interest in studying quality of life in the renal transplant recipients. More specifically, research findings indicate that these patients tend to experience a significant reduction in quality of life in comparison to the general population (4).

The advantages of kidney transplantation are well known. However, life in the post-transplant phase also has negative aspects, such as harsh treatments with immunosuppressive drugs and their related side effects. Furthermore, patients must also endure frequent medical visits, infections, rejection episodes, uncertainty, anxiety and risk of graft loss (5, 6). Therefore, an important task for the future of kidney transplantation is a more detailed specification of the wide range of clinical, environmental and personal factors that can have a negative impact on the patient's health-related quality of life (7). Clearly,

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a more in-depth understanding of these factors is crucial in order to develop interventions that can improve the quality of life of renal transplant recipients (8). In line with this, one of the priorities of the World Health Organization (WHO) is also to enhance the quality of life of people who live with those suffering from the chronic illness (9).

Obesity is a factor that significantly worsens the quality of life for patients suffering from the chronic illness. It has an evident impact on their physical condition (10). More specifically, overweight and obesity in the post-transplantation phase can lead to arterial hypertension, proteinuria and dyslipidaemia, all of which can cause kidney damage and delayed renal function. The main objective of this research study was to analyse overweight and obesity in relation to these graft dysfunction factors and evaluate their effect on quality of life in the first year after kidney transplantation.

SUBJECTS AND METHODS

Subjects

The sample population was composed of 1500 kidney transplant recipients, 897 men and 603 women, 16–80 years of age. All of the subjects periodically visited the post-transplant clinic at the University Hospital Virgen de las Nieves in Granada (Spain). The base diseases are shown in Figure 1. All of the patients met the following inclusion criteria: absence of diabetes mellitus before transplantation; stable renal function before transplantation and one-year monitoring period.

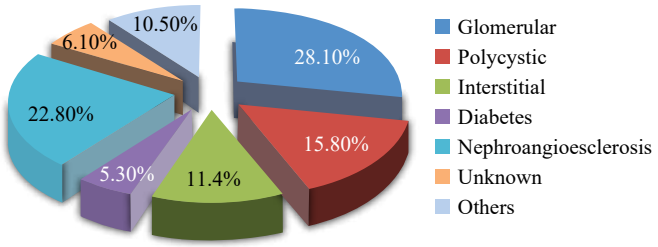

Figure 1: Causes of chronic kidney disease

Methods

All of the patients were given blood tests to measure levels of the following: total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL) and triglycerides. Peripheral blood samples (6 ml) were collected between 8:00 and 9:00 AM by venepuncture into a Venoject II® plastic whole blood tube (TERUMO, autosep®). Blood extraction was performed under fasting conditions. Renal function was measured with the Cockcroft-Gault (CG) formula: GL=((140–age in years) × (weight in kg)) / (72 × serum creatinine)

Renal function deterioration was regarded as an increase in serum creatinine and the presence of high levels of proteinuria. A year after transplantation, the patients were also weighed in kilograms with a Perperson 113481 scale/stadiometer and their height was measured in centimetres. Their body mass index (BMI) was then calculated using the formula: weight (kg)/height (m^2). The subjects' BMI was evaluated based on the following ranges in the WHO classification: (a) underweight (< 18.50); (b) normal weight (18.50–24.9 kg); (c) overweight (25–29.9 kg); (d) obese (> 30 kg). The hypotensive agents used were β-blockers, diuretics, angiotensin-converting enzyme inhibitors (ACE inhibitors) and calcium channel blockers. The immune-suppressive protocol was a triple therapy based on prednisone, consisting of cyclosporine A (CsA) or tacrolimus and microphenolate mofetil (MMF) or azathioprine (AZA).

The dosage of immunosuppressive drugs followed the standard protocol used in the University Hospital Virgen de las Nieves in Granada (Spain). Of the sample, 80% of the graft recipients had taken lipid-lowering agents, such as rosuvastatin, atorvastatin and simvastatin; and they were still being treated with them. Dyslipidaemia was defined as follows: (a) total cholesterol values of > 200 mg/dL (5.17 mmol/L); (b) triglycerides > 200 mg/dL (2.26 mmol/L); (c) diabetes, if fasting blood glucose levels were > 126 mg/dL.

High blood pressure was defined in terms of the criteria established in 2010 by the American Heart Association, namely, blood pressure values exceeding 140/90 mmHg. Proteinuria was regarded as the presence of proteins in the urine, > 150 mg in a 24-hour urine collection. Before being discharged from the hospital, patients were advised to consume 1.4–1.5 g/kg of proteins (30–35 kcal/kg/day) during the first three months after the kidney transplant. Moreover, it was recommended that they avoid sugar and decrease their intake of lipids to less than 30%. After the first three months, patients were advised to reduce their protein intake to 1 g/kg per day. After one year, patients were surveyed and asked about their perception of their health status, specifically in regard to their position as a graft recipient. Accordingly, they had to classify their health status in one of the following categories: (a) Worse than before transplantation; (b) The same as before transplantation; (c) Better than before transplantation.

Statistical analysis

All statistical analyses were performed using the statistical software package SPSS Statistics 20. The results were expressed as frequencies, percentages and mean values ± standard deviation. The differences between groups were evaluated with the analysis of variance (ANOVA). Categories variables were compared with the Chi-square test. All data were expressed as mean value ± standard deviation (X ± SD) and *p*-values lower than 0.05 were regarded as statistically significant.

RESULTS

As reflected in Table 1, age played a major role in the perception of health status. More specifically, an average of 53.71 patients said that they felt worse than before transplantation, whereas 56.82 patients stated that they felt the same. Differences for parameters, such as gender and height, were not statistically significant.

Our results showed that weight was an important variable. Table 1 shows that the patients' mean weight tended to increase in the pre-transplant phase up to six months to a year after transplantation as patients perceived a deterioration in their health status. In contrast, this was not the case for those who stated that their health had improved after transplantation. In this regard, the parameter of high blood pressure was similar to that of weight. The majority of graft recipients with high blood pressure stated that their health was worse or the same as before transplantation. Only a small percentage said that they felt much better (see Table 1).

Proteinuria was also an important variable. Table 1 shows that as levels of protein increased in urine, patients tended to have a worse perception of their health. As reflected in the value ranges in Table 2, the patients with lower percentages of proteins in their urine said that their health was much better than those with higher percentages (proteinuria). In regard to the highest range of values, the results were very significant in comparison to the other intervals.

When the patients' BMI was categorized with the WHO classification, obese graft recipients with the high BMIs were those that stated that their quality of life was worse than before transplantation. In contrast, there were no differences between over-weight and normal-weight patients whose quality of life was the same as before transplantation. In regard to patients whose quality of life improved after transplantation, there was a higher percentage of overweight patients. Another striking result is the extremely high percentage of overweight and obese patients with renal graft loss within the first year after transplantation (Table 3). Exactly the same occurred in the case of kidney function (Table 4). When the BMI was evaluated based on the WHO classification, our results showed that the percentages of patients with underweight, normal weight, overweight and obesity were all greater in those suffering from delayed graft

Table 1: Comparison of quality of life to anthropometric and biochemical parameters

Variables	Worse than before transplantation	Same as before transplantation	Better than before transplantation	*p*-value
Age (years)	53.71 ± 12.65	56.82 ± 8.63	45.32 ± 13.81	<0.001
Gender: male/female (%)	76.55/23.5	58.8/41.2	62.5/37.5	NS
Height (cm)	165.79 ± 9.11	164.04 ± 8.20	163.84 ± 9.26	NS
Pre-transplant weight (kg)	70.46 ± 15.07	67.41 ± 12.93	68.33 ± 13,29	NS
Weight (six months afterward) (kg)	74.72 ± 11.61	70.10 ± 13.80	72.48 ± 12.80	NS
Weight (one year afterward) (kg)	76.82 ± 11.24	70.44 ± 13.30	74.42 ± 13.55	NS
Proteinuria (one year) (mg/dL)	0.35	0.31	0.07	0.012
Hypertension (%)	35.7	35.3	21.3	NS
Hyper-lipidaemia (%)	23.5	5.9	23.3	NS

All data expressed as mean+/- Standard deviation, unless otherwise stated
NS: Not significant.

Table 2: Comparison between quality of life and proteinuria levels

	Proteinuria range (one year afterward)				
Quality of life (one year afterward)	< 0.125 g	0.125–0.250 g	0.250–1 g	1–3 g	> 3 g
Worse than before transplantation (%)	66.7		16.7	16.7	
The same as before transplantation (%)	73.3	6.7	6.7	13.3	
Better than before transplantation (%)	89.8	2.9	5.6	1.4	0.3

$p < 0.001$.

Table 3: Comparison between percentage of patients with graft loss and BMI, according to the WHO (N = 1336)

	BMI according to the WHO classification			
Graft loss within one year	Underweight	Normal weight	Overweight	Obesity
No (%) (N: 1228)	0.4	32.9	39	27.7
Yes (%) (N: 108)			66.7	33.3

NS: Not significant

Table 4: Comparison between delayed renal function (Cockcroft–Gault formula) and BMI, according to the WHO classification

	BMI according to the WHO classification			
Delayed graft function	Underweight	Normal weight	Overweight	Obesity
No (%)	25	49.1	45.8	33.9
Yes (%)	75	50.9	54.2	66.1

$p < 0.01$.

function. The difference had a high level of statistical significance. The patients' quality of life was perceived as poor when renal function was deficient (see Table 5). In contrast, percentages were similar in those patients who stated that their quality of life was better than before transplantation. This difference was also statistically significant.

Table 5: Comparison between quality of life and delayed renal function (Cockcroft–Gault formula)

	Delayed graft function	
Quality of life (one year afterward)	**No**	**Yes**
Worse than before transplantation (%)	13.6	86.4
Same as before transplantation (%)	26.6	73.7
Better than before transplantation (%)	46.1	53.9

$p < 0.01$.

DISCUSSION

The majority of patients in this study were adults, 40–50 years of age (50.8%) with a mean age of 45.0 years (SD = 14.4). This in itself is disturbing because it is a reflection of the early development of kidney disease and its rapid progression in active young people. In this regard, this research differs from previous studies of renal graft recipients, whose age was slightly older (51.1 years) (11).

Evidently, age plays an important role in the acceptance of infirmity. Our results indicate that the kidney transplant patients of a younger age seem to have a greater awareness of the limitations of their illness (12–14). In this regard, various studies show that the kidney graft survival is longer in younger patients (73% and 83%) than in older ones (15–17). According to our results, after the renal transplant, patients experienced a significant gain in weight and BMI (Table 6). This is a serious problem since post-transplant obesity is an important risk factor for the renal graft survival as well as for the development of cardiovascular disease, high blood pressure, diabetes and dyslipidaemias. Furthermore, it is an important cause of morbidity and mortality (18, 19). This is a source of added stress for these graft recipients, who must try to maintain their weight at a level that will not further endanger their health. As reflected in our results, the patients who perceived their health status as the same as before transplantation or worse than before transplantation had the highest BMIs. One reason for this is that they were aware that the weight is a factor that can lead to graft rejection. This is an important problem that must be addressed in clinical work and management because of the possible consequences of overweight and obesity and the difficulty in regaining and maintaining a normal weight (20, 21).

Table 6: Comparison between quality of life and BMI, according to the WHO classification

	BMI according to the WHO classification			
Quality of life (one year afterward)	Underweight	Normal weight	Overweight	Obesity
Worse than before transplantation (%)		18.2	36.4	45.5
Same as before transplantation (%)		41.2	41.2	17.6
Better than before transplantation (%)	0.5	31.1	40.8	27.7

NS: Not significant.

Generally speaking, the kidney transplant patients have suffered from chronic kidney disease over a period of several years. For this reason, many of them experienced lipid disorders even before transplantation (22, 23). Unfortunately, the metabolism of lipids does not return to normal when renal function is recovered after the transplant (24). This signifies that post-transplant renal dyslipidaemia is a relatively frequent metabolic disorder, especially in the first year after transplantation. It is thus of great clinical interest not only because of the high incidence of post-transplant cardiovascular incidents but also because of its possible contribution to the development of chronic graft dysfunction (25). Even though it is not statistically significant, our results point to a possible relation between hyper-lipidaemia and quality of life. Again, the highest percentages pertained to those patients whose quality of life had not improved after transplantation.

Proteinuria was found to be another important factor in our study. When percentages were high, the patients' quality of life significantly worsened because of the ensuing mental, emotional and physical limitations. Physical symptoms include fatigue, lack of energy, sleep disorders, pain, oedemas, general feeling of illness and anxiety. These symptoms reduce the patients' capacity to engage in other activities, especially since there is the need to continuously monitor renal function (26).

Consequently, obesity is frequent in renal graft recipients and is associated with deterioration in cardiovascular parameters and the progression of proteinuria (27–30). As reflected in this study, the patients with a high BMI experienced a reduction in quality of life. Moreover, a high percentage of these patients also suffered from renal graft loss and/or delayed renal function. All of these factors had a negative impact on their health-related quality of life as can be observed in Table 5.

In conclusion, markers of chronic graft dysfunction such as obesity and a high BMI contributed to a reduction in the glomerular filtration rate and ensuing complications in the first year after transplantation. This affected the health-related quality of life of patients with chronic kidney disease by significantly reducing their physical condition and increasing their morbidity and mortality.

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AUTHORS' NOTE

MC José María conceived paper, oversaw data collection, conducted data analysis, wrote manuscript and approved final version. R Artacho participated in the study design, data analysis and interpretation, critically revised manuscript and approved final version. MJ Aguilar Cordero and J Bravo Soto participated in the study design, data analysis and interpretation of data, revision of manuscript and approved final version. RF Castillo participated in the study design, interpretation of data and revision of manuscript and approved final version.

The authors declare that there is no conflict of interests.

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ORIGINAL ARTICLE

Estimated Effects of Climate Variables on Transmission of Malaria, Dengue and Leptospirosis within Georgetown, Guyana

C Boston, R Kurup

ABSTRACT

Objective: *To analyse meteorological data (temperature, rainfall and relative humidity) and vector-borne diseases (malaria, dengue and leptospirosis) to determine trends that may exist between and among variables within the Georgetown area.*

Methods: *This study took on a retrospective approach which used data from the Ministry of Health and Ministry of Agriculture, Hydro-meteorological Department to assess the true nature of the relationship between climate and vector-borne diseases within the Georgetown area. Correlation and regression analyses were done using SPSS 13 and JMP.*

Results: *The results yielded weak positive correlations between climate variables and vector-borne disease with strongest the correlation between P falciparum and P malariae. Leptospirosis showed positive correlation with humidity and dengue showed positive correlation with all three climate variables measured. Projections showed that with a 1°C increase in temperature, 1% increase in relative humidity and 50-mm increase in rainfall, there were significant increases in malaria and leptospirosis.*

Conclusion: *There have been theories that suggest a connection between climate variables and vector-borne disease, however, conclusive evidence does not exist. In the present study, the need for research that yields more unwavering results are highlighted. There is no doubt that climate variables influence vector-borne diseases. Therefore, it is recommended that an interdisciplinary approach be taken to ensure reliability and foster a better understanding between climate variables and vector-borne disease.*

Keywords: Climate change, dengue, leptospirosis, malaria

INTRODUCTION

Climate affects infectious diseases that are transmitted via contaminated water or food. In poor countries, for instance, water-related diseases are especially a problem because of inadequate sanitation. When floodwaters become contaminated with human and animal wastes, the occurrence and often outbreak of disease occurs, *eg*, leptospirosis (1). It has already been established that a relationship exists between rainfall and diseases spread by insect vectors, which breed in water and as such are dependent on surface water availability. Natural disasters including floods, tsunamis, earthquakes, tropical cyclones (*eg*, hurricanes and typhoons) and tornadoes have been secondarily described with the following infectious diseases, including diarrheal diseases, acute respiratory infections, malaria, leptospirosis, measles, dengue fever (DF), viral hepatitis, typhoid fever, meningitis, as well as tetanus and cutaneous mucormycosis (2).

Malaria is noted to be among the diseases listed as sensitive to climate change (3, 4). Dengue fever and dengue haemorrhagic fever (DHF) outbreaks occur in the most tropical and subtropical regions and are the most important emerging arboviral diseases worldwide. The endemic area for dengue extends over 60 countries (5, 6). Leptospirosis is considered to be widespread in many tropical countries, including the Caribbean region and Central and South America (7–9). Most often, the outbreaks occur after severe flooding due to the increased contact with contaminated water (10–12). In Guyana,

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leptospirosis has been detected in humans and livestock, but prior to 2005, no outbreaks had been reported (10, 13–15). The 2005 floods in Guyana saw 34 deaths being attributed to leptospirosis (16).

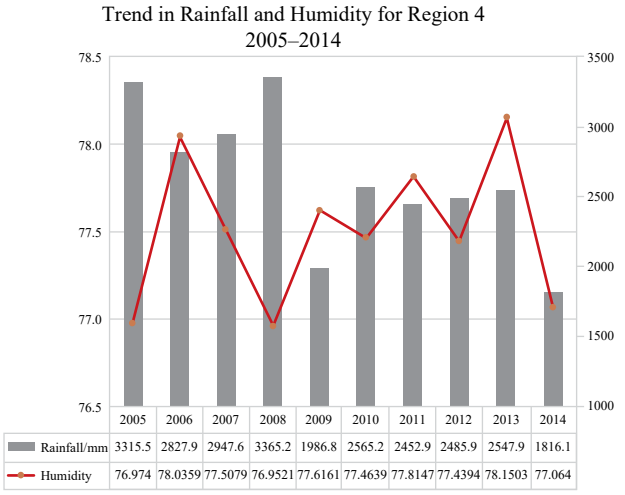
Diseases such as malaria and dengue are notably affected by such variations, as the mosquitos need access to stagnant water in order to breed. However, both wet and dry conditions favour mosquitoes, for example, heavy rains can create as well as wash away breeding sites, although on the other hand, droughts can increase breeding sites by stagnant water accumulation. Vector-borne disease transmission is sensitive to temperature fluctuations also; increases in the temperature reduce the time taken for vectors to breed. Furthermore, increased temperature also decreases the incubation period of the pathogen, resulting in the vector becoming infectious in a shorter time (17). Climatic variations are seen as a major contributor to leptospirosis and because of the transmission routes, increased rainfall often times leads to increased human exposure (18) through both increased survival of the bacteria in the environment and increased exposure of humans to surface water (19). Extreme climatic events and floods have frequently been associated with leptospirosis outbreaks (20, 21). Rainfall also leads to larger rodent populations, further contributing to increased environmental contamination (22). This study therefore aims to identify relationships between climate variables and vector-borne diseases.

SUBJECTS AND METHODS

A retrospective approach was employed to gather information in relation to the prevalence of malaria, dengue and leptospirosis as well as the three climate variables being investigated (temperature, rainfall and humidity). Data relating to temperature, rainfall and relative humidity were collected from the Ministry of Agriculture between 2009 and 2014. The Ministry of Health provided information on the incidence of malaria, dengue and leptospirosis over the same time period. All statistical analyses were done using the Statistical Package for Social Sciences (SPSS) version 13 and JMP software. The permission to conduct this research was approved from the Ethical Review Board of Ministry of Health.

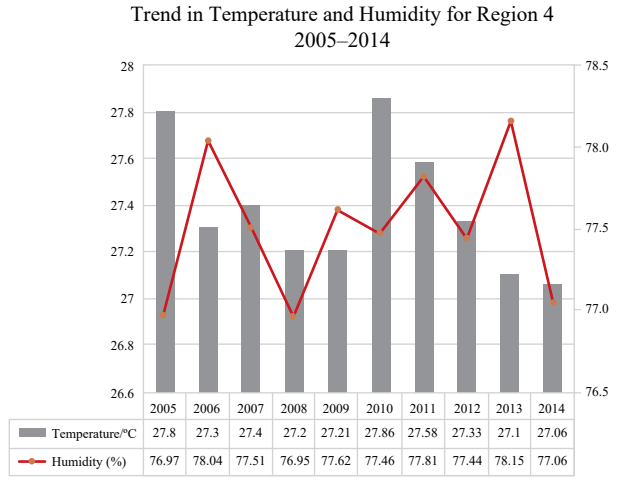
RESULTS

Data provided from the Ministry of Agriculture for the study period of 2009–2014 revealed that there was a mean rainfall of 2309.63 mm with the highest amount of rainfall recorded in 2010 (2565.2 mm). Temperature showed a mean of 27.37°C with 2010 recording the highest temperature (27.9°C), whereas the highest recorded relative humidity was noted in 2009, 2011 and 2013 (78%). Relative humidity for the study period had a mean of 77.50% (Figs. 1 and 2).



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Rainfall/mm	3315.5	2827.9	2947.6	3365.2	1986.8	2565.2	2452.9	2485.9	2547.9	1816.1
Humidity	76.974	78.0359	77.5079	76.9521	77.6161	77.4639	77.8147	77.4394	78.1503	77.064

Fig. 1: Observed variations in rainfall and humidity over the course of the study period (2005–2014).



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Temperature/°C	27.8	27.3	27.4	27.2	27.21	27.86	27.58	27.33	27.1	27.06
Humidity (%)	76.97	78.04	77.51	76.95	77.62	77.46	77.81	77.44	78.15	77.06

Fig. 2: Observed variations in temperature and humidity over the course of the study period (2005–2014).

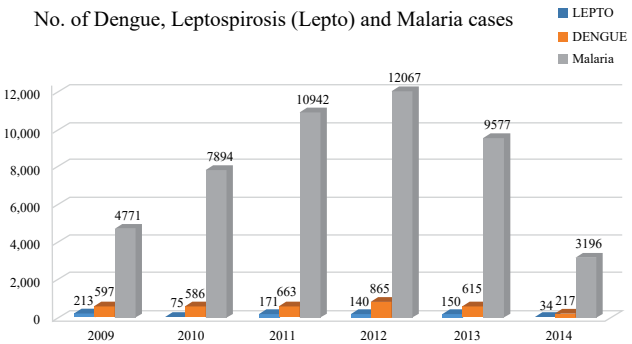


Fig. 3: Chart showing the total number of dengue, leptospirosis (Lepto) and malaria cases for the period 2009–2014.

For each consecutive year, the incidence of malaria recorded the highest frequency followed by dengue and leptospirosis, respectively. The highest annual total for malaria was recorded in 2012; in the same year, dengue recorded the highest frequency followed by leptospirosis in 2009 (Fig. 3). Incidences of dengue showed a weak positive correlation with humidity (r = 0.2) and temperature (r = 0.1). However, the strongest association was seen in relation to dengue incidences and rainfall (r = 0.7) (Fig. 4). The strongest relationship was noted between leptospirosis and humidity (r^2 = 0.6), whereas a negative relationship was observed between leptospirosis and rainfall (r^2 = 0.01) and leptospirosis and temperature (r^2 = 0.0001) (Fig. 5).

Figures 6–8 illustrate the relationships between different malaria species and climatic factors, including humidity, temperature and rainfall.

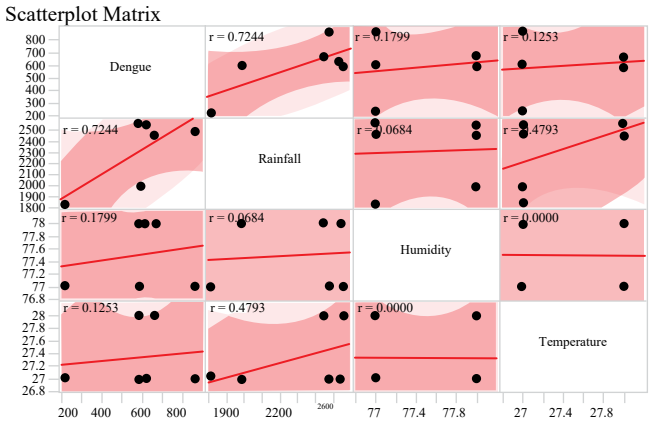


Fig. 4: Graphical comparison of dengue with rainfall, humidity and temperature.

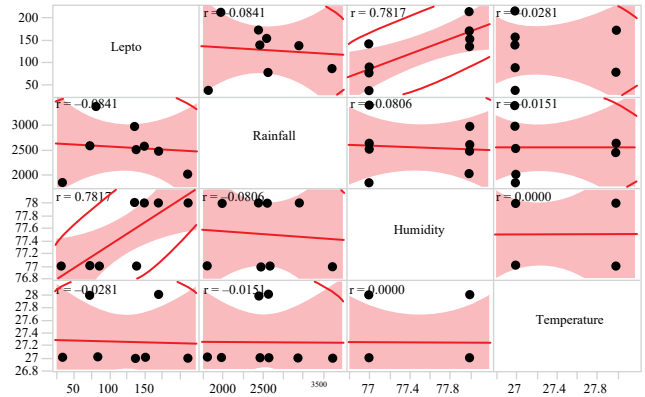


Fig. 5: Graphical comparison of leptospirosis with rainfall, humidity and temperature.

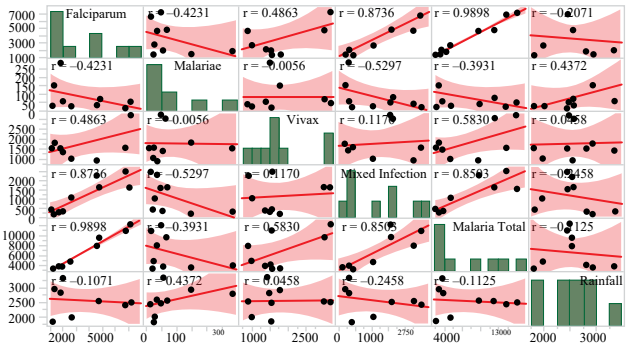


Fig. 6: Graphical comparison of malaria species with rainfall.

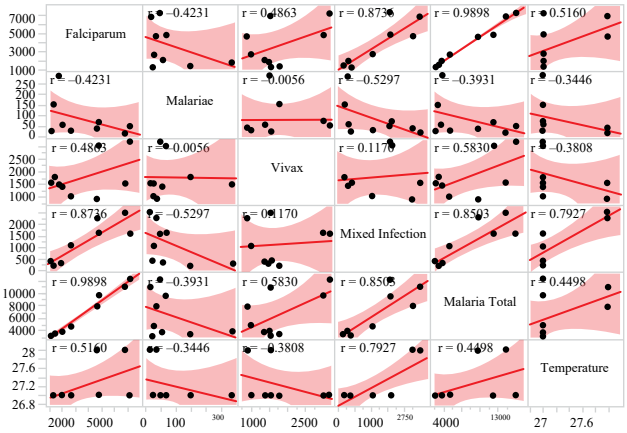


Fig. 7: Graphical comparison of malaria species with temperature.

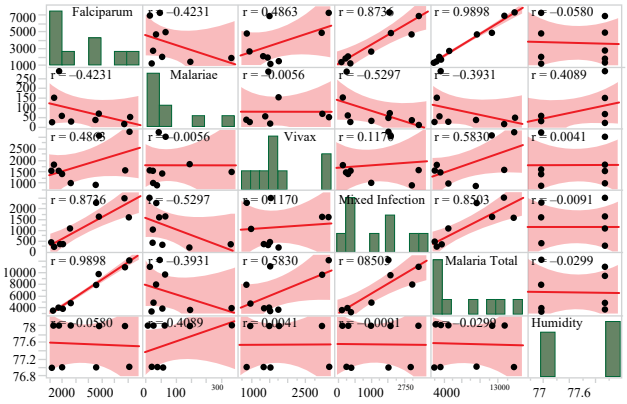


Fig. 8: Graphical comparison of malaria species with humidity.

DISCUSSION

This study has echoed the conclusion of most studies which suggest that either temperature or rainfall favours the increase in dengue, specifically the increase in rainfall. Scientific confirmation exists to show the relationship between climate variables, temperature and rainfall, and dengue (23, 24). A Similar study done in Singapore on incidences of dengue along with vector population in addition to climatic conditions showed that with an increasing temperature, incidence of dengue increases by 8–20 weeks (25). Contrary to projections

made for malaria, the data showed that with an increase of any of the climate variables there would be a decrease in the incidence of dengue.

The strongest relationship in our study was noted between leptospirosis and humidity and a negative relationship was observed between leptospirosis and rainfall and leptospirosis and temperature. This, however, goes contrary to other published studies which showed strong correlation between leptospirosis outbreaks and rainfall (26, 27). Humans become more exposed when environmental conditions, such as wet and hot, that favours *Leptospira* survival persist (28).

A sharp decline in the total malaria incidences was seen after 2012, which showed the highest recorded incidence of malaria for the period. Furthermore, the prediction model used, illustrated considerable increases likely due to rainfall and humidity. However, it should be noted that climate variability does not entirely influence malaria transmission. Factors such as social, biological, vector control measures, ecological settings, study population, population immunity and drug resistance have very influential roles in malaria transmission (29). This information, however, was not used in this study, and lack of should not diminish their importance in truly understanding every dimension of malaria transmission in relation to climate variability. Furthermore, the data collected did not reflect whether the cases identified were duplicates as this can lend to the increase in recorded cases of malaria. In addition, limited or lack of diagnostic capabilities in other regions could possibly account for the increase in total malaria cases.

CONCLUSION

In recent years, the ability to predict local and regional weather, in terms of accuracy, has rapidly been improved due to advances in technology. This has allowed a better understanding of the interaction between climate and the temporal–spatial distribution of vector-borne diseases as well as stimulating research interest in epidemic prediction modelling. It is recommended that an interdisciplinary approach be taken to ensure reliability and foster a better understanding of the relationship between climate variables and vector-borne disease.

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REVIEW ARTICLE

Vicarious Liability—Is It Fair?

A Bethelmy

ABSTRACT

We are now well into the 21st century, and the practice of medicine is almost unrecognizable from what it was a generation ago. New drugs, new surgical techniques and new genetic technologies that aid in the diagnosis and treatment of disease are the order of the day. However, this evolving practice of medicine has been matched by a rapidly growing awareness of patient's rights and the responsibilities of the current generation of medical practitioners towards their patients. As a result of this, the medico legal environment in the Caribbean is becoming increasingly litigious as patients are becoming more concerned about and more educated to, their rights. This is in large part due to increasing familiarity and exposure to the Internet, as well as American cable television. Cases of medical malpractice are becoming more common in Trinidad, Jamaica and Barbados, and it is against this backdrop that the doctrine of vicarious liability in the Caribbean requires urgent reexamination.

Keywords: Liability, medical law, vicarious.

INTRODUCTION

The doctrine of vicarious liability is not a new invention. Indeed, it has been in existence since the 17th century. In *Boson vs Sandford* in 1691, Chief Justice Holt famously remarked that 'for whoever employs another is answerable for him, and undertakes for his care to all that make use of him' (1). While its aims remain laudable even in modern day society, it is a policy that runs counter to the basic principle of tort law, *ie*, that a person should only be held accountable for the wrongs that he/she commits against another. The law normally imposes liability on the wrongdoer himself. Vicarious liability on the other hand renders a defendant liable for the misconduct of *another* party. The seminal example is between employer and employee. Here, the employer is liable for the torts of his employees, provided that they have been committed in the course of the employee's employment. Any claimant thus has two potential defendants: the individual who has committed the harm and his employer.

It is precisely because the concept of vicarious liability runs against the grain that an inherent tension in existing law is produced when decisions are to be made. A lack of understanding, even amongst the judiciary, has contributed to a variety of mixed results in recent years (2). The extension of the doctrine in these cases, which in some has led to the imposition of liability on faultless defendants for acts by those for whom they are held responsible, has led many to question just how fair it is to make innocent parties bear the burden of harm caused by miscreants whose behaviour they strongly abhor.

History

The common law development of vicarious liability can be traced to early medieval times and the concept of the master and servant (or craftsman and apprentice). Here, the master, as employer, possessed all the technical knowledge and gave the servant all the instructions as to how the labour should be carried out. However, the advent of the Industrial Revolution altered this relationship considerably, not only in terms of accident causation and the anonymity of the actual culprit, but the rise of insurance companies and the increasing technological knowledge of the 'servant'. It has long been the norm that medical professionals exercise initiative and discretion in their day-to-day performance of their duties without direct supervision from their employers.

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Thus, the doctrine has been forced to evolve with the times and does so even to this day.

The legal framework for vicarious liability

In order for vicarious liability to be established, three common factors must be present:

(1) The need for a specific type of relationship, *eg*, that of employer/employee.
(2) A wrongful act.
(3) A victim that is harmed in the course of employment or a specific task.

Hence, the doctrine is only confined to acts that are committed within the course of employment. As we shall see later, defining 'the course of employment' can be problematic. Vicarious liability also does not mean that the person at fault is not personally liable; on the contrary, he and the employer are held *jointly* liable. The employee can still be sued directly by the claimant and, in theory, the employer is entitled to recover any damages from the employee. In practice, however, this so-called indemnity right is limited because (a) the employee usually does not have the financial means to indemnify the employer, (b) the employee may simply be dismissed as a result of his actions and (c) it is in keeping with good industrial relations.

In the United Kingdom, a gentleman's agreement exists between insurance companies and employers not to pursue actions against negligent employees, except in cases of willful misconduct (3). Australia has gone a step further by putting this agreement into statutory form (4). Equally, in the United States, all government employees acting within the scope of their employment are protected from any personal liability (5).

Tests used to identify the employer/employee relationship

The control test

In examining the validity of the employer/employee relationship and whether it gives rise to vicarious liability, the starting point has generally been one of control and the ability to exert authority over the employee (6). The archetypal employment relationship was therefore one where the employer could control the employee's work, instruct him what work to undertake and how it should be performed. The appeal of the control test lies in its dual role; it determines for *whom* the defendant will be liable and *why*. The test has been seen not only as one of the existence of the conditions for liability but also as a justification for imposing it (7).

However, by the latter half of the 20th century, changes in employment practices, increasing use of technology and the rise of the professional have served to render the test less useful, except in straightforward cases. Doctors frequently work without direct supervision and would not be expected to be told what to do and how to do it every working day. The control test therefore needs to be reappraised in its relation to modern employment practices.

The totality of the employment relationship test

The common law has gradually moved towards a multi-faceted approach, where it is recognized that the concept of control is no longer absolute but represents one factor out of many in determining whether a contract of employment exists. Other factors may include whether one provides his own equipment, the degree of financial risk taken and the opportunity for profit in the performance of the task. For this reason, the test is also known as the 'composite or economic reality/entrepreneur test' and this is applied in the common law up to the present time.

Determining the scope of vicarious liability

Once it has been established that the correct type of relationship exists, *eg*, that of an employer and employee; it remains to be seen to what extent will the employer be held responsible for his employee's wrongful actions. It is important to note that the employer is not liable for *all* wrongful acts committed by an employee but only those that take place within the course of employment. In medieval times, this was not the case; indeed, a person was liable for all wrongs committed by his servant (8). A change was seen from the 1800s, when in a number of cases courts determined when employees would be on a so-called frolic of their own and the employer was not held to be liable (9). However, even to this day, the distinction between a 'frolic' and being within the course of employment remains problematic.

In determining the scope of liability, there must be a delicate balance. Too restrictive an interpretation will reduce the incentives for an employer to undertake preventative measures and will diminish the ability of a victim to seek redress from a wealthier defendant. Too broad an interpretation will impose an undue financial burden on defendants. In practice, the common law has found it difficult to achieve such a balance between the three members of the vicarious liability triangle: the victim, the employee and the employer. What is clear though is that in all cases the courts focus on the specific

facts of each case and adopt a flexible approach to the course of employment test in each case, guided as they are by the policy of ensuring victim compensation and reaching a just and fair decision.

When determining the course of employment test, the traditional starting point has been the so-called Salmond test (10).

*'*A master is not responsible for a wrongful act done by his servant unless it is done in the course of employment. It is deemed to be done if it is either (a) a wrongful act authorized by his master, or (b) a wrongful and authorized mode of doing some act authorized by the master.*'*

Hence, an employee is held to be acting in the course of employment if his conduct is authorized by the employer or is considered to be an unauthorized means of performing the job for which he is employed. So if an anaesthetist intubates the oesophagus, fails to recognize it and the patient subsequently dies of hypoxia, this is considered an unauthorized means of performing the job. Likewise, if a surgeon leaves a swab in the abdomen, this is also considered unauthorized.

However, in recent years, the usefulness of the Salmond test has come under increasing scrutiny. Whilst it is possible to portray a negligent act as being akin to an unauthorized mode of doing one's job, it is not so straightforward when situations of *intentional* wrongdoing arise. The problem is that if one is to deem a serious criminal offence as an unauthorized mode of performing one's tasks, this requires distorting the Salmond test to include acts that most employers would never dream of condoning.

The close connection test

The Supreme Court of Canada pioneered what is known today as the 'close connection' test. In Bazley vs Curry, the Salmond test was rejected in favour of a policy-based approach to vicarious liability, *ie*, the provision of a just and practical remedy for any damage suffered, as well as the deterrence of future harm (11). Thus, it is fair and just to place liability on an employer when the employer puts into place an enterprise that carries certain risks (so-called enterprise risk). The advantages of this test are (a) its flexibility in adapting to each factual situation and (b) it focuses on the rationale for applying vicarious liability and extends it to cover intentional misconduct. However, flexibility can be misinterpreted as uncertainty, and this leads to a divergence of views amongst the judiciary on application to broadly similar situations.

The British approach to identify a more general test for close connection has been a more composite one, mirroring that of the course of employment test. It was best stated as: *'*Perhaps the best general answer is that the wrongful conduct must be so closely connected with acts the employee was authorized to do that, for the purpose of the liability of the firm or the employer to third parties, the wrongful conduct may fairly and properly be regarded as done by the partner while acting in the ordinary course of the firm's business or the employee's employment.*'*(12) In *Bernard vs Attorney-General of Jamaica* (13), the need for a composite approach was also recognized by Lord Steyn. He noted that 'The correct approach is to concentrate on the relative closeness of the connection between the nature of the employment and the particular tort, and to ask whether looking at the matter…..it is just and reasonable to hold the employers vicariously liable. ……..a relevant factor is the risks to others created by an employer who entrusts duties, tasks and functions to an employee.*'* Although they have avoided adopting the 'enterprise risk' test in its entirety, it is noticeable that it still forms part of the considerations of the British courts. Three key facts are examined by the latter: (a) the specific facts of each case, (b) the employee's purpose and (c) the policy interest in ensuring victim compensation.

CONCLUSION

Vicarious liability is a doctrine that has evolved over time. From the justification of fault in pre-Industrial Revolution times to the welfare considerations of the compensation of innocent victims in a post-Industrial Revolution age, it now exists where the skilled, independent professional works hand in hand with technological advancement and a strong insurance market. For vicarious liability to exist, there must be a specific act, a specific type of relationship, and that act must be committed within the course of employment. Tests to determine the last two factors have metamorphosed to become composite in nature. As ever, the courts are driven in their search for what is a fair and just solution, and vicarious liability represents a compromise; a mechanism that seeks to provide a balance between the needs of innocent victims and the risks posed to society by an employer's enterprise, industrialization and technological advancement.

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CASE REPORT

Tumoural Calcinosis

D Clarke, S Franklin, S Mullings, G Jones

ABSTRACT

Para-articular calcified masses remain a relatively common occurrence where it is most often due to chronic renal failure. The underlying aetiology is usually due to a disorder of calcium metabolism, chronic inflammation, or malignancy. In a small subset, it is due to hyperphosphatemia from an underlying disorder of phosphate metabolism, tumoural calcinosis. Identifying this subset of patients is paramount for effective management as medical management of the associated hyperphosphataemia is critical in lowering the incidence of recurrence.

Keywords: Para-articular calcified masses, tumoural calcinosis.

INTRODUCTION

Tumoural calcinosis is a rare benign idiopathic condition characterized by the presence of tumour like para-articular soft tissue masses (1, 2). These masses may be progressive and affect joint motion. Complete excision of the mass with medical management of phosphate metabolism is usually indicated (3).

A case of tumoural calcinosis in a 14-year-old male is presented here highlighting its progressive nature and management.

CASE REPORT

A 14-year-old boy presented to our outpatient department with a 6 month history of masses to the posterior aspect of his right knee and left elbow. There was no history of trauma, and no family history of similar occurrences. The masses gradually increased in size with tenting of skin. There were no neurological symptoms.

Examination revealed a firm mass in the posterior lateral aspect of popliteal fossa that was not attached to overlying skin. No neurovascular deficits were appreciated. Examination of the left arm revealed a mass to the posterior lateral aspect of the distal arm that was mobile and not attached to overlying skin. Biochemical markers were normal.

Sequential radiographs revealed a progressive increase in size (Figs. 1–4). A decision for surgical excision was made. At surgery, a lobulated mass measuring 15 × 7 × 5 cm was excised from the right knee, there was no attachment to surrounding soft tissue and the inner cavity consisted of a white amorphous substance. A mass similar in description was excised from the left elbow. His postoperative period was uneventful. Six months post-op, there were no signs of recurrence.

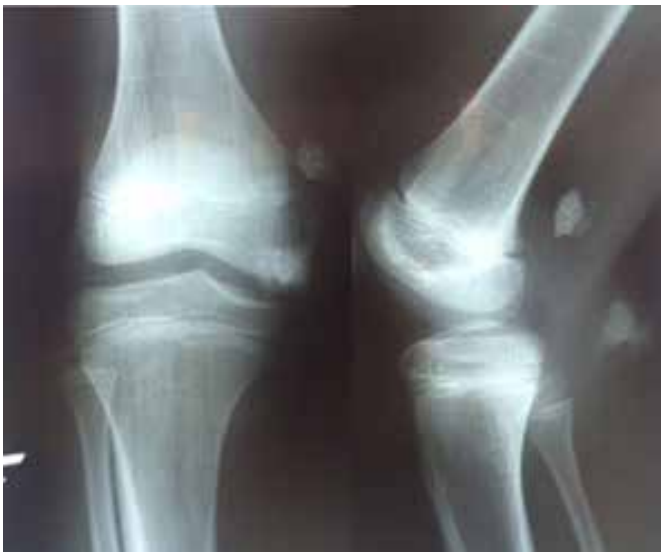

Fig. 1: Anterior posterior and lateral radiographs of knee on presentation.

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Fig. 2: Anterior posterior and lateral radiographs of the right knee 6 months after presentation.

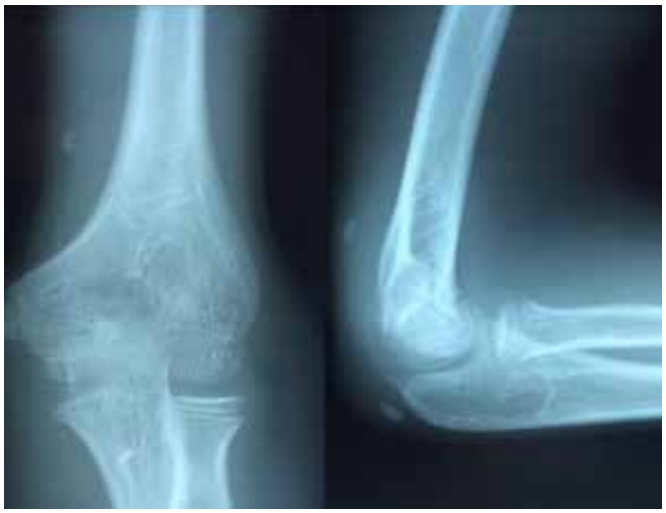

Fig. 3: Anterior posterior and lateral radiographs of left elbow on presentation.

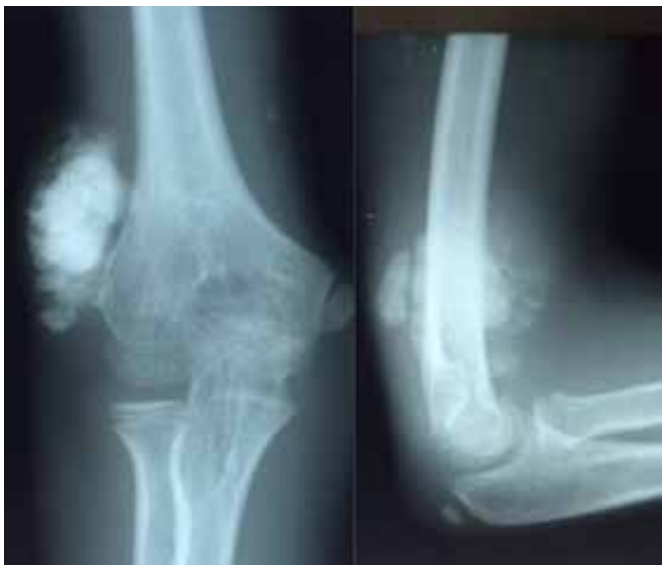

Fig. 4: Anterior posterior and lateral radiographs of left elbow 6 months after presentation.

DISCUSSION

Tumoural calcinosis is a rare condition characterized by the presence of painless firm circumscribed para-articular calcified masses. It was first described by Giard in 1898 and later by Duret in 1899 (4, 5). The term was coined by Inclan *et al* in 1943 (2). In their pivotal article, they defined metabolic criteria and differentiated tumoural calcinosis from other forms of soft tissue calcification. Inclan noted a normal calcium and phosphate level in all three of his reported cases, absence of collagen vascular disorders, and infections inclusive of tuberculosis. The authors made note of the progressive nature of the condition tendency to spread beyond bursal and muscular structures as well as its anatomic distribution in relation to gliding surfaces (2).

The condition has no sexual predilection and commonly occurs in the first or second decade of life as in the index case (6). There is an increased incidence in patients of African descent in keeping with our case (7–9). The condition may be sporadic or familial. Despite early reports of an autosomal dominant inheritance in the familial form by Lyles *et al*; more recent identification of the underlying genetic defect points to an autosomal recessive pattern of inheritance (10–13). Tumoural calcinosis has been linked to loss of function mutations in GALNT3, FGF23, and KLTHO gene that result in the inactivation of FGF-23 (11, 12). In effect, it may be seen as the clinically converse of hypophosphatemic rickets, which is due to a gain of function mutation in FGF23. Biochemically, this mutation is manifested by hyperphosphatemia due to increased renal reabsorption of phosphorus (14, 15). Other biochemical features of tumoural calcinosis include an elevated vitamin D level with normal calcium, parathyroid hormone, and renal function test (14–16). Thus serum calcium, serum phosphorous, urinary calcium (24 hours), serum parathyroid hormone, and serum vitamin D levels are indicated in the evaluation of these patients.

The clinical presentation is usually characterized by the presence of painless para-articular masses. The hip is the most commonly afflicted region followed by the elbow, shoulder, foot, and wrist (17). The lesions tend to progressively increase in size and may ulcerate and discharge a white calcific material (1). As the masses enlarge, they may also cause compressive symptoms and may affect joint motion, thus necessitating surgical excision (18). The characteristic radiographic appearance of tumoural calcinosis is that of multi-lobulated calcified densities separated by radiolucent bands with the absence of osseous destruction as seen in the radiographs of the

presented case (1). Plain radiographs may also demonstrate the characteristic dental lesions, root enlargement, and pulp stones (19). These represent calcific deposits that occupy and obliterate the pulp space. Martinez *et al* also demonstrated the radiographic evidence of calcific myelitis and periosteal reaction in three of their five patients (1). In their review of radiographic imaging in tumoural calcinosis in their patient set, bone scan offered the greatest sensitivity among all imaging modalities (1). Features on magnetic resonance imaging are rather unique with increased signal intensity on T2 weighted films (1). This seems rather paradoxical in lieu of the abundant calcific component. Computed tomography may show the 'sedimentation sign', representing layering of the calcification (20). Plain radiographs in conjunction with the history and biochemical parameters are, however, often sufficient to make the diagnosis.

The presence of para-articular calcified masses on plain radiographs is, however, not an infrequent occurrence. When present, the most common cause of this para-articular soft tissue calcification is chronic renal failure. Other differentials include chronic tophaceous gout, osteoma cutis, calcific myonecrosis, myositis ossificans, calcific tendonitis, synovial chondromatosis, and sarcomas: osteosarcoma and synovial sarcoma.

The underlying aetiology can be classified or stratified according to history and serum chemistry profile into metabolic, dystrophic, and idiopathic forms. Iatrogenic metabolic forms are due to elevated serum calcium levels with or without an associated elevated phosphate level. Examples are calcinosis of chronic renal failure and hyperparathyroidism. Dystrophic causes result from calcification in the presence of a normal calcium and phosphate level and are usually due to an underlying inflammatory disorder. Idiopathic calcification is characterized by normal calcium with elevated or normal phosphate levels. The latter is the group to which tumoural calcinosis exists.

The mainstay of management of tumoural calcinosis is complete excision of soft tissue masses where it may combined with medical management of phosphate dysregulation, *ie* phosphate bending antacid (*eg* aluminium hydroxide) in combination with acetazolamide (21, 22). Complete excision may prove challenging at times due to finger-like projections into surrounding soft tissue increasing the risk of recurrence (3). In cases of recurrence, the lesion tends to be more aggressive (3).

CONCLUSION

Tumoural calcinosis represents a rare form of idiopathic periarticular calcification due to a loss of function mutation resulting in an inactivation of FGF-23. Differentiating tumoural calcinosis from other conditions that may cause soft tissue calcification is critical to the management to prevent the added morbidity of over treatment.

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CASE REPORT

FDG PET/CT Findings in Diagnostic Evaluation of Mononucleosis Mimicking Malignant Lymphoma

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ABSTRACT

A 43-year-old male complaining about high fever, night sweats, cough and unintentional weight loss for 2 weeks was admitted to the hospital. His blood analysis showed that the white blood cell count was 24.1 × 109/L with 58.5% lymphocytosis, where some of them were atypical lymphocytes. Laboratory analysis also showed elevated erythrocyte sedimentation rate, liver enzymes and lactate dehydrogenase. Initially, the Epstein–Barr virus (EBV) serology was found to be negative. Additional imaging methods showed hepatomegaly and cervical, axillary, mediastinal and hilar lymphadenopathy. Due to persistency of clinical symptoms and laboratory findings, we suspected lymphoma with B symptoms and performed positron emission tomography/computed tomography (PET/CT) with [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) to determine the appropriate lymph node for biopsy. The [^{18}F]2-fluoro-2-deoxy-D-glucose PET/CT scan showed pathological FDG uptake in numerous cervical, thoracic and abdominal nodes, liver, spleen and bone marrow. Epstein–Barr virus viral capsid antigen IgM was found to be positive and resulted in acute EBV titres. The patient's abnormal FDG PET/CT scan was most likely secondary to acute EBV infection. The patient was closely monitored without performing lymph node biopsy, and it was observed that symptoms regressed clinically and laboratory results decreased within the normal range in the follow-up controls performed after two months. Our case report indicates that coexisting FDG uptake in the spleen more than in the liver and high FDG uptake in the Waldeyer's ring should be taken into consideration in favour of EBV infection.

Keywords: Epstein–Barr virus, [^{18}F]2-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography, infectious mononucleosis, lymphoma, splenic uptake.

INTRODUCTION

Epstein–Barr virus (EBV) may cause infectious mononucleosis (IM), characterized by fever, pharyngitis and general lymphadenopathy. Epstein–Barr virus is also associated with a variety of malignancies, including Burkitt lymphoma, nasopharyngeal carcinoma and Hodgkin's lymphoma (1).

Exposure to EBV predominantly occurs through salivary contact in early adulthood during the first two decades of life, and approximately 90% of adults worldwide are EBV positive (1, 2).

Malignant lymphomas have many histological subtypes and can be confused clinically with other lymphoproliferative diseases caused by infection and inflammation, especially EBV (3, 4).

The use of positron emission tomography/computed tomography (PET/CT) with [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) has evolved in the last few decades for

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diagnosis, staging and treatment follow-up in oncology. However, because of the uptake of FDG in non-neoplastic aetiologies, such as inflammatory, reactive, or infectious reasons, PET imaging is not specific, unfortunately in the field of oncology.

Medical history, clinical findings, serological tests, radiological tests and histopathological investigations have great importance in terms of diagnosis and treatment to be applied in the improvement of lymphadenopathies. In this report, we present a case with EBV infection mimicking lymphoma with clinical symptoms and imaging PET/CT findings, and highlight the need to consider infections when evaluating FDG-PET/CT images of patients with generalized lymphadenopathy.

CASE REPORT

A 43-year-old male patient associated with fever, cough, night sweating and 8 kg unintentional weight loss was referred to our hospital from a health centre with a preliminary diagnosis of lymphoma.

He did not have a significant medical history, and his complaints started 15 days prior to being admitted to the hospital. A physical examination of the patient who had been hospitalized for 2 days in another health centre 2 days prior was unremarkable, except for pharyngeal hyperaemia and positive jugulodigastric painful lymphadenopathy; no organomegaly was noted. The results of the laboratory investigations obtained from the other health centre is presented in Table 1. Atypical lymphocytes and a few basket cells were observed on the peripheral smear. Electrolytes and blood creatinine levels were found to be normal. Serological tests for Brucella infection (Rose Bengal, Wright agglutination) and EBV were negative. The chest X-ray showed no infiltrative abnormalities. Additional imaging was performed and CT of the thorax/abdomen showed axillary (12 and 15 mm), paratracheal (19 mm), periportal (16 mm), paraaortocaval (< 10 mm) lymphadenopathy and hepatomegaly (17.6 cm), but no splenomegaly was observed.

After admission to our hospital, the patient was closely monitored at the otorhinolaryngology clinic. The patient's fever ranged between 38.5ºC to 39ºC and it was reduced to the normal range following intravenous 3 × 1-g paracetamol administration. Laboratory test results from our hospital are summarized in Table 1. Bilateral cervical lymphadenopathies (left 24 × 17 mm and right 19 × 10 mm) were found during cervical ultrasonographic examination.

Table 1: The laboratory test results

Test	Other health centre	Our hospital	Follow-up control after 2 months	Normal range
WBC (10^9/L)	24.1	16.1	7.5	4–10
Lymp (10^9/L)	14.1	10.7	3.5	1.2–3.2
ESR (mm/h)	54	73	8	< 20
ALT (U/L)	77	71	44	10–40
AST (U/L)	59	54	24	15–40
LDH (U/L)	968	888	192	< 248
CRP (mg/L)	84	143	5	< 8
ALP (U/L)	256	84	54	40–120
GGT (U/L)	230	183	33	< 55
DSB (mg/dL)	0.4	0.3	0.1	< 0.2
TSB (mg/dL)	1.3	1.3	0.7	0.3–1.2

WBC = white blood cells; Lymp = lymphocytes; ESR = erythrocyte sedimentation rate; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; CRP = C-reactive protein; ALP = alkaline phosphatase; GGT = gamma glutamyl transferase; DSB = direct serum bilirubin; TSB = total serum bilirubin.
Bold letters indicate abnormal results.

Diagnosis of lymphoma could not be excluded due to cervical, axillary, thoracic, abdominal and inguinal lymphadenopathies and loss of unintentional 8 kg weight in the last 3 weeks. Therefore, FDG PET/CT was performed on the patient to identify the appropriate lymph node for biopsy.

Increased metabolic activity with standardized uptake value (SUVmax) of 15.6 in the Waldeyer's ring was noted (Figure 1). In addition to that, the scan revealed pathological FDG uptake in enlarged lymph nodes in the bilateral cervical regions (15 mm, SUVmax: 7.0), axillas (17 mm, SUVmax: 7.2), lung hili (< 10 mm, SUVmax: 5.3), inguinal regions (< 10 mm, SUVmax: 4.7) and impaired liver/spleen ratio (SUVmax: 4.6/7.1, respectively). Additionally, diffuse metabolic activity increase in the axial and appendicular skeletal system of bone marrow was noted (SUVmax: 6.1). Findings were suspicious for a lymphoproliferative disease and cervical lymph node biopsy and an additional bone marrow biopsy was planned. However, according to repeated viral serology test results revealed EBV *viral capsid antigen* IgM as positive neither lymph node, nor bone marrow biopsies were performed. The patient was closely monitored and symptoms regressed clinically (spontaneous clinical improvement was observed). It has been observed that most of the laboratory results were found to be in the normal range in follow-up controls performed two months later (Table 1).

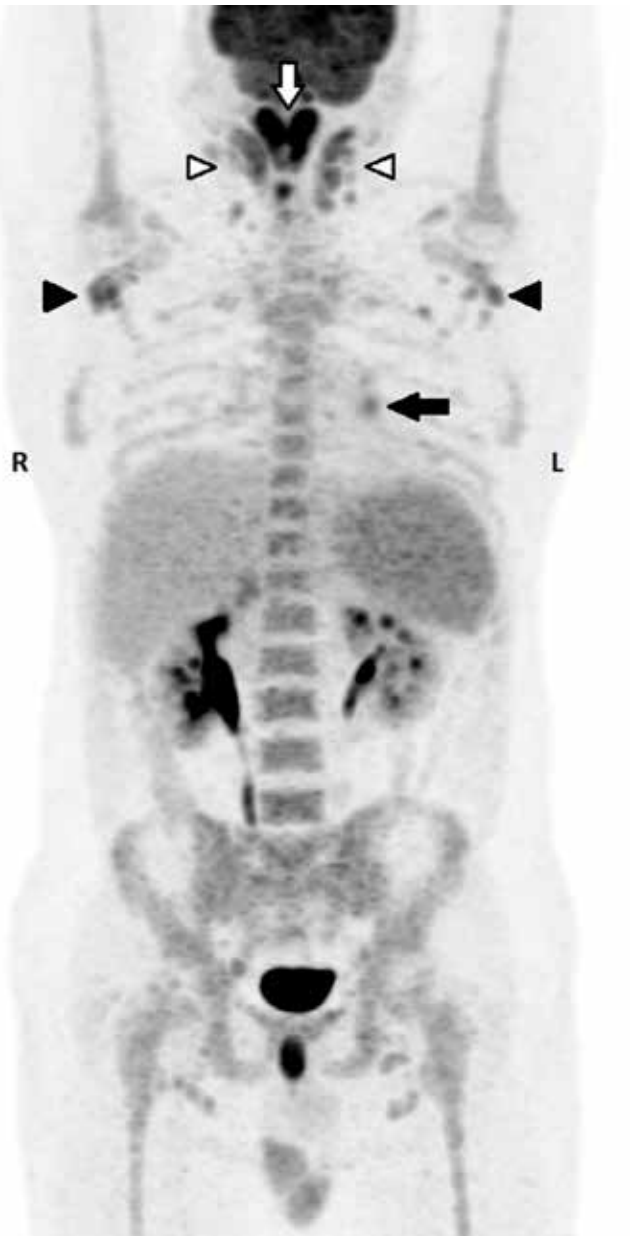

Figure 1: Maximum intensity projection (MIP) image of [^{18}F]2-fluoro-2-deoxy-D-glucose- positron emission tomography/computed tomography shows elevated FDG uptake in the Waldeyer's ring (white arrow), lung hili (black arrow), bilateral cervical (white arrowheads) and axillary (black arrowheads) lymph nodes. The splenic uptake is diffused and significantly greater than the liver uptake.

DISCUSSION

Acute EBV infection is generally inapparent or is a self-limited illness that lasts 2–3 weeks. Clinically apparent infectious mononucleosis is more common in populations after the first decade of life (1). Since our case was older (at age 43) and showed clinical symptoms longer than 3 weeks, a FDG PET/CT scan was performed in order to rule out lymphoma, which might be seen along with EBV infection.

Acute EBV infection may present in different aspects and can mimic malignant lymphoma at presentation. Differential diagnosis between EBV related lymphadenopathy and lymphoma is difficult based on clinical findings and imaging techniques. Because circulating cell-free EBV DNA may be detected in plasma and serum of patients with EBV-associated tumours, detecting anti-VCA IgM is more valuable than EBV PCR to diagnose acute EBV infection and differentiate suspicious lymphomas (5).

Cases of EBV infections diagnosed as various types of lymphoma were reported in the literature (3, 4). In a case report it is interestingly stated that during chemotherapy for biopsy-proven Hodgkin's disease intense increased FDG uptake due to asymptomatic EBV infection was noticed in multiple lymph nodes and spleen (6).

Inflammation and infections are the most well-established causes of false positive interpretations of FDG PET/CT as suspicious of malignancy due to increased glucose metabolism turnover. Diffuse increased splenic uptake in FDG-PET refers lymphoma, sarcoidosis, malaria, extramedullary granulopoiesis, congestive splenomegaly, toxoplasmosis, infectious mononucleosis, varicella infection, myelofibrosis and beta-thalassemia (7, 8). In normal subjects, the uptake of FDG in the spleen is less than in the liver (9). Greater splenic FDG uptake than hepatic uptake is compatible with lymphomatous involvement of the spleen (8). However, more elevated diffuse FDG uptake in the spleen than in the liver and FDG uptake in the primary nasopharyngeal lesion have been reported in some cases with acute mononucleosis (2, 7, 10).

We observed greater splenic FDG uptake than the hepatic uptake and high FDG uptake in the Waldeyer's ring in our case. Since then, our case was diagnosed as EBV infection, however, the biopsy was not performed. Haematological and biochemical analyses showed a decrease in white blood cell lymphocytes, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase and bilirubin values pointing out that the case was infectious mononucleosis (Table 1).

Since PET/CT is not a diagnostic tool to detect a primary EBV infection in daily clinical practice, only a few cases have been reported about PET/CT findings of EBV infections (6, 10). Although no specific FDG-PET/CT findings to distinguish between EBV-related lymphadenopathy and lymphoma were reported when encountering patients with generalized lymphadenopathy with FDG uptake in the nasopharynx and FDG

uptake in the spleen more than in the liver, it should be taken into consideration in favour of EBV infection. For accurate diagnosis and appropriate medical approach, not only laboratory findings, but also the evaluation of both clinical features and course of the disease is essential.

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CASE REPORT

A Simple and Effective Treatment Alternative in an Idiopathic Gingival Enlargement Case

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ABSTRACT

Idiopathic gingival fibromatosis is a rare condition characterized by enlargement of the gingival tissues, causing aesthetic and functional problems. The condition is caused by various factors including inflammation, neoplasia, or heredity. A 55-year-old male patient, with no previous history of drug use or family history of gingival fibromatosis, presented with a slow-growing tissue in both the maxillary and mandibular anterior-lingual sites. After the clinical examination and taking the patient's medical history, the enlarged tissue was removed with a Nd:YAG laser surgery procedure. Tissue samples were evaluated histopathologically, revealing squamous epithelium with underlying fibrous, connective tissue and inflammatory cell infiltration in the epithelium. Through clinical and histopathological analyses, the case was diagnosed as idiopathic gingival fibromatosis. Moreover, the patient was followed for 3 months, and no recurrence was observed in the surgical areas. The Nd:YAG laser surgery also seemed very practical and effective.

Keywords: Idiopathic gingival enlargement, Nd:YAG laser, treatment

INTRODUCTION

Idiopathic gingival fibromatosis (IGF) is a rare condition of unknown aetiology and pathology (1), characterized by enlarged maxillary and mandibular gingiva, causing aesthetic and clinical symptoms, including pain, speech disturbances, teeth displacement, occlusion problems, increased risk of caries, and periodontal disorders. Diagnosis is based on the patient's medical, dental and family history, and histopathological examination (2). We present the case of a 55-year-old male diagnosed with IGF in the mandibular and maxillary anterior regions, treated with a Nd:YAG laser surgery.

CASE REPORT

A 55-year-old male patient visited the Department of Periodontology, Faculty of Dentistry, Cumhuriyet University, complaining of gingival bleeding, difficulties in eating, halitosis and aesthetic concerns due to gingival enlargement. The patient first noticed the enlarged tissue 10 years earlier and reported that it slowly increased in size. His family history was not significant for disease transmission. There was no history of medications that could indicate drug-induced gingival enlargement. His physical appearance was normal, and no hormonal abnormalities were observed. Neither traumatic habit nor removable prosthesis was associated with the enlargement, nor was there any extraoral pathology. There were no other significant systemic or medical findings. Intraoral examination revealed generalized gingival overgrowths of the anterior sides of both the maxillary and mandibular arches, which affected the vestibular and palatal surfaces.

The enlarged gingiva caused teeth diastemas and covered from one-half to two-thirds of the crowns. The patient had lost his mandibular, left, central incisor due to trauma 10 years previously. The enlarged gingiva was pink in colour, firm, and resilient in consistency (Fig. 1).

The patient's level of oral hygiene was poor. Before surgery, phase I periodontal treatment was performed in order to achieve optimal plaque control and to eliminate the inflammation. The patient returned at one-week intervals for treatment to control his oral hygiene. After three

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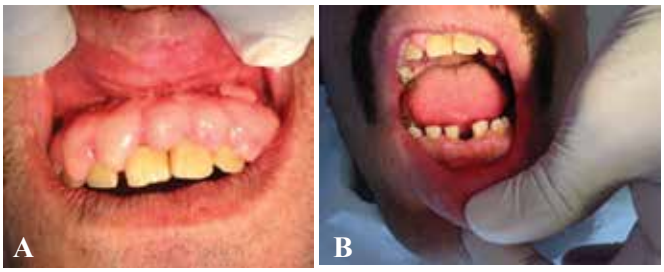

Fig. 1 (A, B): Intraoral views at baseline.

weeks, the inflammation was controlled sufficiently so that the enlarged gingival tissue could be removed with the Nd:YAG laser device (Deka, Calenzano Firenze, Italy). A 3-W, 100 mJ therapy surgical protocol was used. Post-operatively, 0.12% chlorhexidine oral rinse and an anti-inflammatory drug (twice daily) were prescribed.

The excised tissue was sent for the histopathological examination. The histopathology revealed squamous epithelium with underlying fibrous, connective tissue under low-power magnification (×40) (Fig. 2).

Moreover, under high-power magnification (×100), inflammatory cell infiltration was observed in the epithelium (Fig. 3).

Good tissue healing was observed when the patient was examined 1 week after the surgery. The patient was examined 3 months later at a follow-up visit, and there was no recurrence, and the patient seemed good clinically (Fig. 4). The patient's oral health is still under control.

DISCUSSION

The classification of gingival fibromatosis (GF) is controversial and there is no consensus of the classification in the literature. However, Takagi *et al* classified it into the following: (a) isolated familial gingival fibromatosis; (b) isolated idiopathic gingival fibromatosis; (c) gingival fibromatosis with hypertrichosis; (d) gingival fibromatosis with hypertrichosis and mental retardation and/or epilepsy; (e) gingival fibromatosis with mental retardation and/or epilepsy; and (f) gingival fibromatosis associated with the other diseases with formation of syndromes (3). Otherwise, gingival fibromatosis may exist as an isolated finding or as a part of a syndrome.

The syndromes associated with GF are the Rutherford syndrome (gingival fibromatosis and corneal dystrophy), the Laband syndrome (gingival fibromatosis, ear, nose, bone, and nail defects, with hepatosplenomegaly), the Cross syndrome (gingival fibromatosis, microphthalmia, mental retardation, athetosis, and hypopigmented skin), the Murray-Puretic-Drescher syndrome (gingival fibromatosis with multiple hyaline fibromas), the Jones syndrome (gingival fibromatosis with sensorineural deafness), and the Byars-Jurkiewicz syndrome (gingival fibromatosis, hypertrichosis and giant fibroadenomas of the breast) (4).

Idiopathic gingival enlargement is a slowly progressive disease, and the enlarged tissue may be localized to specific areas of the mouth, usually the labial gingiva

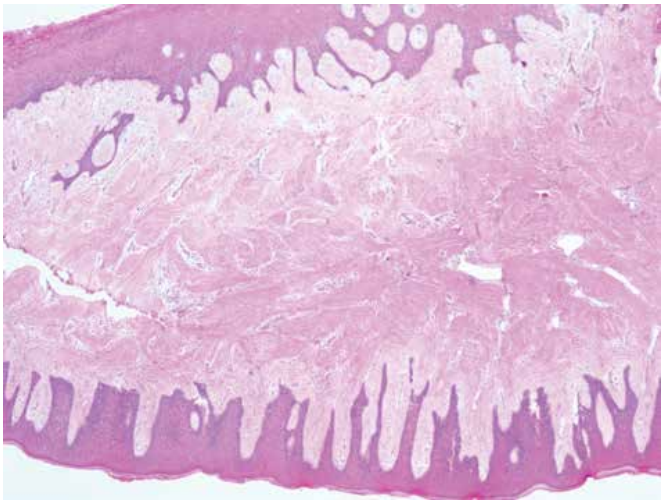

Fig. 2: Squamous epithelium with underlying fibrous, connective tissue (×40).

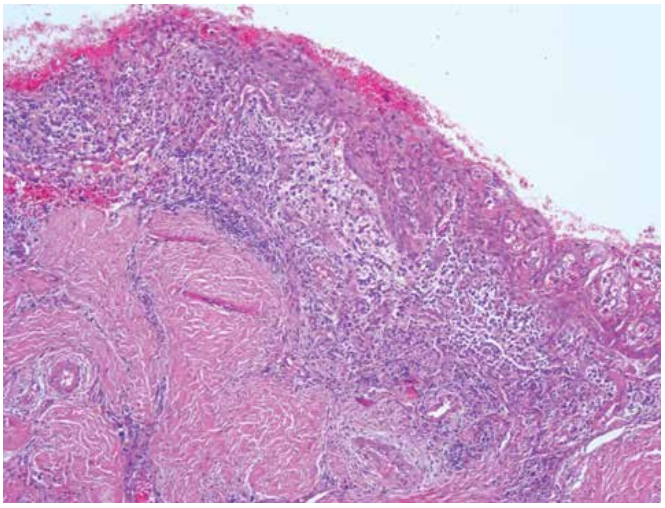

Fig. 3: Inflammatory cell infiltration into the epithelium (×100).

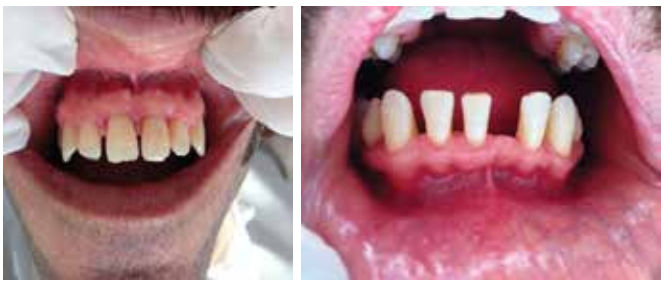

Fig. 4: Intraoral views after surgery (3 months).

around the lower molars and the maxillary tuberosity. The enlargements may involve a few teeth or all teeth according to the disease severity (5).

In our case, we used the Nd:YAG laser to remove the enlarged tissue. In a case report by Develioglu *et al* (6), an atypical gingival enlargement was removed using the Nd:YAG laser and an uneventful result was achieved. This laser type is very practical, and its usefulness is accentuated by both patient outcomes and its use by the surgeons.

In the literature, several idiopathic gingival enlargement cases are reported. Similar to our case, Jayachandran *et al* (7) reported an idiopathic gingival fibromatosis in a 30-year-old woman. She presented with a generalized, severe gingival overgrowth involving the maxillary and mandibular arches. The patient's medical and family history was non-contributory, and she was not receiving any medication that could contribute to the gingival enlargement. A full-mouth undisplaced flap surgery was performed. There was no recurrence during 2 years of follow-up. In our case, the enlargement was located only at the anterior site of the maxillae. No reason was found for why the enlargement was located on only the anterior side in our case.

Similarly, Shetty *et al* (8) reported on a 13-year-old female patient with IGF. She did not have any history of drug use. Also, her familial and postnatal history was non-contributory. After completing phase I treatment, a quadrant-wise gingivectomy was performed under local anesthesisa, using four different techniques (ledge and wedge technique, external bevel gingivectomy, electrocautery and diode laser). The use of the laser and electrocautery provided excellent haemostasis and better immediate post-operative results. We achieved a good result using the Nd:YAG laser.

On the other hand, Patussi *et al* (9) reported a case of hereditary gingival fibromatosis in a 6-year-old, female patient. The gingival hyperplasia extended from the anterior to retromolar, right mandible, surpassing the occlusal plane, which caused difficulty with lip closure and the imprint of her upper teeth on the surface of the lesion. A surgical excision was performed. The histopathological analysis confirmed the diagnosis of fibromatosis. There were no signs of recurrence at the follow-up approximately 20 months later. Our patient was older, and the laser was used to remove the fibromatosis.

In summary, idiopathic gingival enlargement can be seen in the clinical practice. Which treatment techniques best prevent recurrence is still unknown, but some practical techniques such as the Nd:YAG laser could be considered in treating these cases.

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CASE REPORT

Uncontrolled Systemic Inflammatory Response Syndrome by Cardiopulmonary Bypass

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ABSTRACT

It is known that the use of a cardiopulmonary bypass (CPB) during cardiac surgery leads to leukocyte activation and may, among other causes, induce organ dysfunction due to increased leukocyte recruitment into different organs. In our patients, pathophysiologically severe systemic inflammatory response syndrome, uncontrolled CPB-induced inflammation, chylomicrons and very low density lipoproteins or immune complexes have been shown to develop immune-dependent agglutination by C-reactive proteins in CPB, which could result in vascular occlusion and resultant infarction.

Keywords: Cardiopulmonary bypass, leukocyte, thoracic surgery

INTRODUCTION

Socha *et al* (1) found that during cardiopulmonary bypass (CPB), phospholipase A_2 degrades arachidonic acid, leading to inflammatory mediators such as leukotrienes, prostaglandins and thromboxanes. The action of these substances triggers adhesion and neutrophil activation, vasoconstriction, tissue injury, platelet aggregation and the ischaemic organ change (2). The differential diagnosis can be divided into three categories: emboli from the cardiac and arterial systems, acquired hypercoagulability disorders, and syndromes which lead to peripheral vascular pathology (1).

CASE REPORT

A 45-year-old woman secondary to rheumatic fever and aortic regurgitation was scheduled for aortic valve replacement. Pre-operative echocardiography revealed severe aortic regurgitation. She denied any cerebral symptoms, including headache, dizziness, transient ischaemic attacks or strokes in her medical history; the patient was found to be fully conscious, alert and oriented with stable vital signs. The blood pressure was 110/80 mmHg, and the diastolic murmur was audible over the mitral area. The physical exam revealed intact cranial nerves, motor power and sensation. There was no evidence of vasculitis such as Osler's nodes, Jane way pad, palmer erythema or cyanosis of fingers. The blood investigation showed an erythrocyte sedimentation rate of 4 mm with no leucocytosis (white blood cells = 10 000 cells/mm^3). The electrolytes and kidney and liver function were within normal limits. The chest X-ray was normal. Electrocardiogram showed no change. The patient scheduled for re-operative aortic valve replacement. Intra-operatively, the aortic valve was tricuspid and was not calcified. The wall of the aorta in the sinus area appeared thin, but there was no root dilatation or wall calcification. A standard CPB with bicaval cannulation was initiated, and cold cardioplegia was performed for myocardial protection after aortic cross-clamping. The aortic valve was carefully excised from the aortic annulus. After an appropriate prosthetic valve was selected, it was placed using five 2/0 non-absorbable monofilament polypropylene sutures with 1/2-circle 17-mm needles with continuous sutures. The aortotomy was closed with a double-layer suture of 4–0 polypropylene; the patient was weaned successfully off CPB with inotropic support and transferred to the intensive care unit. After 6 hours, blood pressure reduced and central

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venous pressure elevated and extremity became cool and cyanotic (Figure 1). Inotropic support was started with dobutamine and adrenaline (2 and 1 μg/kg/min) subsequently. After 3 days, inotropic drugs tapered and discontinued, and blood pressure stabilized, but cyanosis changed to dry gangrene (Figure 2). After 2 weeks, the acral part of lower and upper extremities auto-amputated and pecimens were sent to the pathology. The possibility of systemic embolization was ruled out by echocardiography, and carotid Doppler study, coagulation profile and a disseminated intravascular coagulation workup were all normal. The patient was started on aspirin, pentoxifylline and heparin. The parts were kept warm, and undue handling was avoided. In histopathological exam, there was only non-specific vasculitis with thrombosis.

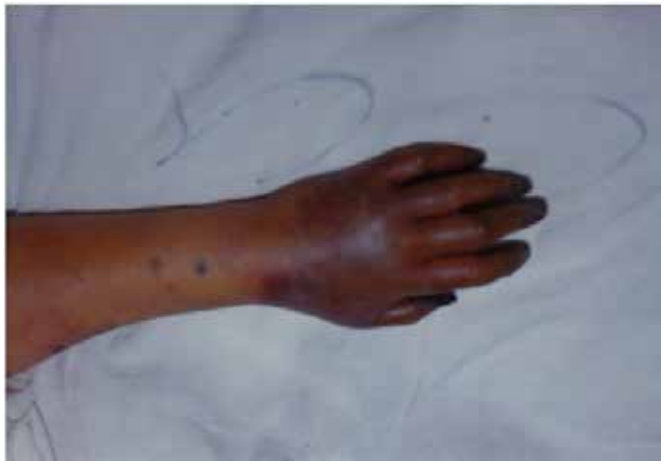

Fig. 1: Shows left-hand ischaemia.

Fig. 2: Shows right-hand ischaemia.

The patient had not regained full consciousness on the following morning; however, she was found to be quadriplegic with non-voluntary movements of the four limbs or face. Both pupils were small and fixed. Magnetic resonance imaging of the brain revealed normal great artery and oedema of the brain cortex (Figure 3). Prolonged ventilatory support was maintained, and eventually a tracheostomy was performed to facilitate tracheobronchial suctioning and weaning. Facility for ultrasonography of the abdomen did not exist in our centre; however, abdominal ascitic fluid amylase was normal. A computed tomography scan of the abdomen was not done as the patient could not be shifted. Acute renal failure with anaemia was managed and kidney was recovered completely. However, the patient remained in a comatose state for 4 weeks with no neurological improvement. Despite all ventilatory, nutritional and nursing support, the patient died eventually of hepatic failure and generalized sepsis. Post-operative laboratories measurements included negative antinuclear antibodies and rheumatoid factor, and the elevation of C4–C3 and tissue necrotic factor alpha (TNF-α) as components of complement, but the Hepatitis B surface antigen (especially in polyarteritis nodosa) was negative. The patient did not have predisposing factors, such as hypertension, arthrosclerosis or diabetes, and the hypercoagulability state was rolled out by the normal serum level of protein C–S, factor of V Leiden and von Willebrand disease. The pathologic exam showed no specific vasculitis as seen in inflammatory response in CPB.

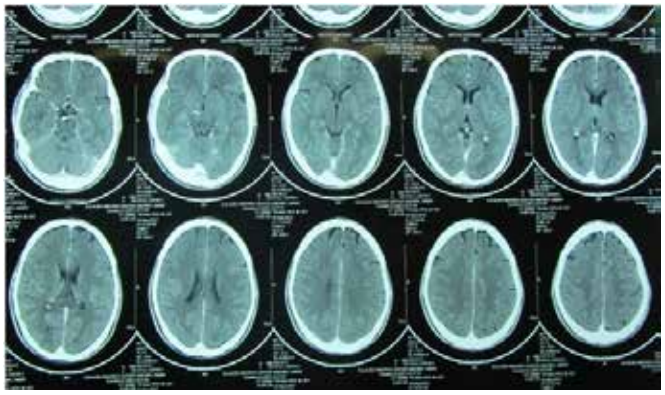

Fig. 3: Shows non-specific brain oedema caused by inflammation.

DISCUSSION

Distal organ ischaemia or acral parts involve arterioles with external diameters of 500–900 nm that may be affected by pathology variables, such as cholesterol emboli, immune complexes produced by CPB, atherosclerotic plaque or vasculitis syndrome (3). The most important differential diagnosis of CPB-induced systemic inflammatory response syndrome (SIRS) is cholesterol crystal emboli (CCE).

The presence of four or more risk factors should be taken as presumptive evidence of CCE. The risk factors that were not found in our patients include atherosclerotic plaque, hypertension, thrombolytic therapy male gender, smoking, hypercholesterolaemia, diabetes and resuscitation (4). The pathognomonic sign of CCE that was not seen in our patient was the needle-shaped cleft in the arteriole wall (5). Some studies found that, however, various treatment strategies have been tested to reduce the severity of the systemic inflammation induced by CPB and to improve the treatment, including anti-inflammatory drugs, novel components of the CPB and new surgical techniques, or anaesthetic drugs or technique but no single strategy has been proven effective; yet some of these drugs were evaluated in presiding studies (6–8). Production of humoral inflammatory mediators and priming of neutrophils by exposure to the CPB apparatus enable a 'post-pump' syndrome characterized by a SIRS and its anti-inflammatory counterpart, termed the compensatory anti-inflammatory response syndrome (9). Interleukin (IL-18) plays a central role in regulating and balancing these responses. IL-18 regulates the expression of the potent pro- and anti-inflammatory mediators, TNF-α (10) and IL-10 (11). In accord with this, Morgan found that the TT genotype was associated with an increased serum IL-18 concentration and also with an increased serum TNF-α and decreased serum IL-10. The increased serum TNF-α and decreased serum IL-10 levels are associated with an increased organ dysfunction (12).

CONCLUSION

The tremendous effect of the inflammatory response to ischaemia reperfusion and the use of CPB indicate the need for measures that might if not inhibit it, at least mitigate it. Thus, the control of risk factors, the reduction of ischaemic cardiovascular events, technical training for off-pump surgery as well as advances in anti-inflammatory therapy are measures to be reinforced while research should be encouraged so that these objectives are achieved.

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CASE REPORT

The Reduction in the Demand for Nicotine Due to Pregabalin and Gabapentin: Two Cases

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ABSTRACT

Pregabalin and gabapentin are a new-generation anti-epileptic drugs. They show their effects through voltage-gated, calcium channels. Sedation and cognitive dysfunctions are among their side effects. There are some investigations which show that pregabalin and gabapentin may help in quitting smoking. In this study, two patients are presented: one who smoked 60 cigarettes per day for 10 years and her urge to smoke decreased after pregabalin treatment and she quitted smoking; and the other who smoked 40 cigarettes per day for 20 years and his urge to smoke decreased after gabapentin treatment and he quitted smoking. The use of pregabalin and gabapentin in the treatment of smoking cessation is discussed as well as their side effects.

Keywords: Gabapentin, nicotine, pregabalin, smoking

INTRODUCTION

Pregabalin and gabapentin are gamma-aminobutyric acid (GABA) analogues. They show their effects through voltage-gated, calcium channels (1). Only four studies that investigated the effect of pregabalin and gabapentin on the urge to smoke were found by searching MEDLINE (2–5). In these studies, some methodological problems, such as small sample size, short duration of treatment and a higher dropout rate, were present. In these studies, it was found that gabapentin and pregabalin decrease the urge to smoke compared to baseline studies. In this article, two long-time smokers—one who quitted smoking after the use of gabapentin and the other who quitted after the use of pregabalin—are presented.

CASE 1

A 39-year-old college graduate, married for eight years, and a mother of one female patient applied to the clinic with panic disorder symptoms. She was treated for panic disorder for 12 years. Despite the fluoxetine (40 mg/day) and alprazolam (3 mg/day) treatment, she had panic attacks a few times per month. Therapeutic drug monitoring (TDM) of fluoxetine and alprazolam was measured. The fluoxetine level was determined as 59.39 ng/mL (a therapeutic reference range: 120–500 ng/mL) and the alprazolam level was determined as 523.04 ng/mL (5–50 ng/mL) (6). According to these results, the fluoxetine level was evaluated as very low, and the alprazolam level was evaluated as very high. Due to the ineffective treatment, venlafaxine (75 mg/day) and pregabalin (300 mg/day) were initiated to her. Two weeks later, TDM of venlafaxine was determined as 123.78 ng/mL (100–400 ng/mL) and TDM of pregabalin was determined as 3.82 μg/mL (2–5 μg/mL) (6). Although the patient smoked 60 cigarettes per day for 10 years, she claimed in the fourth month of her treatment that she no longer had the urge to smoke, and quitted smoking. She said that she tried to quit smoking in the past but could not because she liked smoking. Due to the venlafaxine and pregabalin treatment, her anxiety scores decreased from 33 to 8. Her alprazolam (3 mg/day) treatment was terminated.

CASE 2

A 44-year-old college graduate, married for 10 years, and the father of a child patient, was admitted to the clinic for the treatment of alcohol dependence. He was hospitalized and escitalopram (20 mg/day), gabapentin (1200 mg/day) and diazepam (15 mg/day) treatment were initiated. Two weeks later, TDM of escitalopram

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was determined as 33.46 ng/mL (15–80 ng/mL) and TDM of diazepam was determined as 148.75 ng/mL (200–2500 ng/mL) (6). Although he smoked 40 cigarettes per day for 20 years, in the fourth month of his treatment, he quitted smoking. He also currently continues to stay away from alcohol.

DISCUSSION

Nicotine stimulates the mesolimbic dopaminergic system and creates the effect of reward by increasing dopamine release in the nucleus accumbens (7). The nucleus accumbens contains GABAergic synapses (8). Vigabatrin (a new generation of anti-epileptic which prevents nicotine-dependent dopamine release in the nucleus accumbens of rats by inhibiting the GABA transaminase enzyme and thereby reducing the degradation of GABA), reduces the level of GABA and reduces nicotine self-administration (9, 10). Similarly, the baclofen, a $GABA_B$ receptor agonist, reduces nicotine self-administration (11). Baclofen was examined in 30 smokers for nine weeks. In this double-blind, placebo-controlled study, the incidence of daily smoking among the subjects who used baclofen was significantly lower than the placebo group (12). Positron emission tomography (PET) and limbic $GABA_A$ receptor levels were not high in the subjects who quitted smoking. These findings show that, in nicotine dependence, there are irregularities in the limbic $GABA_A$ receptor system (13). In light of these studies, drugs which increase GABAergic transmission may be useful in the treatment of nicotine addiction. However, there are a few studies which investigate drugs acting on the GABA in the treatment of nicotine addiction. In a recently published review study, new drug possibilities in the treatment of smoking cessation and the effects of glutamatergic and GABAergic systems in nicotine addiction are discussed (14). According to this study, the nicotine-dependent reward system is blocked and nicotine-seeking behaviour is prevented, due to the suppression of the glutamatergic transmission and increase of the GABAergic transmission. The authors emphasized the effects of the glutamatergic and GABAergic drugs in the treatment of nicotine addiction.

One of the two cases presented in this paper quitted smoking after the pregabalin treatment and the other, after gabapentin—a pharmacological-like drug treatment. It is remarkable that each of the cases quitted smoking in the fourth month of their treatment. In the studies which investigate the effects of pregabalin, gabapentin and other GABAergic drugs on smoking, the duration of treatment is less than 16 weeks. Therefore, in these studies, the difference, compared to placebo, may not be detected. Placebo-controlled and double-blind studies which investigate the use of pregabalin and gabapentin in a wide sampling, and observe for more than 16 weeks, are needed.

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