Arthralgia Accompanying Typhoid Fever in Children: Single Centre Experience

MS Bektaş[1], F Aktar[2], S Gürel[3], S Gülşen[4]

ABSTRACT

Aim: To determine the general characteristics of children with arthralgia associated with typhoid fever.

Material and Method: General characteristics of the disease and laboratory of children diagnosed with typhoid fever and accompanying arthralgia were investigated from the hospital records. Arthralgia was determined regarding the patients' personal reports.

Results: We retrospectively evaluated the records of 100 patients (46 female and 54 male) with a mean age of 8.78 ± 4.66 years (range: 5–213 months). The most common locations were knee joint (n: 40) and ankle (n: 39). Regarding hematological findings; leukocytosis was present in 36 patients and leucopenia was present in eight patients; anaemia was present in 12 patients; and abnormalities in thrombocyte count was present in 32 patients. Mean platelet volume was determined to be lower than normal limits in 33 patients. In seven patients, the treatment was started with ampicillin or TMP-SMX but because of the unresponsiveness the treatment was changed with ceftriaxone.

Conclusion: We determined that, in children with arthralgia accompanying typhoid fever; muscle pain and organomegaly were the most common symptoms accompanying arthralgia while knee joint and ankle were the most commonly affected joints. In treatment 3rd generation cephalosporin should be kept in mind in unresponsive patients.

Keywords: Arthralgia, children, typhoid fever

From:[1]Lokman Hekim Hospital, Pediatric Health and Disease Clinic, Van, Turkey, [2]Department of Pediatric Infectious Disease, Dicle University School of Medicine, Diyarbakır, Turkey, [3]Medical Park Usak Hospital, Pediatric Health and Disease Clinic, Usak, Turkey and [4]Kurtköy Ersoy Hospital, Pediatric Health and Disease Clinic, Istanbul, Turkey.

Correspondence: Dr M Bektaş Lokman Hekim Hospital, Pediatric Health and Disease Clinic Van, Turkey. Email: selcukbektas008@gmail.com

INTRODUCTION

Typhoid fever is a severe systemic illness caused by the bacterium Salmonella Typhi and commonly characterized with features of fever and mainly gastrointestinal manifestations including abdominal pain (1). Severe headache, lobar pneumonia, isolated arthralgia, urinary symptoms, neurologic manifestations such as delirium or rarely pancreatitis, meningitis, orchitis or osteomyelitis may accompany the gastrointestinal symptoms and fever (2).

Unfortunately, typhoid fever is still a major public health problem in areas with poor sanitation and limited access to safe water since the disease spreads via ingestion of food or water contaminated with human feces from patients excreting the microorganism (2–4).

Typhoid fever was reported to be very common in developing countries along with an estimated 120 million infections and 700 000 annual deaths occurring worldwide (5). Arthralgia or arthritis is rarely the only symptom at manifestation of typhoid fever (6). Conversely, joint pain commonly accompanies fever and abdominal pain in patients with typhoid fever. Walters *et al* reported that 71% of patients were having joint pain during the disease (7). All through the disease course, arthritis may be septic or reactive (8). However, the data about the joint pain associated with the typhoid fever is still limited. In this study, we aimed to determine the general characteristics of children with arthralgia associated with typhoid fever.

MATERIAL AND METHOD

Patients

In this retrospective study, the hospital records of 100 children who were diagnosed with arthralgia accompanying typhoid fever in Van Obstetrics and Children Hospital and Diyarbakır Children Hospital between January 2011 and December 2012 were evaluated. The study was approved by the local Ethical Committee.

The diagnostic criteria for typhoid fever were; 1) Isolation of *S typhi* in blood cultures, 2) In patients having symptoms concomitant with typhoid fever, presence of antibodies against *S typhi* O and H antigens above 1/200 in Gruber-Widal test or an increase of four times or more in repeated tests with an at least ten days interval (3).

Demographic features, general characteristics of the disease, laboratory data at the time of diagnosis and treatment modalities of all patients were investigated from the hospital records. The most painful joints were recorded. Arthralgia was determined regarding the patients' personal reports.

Statistical analyses

The data were analysed using SPSS 21. Descriptive statistics were performed. Numerical variables were expressed as mean ± standard deviation and categorical variables were analysed as frequency and percentage, $p < 0.05$ was considered statistically significant.

RESULTS

We retrospectively evaluated the records of 100 patients (46 female and 54 male) with a mean age of 8.78 ± 4.66 years (range: 5–213 months) who were diagnosed with typhoid fever and having arthralgia. When the patients were sub-grouped regarding their age; two were younger than two years of age, 39 were between two to six years of age, 30 were between 7–12 years of age and 29 were older than 12 years old (Fig. 1). The season at the diagnosis was spring in 35 patients, summer in 40 patients, autumn in ten patients and winter in 15 patients (Fig. 2). In 75% of cases, the diagnosis was performed in spring and summer. The diagnosis was performed in the first week after the beginning of symptoms in 34 patients; in 2nd week in 57 patients and in 3rd or 4th weeks in the remaining nine patients.

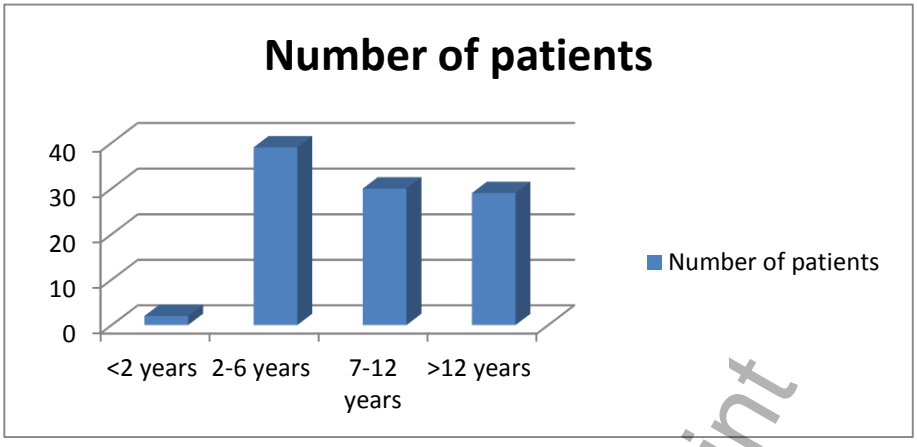

Fig. 1: Distribution of patients regarding age groups.

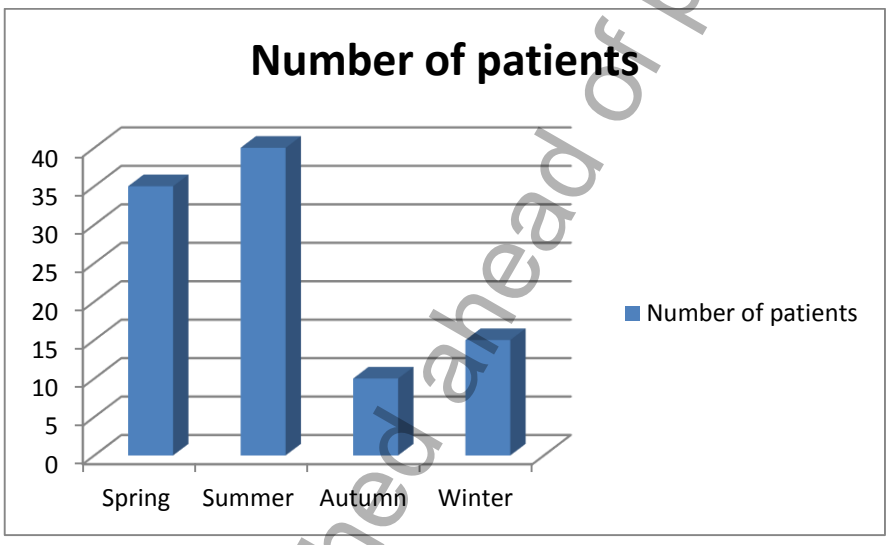

Fig. 2: Distribution of patients regarding the season at diagnosis.

Arthralgia was present in all patients since it was the inclusion criteria. The distribution of involved joints is summarized in Table 1. The most common locations were knee joint (n: 40) and ankle (n: 39). Accompanying symptoms and signs of the patients were also recorded. Among those; muscle pain was present in 59 patients, fever was present in 40 patients, organomegaly was determined in 57 patients and rose spots was present in five patients (Table 2). In this study all patients were infected with *S typhii*. In diagnosis, Widal test was positive in 92 patients and blood cultures were positive in 45 patients. At the time of diagnosis, the results of complete blood count and biochemical analyses are summarized in Table 3.

Table 1: Distribution of involved joints regarding arthralgia.

Location	Number of patients
Knee joint	40
Ankle	39
Costochondral joint	11
Sacroiliac joint	3
Elbow	3
Hip joint	2
Cervical joint	1
Wrist	1

Table 2: Presence of organomegaly among patients.

Type of organomegaly	Number of patients
Hepatomegaly	17
Splenomegaly	27
Hepatosplenomegaly	10
Hepatomegaly and lymphadenopathy	3

Table 3: The results of complete blood count and biochemical analyses among participants.

	Mean ± standard deviation	Range
Haemoglobin	11.97 ± 1.10	7.8–13.9
White blood cell count	12.51 ± 6.69	2.10–26.80
Platelet count	282030.0 ± 174291.03	10 000–80 2000
Mean platelet volume	7.94 ± 1.00	6.40–11.00
AST	57.01 ± 33.60	21.00–217.00
ALT	51.47 ± 40.68	16.00–248.00
LDH	1246.87 ± 516.62	561.00–2765.00
Sedimentation	59.34 ± 24.5021.10	13.00–108.00
C-reactive protein	43.77 ± 21.10	3.00–106.00

Regarding those results; leukocytosis was present in 36 patients and leukopenia was present in eight patients; anemia was present in 12 patients; thrombocytopenia was determined in 19 patients and thrombocytosis was present in 13 patients. Mean platelet volume was determined to be lower than normal limits in 33 patients.

In treatment, ampicillin was prescribed in 31 patients, ceftriaxone was prescribed in 41 patients, ciprofloxacin was prescribed in 11 patients and trimethoprim-sulphometaxasole (TMP-SMX) was prescribed in ten patients. All those patients were treated successfully with the treatment. On the other hand, in three patients, the treatment was started with ampicillin but because of the unresponsiveness the treatment was changed with ceftriaxone and in three patients the treatment was started with TMP-SMX but because of the unresponsiveness the treatment was changed with ceftriaxone.

DISCUSSION

In this study, we assessed the general characteristics of children with arthralgia accompanying typhoid fever and we have determined that, there was a slight male predominance with a male/female ratio of 1.17. The most commonly affected joints were knee joint and ankle. Muscle pain, organomegaly and fever were the most common symptoms accompanying arthralgia. To the best of our knowledge, this study is one of the largest studies performed on children with arthralgia associated with typhoid fever.

The data about the joint symptoms and Salmonella infections is limited in literature. Joint pain was reported in 153 of 190 patients (81%) in a large outbreak of typhoid fever (9). In a cohort exposed to an outbreak of Salmonella typhimurium, 20% of children reported joint symptoms while this ratio was 43% in adults. Similarly, reactive arthritis was also more common in adults compared with the children (24% *vs* 12%). In that study, arthritis was

reported to be affecting the lower limbs predominantly in an oligoarticular pattern (10). In our study the most commonly affected joints were also knee joint and ankle. We only recorded the most painful joints and for that reason we could not talk about the number of involved joints.

In another study about the clinical features of typhoid fever in children from our country, patients were most commonly admitted in July and October, arthralgia was present in 21% and abdominal pain was present in 24% of patients. In that study, abnormal platelet count, anaemia and leukocytosis was reported in 19%, 16% and 16% of patients, respectively while decreased mean platelet volume was reported in 31% of cases (11). In our study, leukocytosis (36%) and abnormal platelet count (32%) were reported to be higher compared with this study. Decreased mean platelet volume was determined with a similar rate (33%). In a study of Herbinger *et al*, CRP was reported to be increased in all patients with typhoid fever as a useful acute phase reactant (12). In this study, in 99 of 100 patients CRP was higher than the upper limits.

In a recent review, it was reported that, in Asia the overall enteric fever occurrence was highest in the 5–9 year age group followed by the 10–14 years of age (13). In this study we determined that, the highest number of patients were in 2–6 year's group followed by 7–12 years of age group. Duration of illness before treatment was reported as an important factor that may contribute to the severity of the disease together with the inoculum size and the immune status of the patient (14). In our study, 91% of patients were diagnosed in first two weeks after the initial symptoms.

In general, the clinical pictures of the patients were not very silent in this study since muscle pain and/or organomegaly was accompanying arthralgia in more than half of our patients. In a systematic review, Azmatullah *et al* reported that fever was consistently noted in all age groups of patients while anemia, leukocytosis and hepatomegaly were more common among pre-school children while leucopenia and abdominal pain were more common in school age group and headache and abdominal distension were determined in older age groups (15).

Since the number of patients included in this study was not very high, we did not compare the symptoms or signs regarding age-based subgroups of the patients.

For the diagnosis of typhoid fever, culture and isolation of *S typhi* is the gold standard especially during the 1st week; however, some factors such as low levels of bacteremia or time passed to the laboratory may affects the diagnostic accuracy of blood cultures (16). On the other hand the Widal agglutination test is relatively cheap and easy to perform (17). Enabulele *et al* reported that, among 271 blood samples 124 (45.76%) were positive following a Widal agglutination test and 60 (22.10%) blood samples grew Salmonella organisms on blood culture (18). In our study, Widal test was positive in 92% of patients and blood cultures were positive in 45% of patients.

In treatment of typhoid fever traditional first-line agents are chloramphenicol; ampicillin; and co-trimoxazole and fluoroquinolones are the second line agents (19). Although, there are some doubts about ciprofloxacin treatment in children, Doherty *et al* reported that, there were not any significant adverse effects on ponderal, linear or knemometric growth, or on the incidence of arthritis/arthralgia during six months follow-up in children less than six years of age diagnosed as typhoid fever and 39% of whom received ciprofloxacin in treatment (20). In this study, 79% of patients were treated with either ampicillin or ceftriaxone.

However, the emergence of drug-resistance and changing patterns of multi-drug resistant microorganisms has been associated with alterations in the severity and clinical profile of enteric fever (15, 21). Recently Ali *et al* reported that multidrug resistance, defined as resistance to the three first-line classes of antimicrobial agents (chloramphenicol, ampicillin, and trimethoprim/sulfamethoxazole) was 44.5% in *S typhi* without any differences between age groups and gender. Any resistance was not found to third-generation cephalosporins in that study (22). We have reported that, three patients were unresponsive to ampicillin and four patients were unresponsive to TMP-SMX treatments and all those seven patients responded to

the ceftriaxone treatment. Lower antibiotic resistance rates reported in our study may be due to the involvement of only children in this study; since antibiotic resistance was attributed to misuse of antimicrobials (23).

There are some limitations of this study that should be mentioned. First the data was obtained from patients attending a single centre that may induce bias in data analyses. However, our centre was a tertiary centre in an urban region catering to a wide population. Secondly, we only recorded the most painful joints and did not analyse the presence of reactive arthritis.

CONCLUSION

In conclusion, we determined that, in children with arthralgia accompanying typhoid fever; muscle pain and organomegaly were the most common symptoms accompanying arthralgia while knee joint and ankle were the most commonly affected joints. In treatment 3rd generation cephalosporin should be kept in mind in unresponsive patients. Larger studies assessing the epidemiological features of typhoid fever are warranted in order to suspect from this disease in differential diagnosis of arthralgia.

AUTHORS' NOTE

The manuscript has been seen by all authors. It has not been submitted in similar form for publication elsewhere. No financial support has been obtained.

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