Original Article

Challenges in the diagnosis and management of Pediatric Rheumatology in the developing world: Lessons from a newly established clinic in Yemen

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ABSTRACT

Pediatric rheumatology is still considered a mysterious branch of pediatric medicine, especially among developing countries. Long-term consequences usually follow delayed diagnosis, referral, and management of rheumatic disorders. We aim to describe the clinical spectrum and the frequency of pediatric rheumatic diseases (PRDs) in AL-Mukalla hospital in Hadhramout province/Yemen. A case record retrospective study was conducted among all patients who attended the pediatric rheumatology clinic in Al-Mukalla hospital (from January 2010 to December 2016) with a musculoskeletal complaint or systemic symptoms suggestive of rheumatic disease. Data collected included: gender, address, age at the onset of symptoms, initial manifestations, the presence of complications, referral diagnosis, final diagnosis and the lag period before attending the rheumatology clinic. PRDs were present in 86% (37/43) of cases, 83.8% (31/37) were from Hadhramout province. Male to female ratio was 0.9:1 (Male: 18; Female: 19) and the commonest age group affected was (>9-12) years. The mean age at first presentation was 8.859 ± 4.11 years (four months-14 years). One year (0.13-98.4 months) was the median time before referral to the rheumatologist. About 70.3% of cases were referred from other specialists or peripheral hospitals. Joint swelling (54.1%) was the most common presentation and juvenile idiopathic arthritis (24.3%) was the commonest diagnosis. The discrepancy between the referral and the final diagnosis was noticed in 21(48.8%) cases. Only eight cases (18.6%) matched the final diagnosis. Two patients died with a mortality rate of 5.4%. Knowledge of the spectrum and incidence of PRDs will increase the awareness of specialists and general practitioners for early referral and diagnosis to avoid long-term sequels.

Keywords:

Arthritis, Mukalla, Pediatric rheumatic diseases, Rheumatology, Yemen.

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INTRODUCTION

Rheumatic disorders are one of the largest health problems in the world in both developed and developing countries. They are among the commonest causes of morbidity and disability in Asia, Africa and Latin America [1-2].

Childhood-onset rheumatic diseases remain one of the chronic conditions with high risk of mortality and a long-term disability if not recognized and treated properly [3]. It affects approximately 300,000 children in the United States [4-5].

In developing countries, difficult estimation of PRDs prevalence is usually related to decreased awareness of physicians towards rheumatic diseases in children, lack of pediatric rheumatology service and directed attention towards the communicable diseases in comparison to non-communicable rheumatic disorders [6-8]. The confusing presentation of musculoskeletal (MSK) symptoms – which are the primary features of rheumatic diseases – in other systemic disorders as metabolic, endocrine, neoplastic and infectious conditions is considered related too [3,9-10].

Yemen is a developing country; thorough web search did not reveal any published PRDs registry in Yemen. To our knowledge, there are no officially recognized separate pediatric sub-specialities including pediatric rheumatology, all cases are managed by general practitioners, orthopaedic surgeons or general physicians and most of the cases are treated symptomatically without having a specific diagnosis.

Mukalla is the capital of Hadhramout; the largest province in Yemen. It is the third largest city in Yemen, with an area of 1963.05 km^2, located 480 km east of Aden. The total population is approximately >500,000 people (year 2005) [11]. Healthcare facilities in the coastal plain of Hadhramout include ten hospitals and 203 primary healthcare centres including four family medicine centres (statistics from Hadhramout health office).

Our pediatric rheumatology clinic was established in Al-Mukalla hospital in January 2010. We started to register pediatric rheumatic cases, provide a proper diagnosis based on validated criteria and increase the awareness of physicians and families towards the diagnosis and treatment of PRDs.

This study was conducted to determine the spectrum and frequency of diseases seen in the pediatric rheumatology service in Al-Mukalla hospital aiming to make the importance of such subspecialty visible and obvious to physicians as this might contribute to decreasing long-term morbidity and disability resulting from delayed referral and diagnosis.

METHODS

A Retrospective descriptive study using case records was conducted over a period of seven years (January 2010–December 2016). It included all patients attending the rheumatology clinic in the pediatric department in Al-Mukalla hospital and all patients with either MSK complaint or systemic symptoms suggestive of rheumatic disease, referred from the pediatric clinic, peripheral hospital or pediatric ward for rheumatology review. Patients who exceeded 16 years of age at the time of disease onset and patients with non-rheumatic diagnosis (malignancy, orthopaedic, inflammatory bowel disease, infection, endocrine and metabolic) were not included in PRDs data analysis.

All patients underwent a full detailed history and physical examination. Laboratory investigations including full blood count, liver and renal functions and inflammatory markers were routinely obtained. Radiological studies, bone marrow study and skin biopsy were requested as needed. Investigations aimed at obtaining a specific diagnosis, assessment of disease activity or for treatment modification.

The clinical diagnosis was based on validated criteria such as American College of Rheumatology (ACR), International League of Association of Rheumatology (ILAR), Systemic Lupus International Collaborating Clinics (SLICC) and other validated criteria for rheumatic diseases [12].

Patients' charts were reviewed for the following variables: gender, address, age at the onset of symptoms, initial manifestations, the presence of complications, referral diagnosis, final diagnosis and the lag period; which is the time from the onset of the first symptom until visiting the rheumatology clinic. Descriptive analysis of data was done using SPSS 17.

RESULTS

Records for a total of 43 patients seen at the pediatric rheumatology clinic were reviewed in the study. Thirty-seven cases (86%) had PRDs and six cases (13.95%) had non-rheumatic conditions.

Twenty-six (70.3%) PRD cases were referred: Sixteen cases from pediatric specialists (43.2%), two cases from an orthopedic surgeon or a dermatologist (5.4%), six cases from peripheral hospitals (16.2%) and two cases were diagnosed in the pediatric ward (5.4%). Eleven cases (29.7%) were visiting our clinic for the first time after a long journey through different private clinics. Cases were collected over a period of seven years (January 2010–December 2016) with an overall gradual increment in the frequency of patients (figure 1).

The majority of PRD cases (83.8%) were from Hadhramout province. Males form 18 cases (48.6%) and females form 19 cases (51.4%) with a male to female ratio of 0.9:1. The age at first presentation ranges between four months and 14 years (mean 8.859 ± 4.11). The commonest age group affected was (9-12years).

Joint swelling (54.1%) was the most common MSK presentation documented in PRD patients followed by fever in 51.4% of cases and arthralgia in 37.8% of cases. Other manifestations including extra-articular or organ based features are shown in Table 1.

Table 1- Articular and extra articular manifestations among PRDs patients attending rheumatology clinic in Mukalla hospital.

Sign/symptom	Number (n)	Percentage (%)	Sign/symptom	Number (n)	Percentage (%)
Fever	19	51.4	Hepatomegaly	1	2.7
Arthralgia	14	37.8	Splenomegaly	1	2.7
Joint swelling	20	54.1	General weakness	6	16.2
Limb contracture	1	2.7	Photosensitivity	1	2.7
Skin rash	11	29.7	Hair loss	2	5.4
Abdominal pain	3	8.1	Skin changes	3	8.1
Chest pain	5	13.5	Morning stiffness	3	8.1
Mouth ulcer	4	10.8	Finger ulcers	1	2.7
Lymph node enlargement	0	0	Hematuria	3	8.1
Murmur	1	2.7	Gangrene	1	2.7
Joint laxity	2	5.4	Delayed walking	0	0
Weight loss	5	13.5	Myopathy	1	2.7

All PRD cases were diagnosed and classified according to validated criteria specific for different rheumatology cases [12]. As shown in Table 2, juvenile idiopathic arthritis (JIA) was the most frequent PRDs, diagnosed in nine patients (24.3%); systemic JIA (SJIA) (44.4%) was the commonest type of JIA. Systemic connective tissue diseases (CTDs) were diagnosed in nine cases (systemic lupus erythematosus (SLE) 5 patients, scleroderma 3 patients and juvenile polymyositis (JPM) 1 patient). Arthritis-related to infection was diagnosed in six patients (16.3%). Vasculitis was noticed in three cases (8.1%). Familial Mediterranean fever (FMF), an auto-inflammatory disease was diagnosed in four cases (10.8%). Sarcoidosis and juvenile ankylosing spondylitis were among the least frequent PRDs. Hypermobility syndrome, as a cause of non-inflammatory MSK pain, was diagnosed in two patients (5.4%) (Table 2).

After reviewing the medical records of the 43 patients attending the rheumatology clinic, we found a discrep-

ancy between the referral diagnosis and the final diagnosis in 21 (48.8%) cases (Table 3), 14 cases (32.6%) were treated symptomatically with no specific diagnosis and lastly turned to be related to PRDs. Only eight cases (18.6%) had matching with the final diagnosis.

The most common non-rheumatic diagnosis with MSK presentation was leukaemia seen in two patients, osteogenesis imperfect in one case, spondyloepiphyseal dysplasia in one case, Crohn's disease in one case and one patient diagnosed as a case of pigmented villonodular synovitis. Delay in accurate diagnosis was obvious in our study as it showed a median lag period of 12 months (range 0.13–98.4 months) before referring the patient to the rheumatology clinic.

Table 2- Spectrum of pediatric rheumatic diseases presented to the rheumatology clinic in Mukalla hospital.

Disease type	Frequency	Percentage (%)
Chronic arthritis		
Oligo articular JIA*	3	8.1
Polyarticular JIA* (RF** negative)	2	5.4
Systemic JIA*	4	10.8
Enthesitis related arthritis		
Juvenile ankylosing spondylitis	1	2.7
Systemic connective tissue diseases		
Systemic lupus erythematosus	5	13.5
Juvenile polymyositis	1	2.7
Scleroderma	3	8.1
Vasculitis		
Henoch-schonlein purpura	1	2.7
Kawasaki	1	2.7
Polyarteritis nodosa	1	2.7
Granulomatous inflammatory disease		
Sarcoidosis	1	2.7
Arthritis related to infection		
Post streptococcal reactive arthritis	2	5.4
Rheumatic fever	2	5.4
Septic arthritis	1	2.7
Osteomyelitis	1	2.7
Autoinflammatory syndrome		
Familial Mediterranean fever	4	10.8
Non inflammatory MSK*** pain		
Hypermobility syndrome	2	5.4
Avascular necrosis of the hip (Perthes' disease)	1	2.7
Non specific	1	2.7
Total	37	100

*JIA: Juvenile idiopathic arthritis, ** RF: Rheumatoid factor,***MSK: musculoskeletal.

Medications used after diagnosing the patients included: Nonsteroidal anti-inflammatory drugs (NSAIDs) which were used in 16 cases (43%), oral prednisolone in 20 cases (50%), intravenous methyl prednisolone in 9 cases (24.3%), hydroxychloroquine was used in SLE cases, in one patient with JIA and one patient with dif-

fuse cutaneous scleroderma. Subcutaneous methotrexate was used in seven patients (JIA 3, scleroderma 1, JPM 1, sarcoidosis 1, SLE 1). Azathioprine was used in three cases (SLE 2, JPM 1). Mycophenolate Mofetil was used in three patients (SLE 1, diffuse cutaneous scleroderma 2). Biologics were used in two cases: etanercept in one case of bilateral sacroiliitis (juvenile ankylosing spondylitis) and infliximab in a case of sarcoidosis. Non-rheumatic cases were referred to other departments or abroad for further evaluation and management.

Table 3- Cases with discrepancy between primary and final diagnosis.

Case number	Primary (referral) diagnosis	Final diagnosis
1	Systemic JIA*	Leukemia
2	Rheumatic fever vs JIA*	Sarcoidosis
3	Rheumatic fever	Polyarticular JIA*
4	JIA*	Diffuse cutaneous scleroderma
5	JIA*	Systemic lupus erythematosus
6	JIA*	Juvenile ankylosing spondylitis
7	Kawasaki	Familial Mediterranean fever
8	Septic arthritis	Systemic JIA*
9	Polyarticular JIA*	Leukemia
10	Sickle cell crisis	Salmonella osteomyelitis
11	JIA*	Systemic lupus erythematosus
12	Post streptococcal reactive arthritis	Oligo JIA*
13	Renal problem (hematuria)	Familial Mediterranean fever
14	Transient synovitis	Avascular necrosis of the hip
15	Pyrexia of unknown origin	Systemic lupus erythematosus
16	Glomerulonephritis	Systemic lupus erythematosus
17	Infective endocarditis	Systemic JIA*
18	Polyarticular JIA*	Spondyloepiphyseal dysplasia
19	Rickets	Osteogenesis imperfecta
20	Polyarticular JIA*	Pigmented villonodular synovitis
21	Polyarticular JIA*	Crohn's disease

*JIA: Juvenile idiopathic arthritis.

Regular follow up of the patients showed a good response generally. Complete remission (clinically and by laboratory investigations) was noticed in 26 cases (70%), partial remission in six cases (16.5%), one patient (2.7%) stopped the treatment and two patients (5.4%) lost follow up. Two patients (5.4%) died; one case of SJIA complicated with hepatic encephalopathy and multi-organ failure as a part of macrophage activation syndrome (MAS), the second case of SLE recovered from atypical presentation of MAS but died later on with disease activation and intractable heart failure as a result of noncompliance to treatment.

DISCUSSION

Pediatric rheumatic diseases are chronic illnesses with a major effect on both children and their families as they are associated with potential physical disability, affecting the quality of life and carrying a significant economic burden either directly or indirectly [13-15].

Most of the western countries have outlined the scope and distribution of local pediatric rheumatology practices [16-18]. Four Canadian provinces show a prevalence of systemic autoimmune rheumatic diseases of 2 cases/10,000 resident ≤ 18 years [19]. Rosenberg AM, reported 50.9% cases with PRDs in pediatric rheumatology clinic at university in Saskatchewan in Canada [20]. Studies estimated that 1.7 to 8.4 million children in the world have undiagnosed chronic arthritis [12, 20].

The prevalence of rheumatic diseases in developing countries is unknown [1] or difficult to estimate as many children remain undiagnosed due to lack of

facilities, awareness or lack of trained personnel in medical profession [7]. In Africa, only a few reports on PRDs were published [6, 8, 21-22]. Prevalence of PRDs referred to the childhood rheumatology clinic was 57.8% and 2.8% reported in Singapore and Nigeria respectively [3,21]. Migowa A et al, reported PRDs in 0.32% of hospital admitted cases in Kenya in 2011 [10].

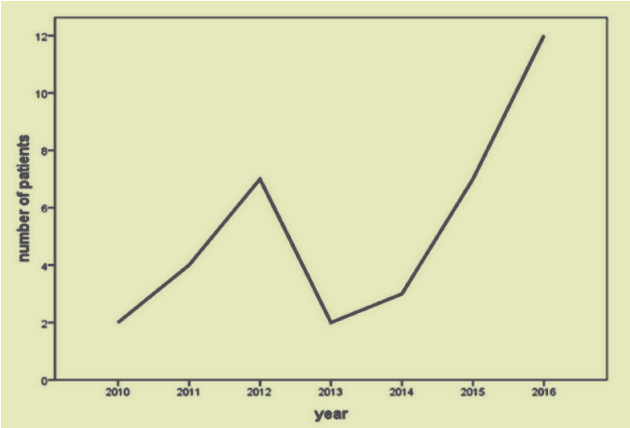

Figure 1- Annual frequency of PRD patients attending rheumatology clinic in Mukalla hospital.

In our study, a total of 43 cases with MSK complaint attending the pediatric rheumatology clinic were reviewed, among which 37 cases (86%) were diagnosed as PRDs (Table 2).

A progressive gradual increase in the number of patients attending the clinic was noticed during the study period (figure 1). Increase the awareness of the patients' families allows them to advise others with MSK complaint to visit the pediatric rheumatology clinic. In our study, Hadhramout province showed the highest frequency of PRD cases attending to the clinic, this might be related to the presence of the clinic in this province while others need a long journey to reach Hadhramout.

Variable gender predominance was reported in different studies; some studies reported a female predominance [8,19,21] while other studies showed male predominance [10] or an equal gender distribution [3]. This variability depends mostly on the predominant spectrum of PRDs to which male or female gender is related [10]. Our study showed a nearly equal involvement for both genders with a male to female ratio of 0.9:1. The mean age at disease onset was 8.859 ± 4.11 years (commonest age group was >9-12 years), this finding was near to those reported in the US where the mean age for PRDs was 7 ± 5.76 years [15] and 9.29 ± 4.53 years in a study done in Singapore [3], and less than the mean age of 14 years reported in Nigeria [21].

Musculoskeletal pain is a frequent complaint among children with rheumatic diseases [7,23,24]. Olaosebikan et al, reported MSK pain in 91.2% cases of PRDs [21]. In our study, joint swelling was noticed in 51.4% of PRD patients followed by fever and arthralgia.

Extra-articular and other systemic manifestations included; uveitis and hepatosplenomegaly in a patient with sarcoidosis, Interstitial lung disease in patients with scleroderma, valvular heart disease in rheumatic fever, lupus nephritis in SLE, persistent microscopic hematuria in FMF, finger tip gangrene in polyarteritis nodosa and cardiac extra systoles in a patient with JPM.

Difficulty in diagnosis faces rheumatologists is the result of the fact that MSK complaint mimic primary manifestation of a wide range of non-rheumatic diseases [25] in addition to the tricky atypical presentation of some rheumatic or CTDs which present initially with vague systemic manifestations as unexplained prolonged fever before the appearance of the full picture of the original disease. Olaosebikan et al, reported that 60% of children referred with a suspected rheumatic condition, didn't have confirmed rheumatic diagnosis [21]. Leukemia and other malignancies were considered as a great mimic of rheumatic diseases [9, 26]. About 1/3 of childhood leukaemia presented with MSK pain [12]. Sickle cell crisis and neck pain post meningitis were reported as causes of MSK pain [10].

Exact matching between the referral diagnosis and our final diagnosis was seen in eight (18.6%) cases, which is much less than the percentage reported in Kenya in which 84.6% matching was noticed between the diagnosis of the treating physician using ICD-10 diagnostic codes and the rheumatologist [10].

The presence of different validated guideline criteria; ILAR criteria for JIA, ACR and SLICC criteria for SLE, Bohan and Peter criteria for JDM/Polymyositis and other valuable diagnostic criteria for other rheumatic diseases [12,27-28], all played a major role in establishing an accurate diagnosis for PRDs.

Frequencies and spectrum of PRDs vary in different studies [3,21]. JIA was reported as the most frequent diagnosis by pediatric rheumatologists [7,8,10,18,21,24-25,29]. In our study, JIA (24.3%) forms the commonest cause of PRDs with SJIA (44.4%) considered as the most common type of JIA, this was consistent with reports from Mumbai and Japan were SJIA forms 42% and 50%, respectively [9,30]. This finding could be attributed to the attitude of dealing with most cases of oligo and polyarticular JIA as outpatients while patients with SJIA usually referred or admitted because of their vague presentation [31]. In Nigeria, polyarticular JIA (50%) was the most frequent type of JIA while SJIA (17.8%) was the least frequent type [21]. Salah S et al and Tzaribachev et al, reported oligo JIA as the commonest type followed by polyarticular JIA and SJIA forming the least common JIA [22,31].

SLE was the second diagnosis in frequency, it forms 13.5%, and this result was higher than those reported in Singapore (6.2%) [3] and Austria (5.6%) [29]. FMF was diagnosed in 10.8% of cases and scleroderma either localized or diffuse was present in 8.1% of cases. Arthritis-related to infection as PSRA and RF were usually treated in outpatient and private clinics without a referral. Other diagnoses showed a much less frequency (Table 2).

Variability in PRDs diagnosis was noticed in our study, although the number of patients is not large. This is because simple and usual causes of MSK complaint were treated without a referral. The majority of cases referred by pediatric specialists either for high suspicion for a rheumatic disease, unexplained chronic arthritis, vague MSK pain, poor response to treatment and unexplained positive antinuclear antibody (ANA) or high ESR. This was consistent with the results reported by Correll et al [5] and Mac Ghee et al [25].

Delay in referral results in a prolonged interval of untreated active disease, which has an adverse impact on prognosis [24]. In Nigeria, the mean duration of symptoms before the diagnosis was made was 18 months [21]. Foster et al, reported a median time of 20 weeks before referral to rheumatologist [24]. In our study, the median time for the lag period before referral to the rheumatologist was 12 months.

Delayed diagnosis is not a problem unique to developing countries. Rodriguez et al, reported a documented delayed diagnosis in USA in which there are about 300 certified pediatric rheumatologists [23]. Fosteret al, reported a large majority of patients in UK, reach the clinic after complex pathways [24].

In our opinion, there is a similarity in the factors that play a role in delayed diagnosis and referral of PRDs seen during our practice in Hadhramout and those reported by different studies before. These factors can be summarized as:

1. Difficulty in recognizing the diagnosis, which might be explained by the shortage of pediatric rheumatologists as well as a general lack of awareness of this subject [6] and the technique of pediatric MSK examination at the primary care level [9,26]. Myers et al, reported a limited number of patients being asked about MSK symptoms or even had full joint or gait examination, even in those children presenting with “limp” [32].
2. The widespread belief that arthritis does not occur in children [21,25].
3. Many cases were primarily managed by either adult or pediatric orthopaedic surgeon before referral [5, 9, 24, 31].
4. Systemic involvement in PRDs as nephritis in SLE, uveitis in JIA, and cardiac affection in RF and Kawasaki disease might delay referral to the pediatric rheumatologist as such patients are visiting other specialists according to the presenting complaint [7].
5. The slow and insidious natural evolution of certain rheumatic conditions [7,9,31].
6. The initial diagnostic confusion resulting from the complex and vague clinical presentation similarities of some PRDs as CTD and childhood malignancy and infection [21].
7. Late presentation and delayed diagnosis may be due to poverty, lack of awareness, and inadequate healthcare infrastructures and personnel [6,21].
8. The distance of the patient’s place of residence to the pediatric rheumatology centre [5,26, 31].
9. Pediatric rheumatology is a new speciality in Hadhramout. There are no special training programs, no concentration on continuing medical education sessions in PRDs. Inadequate knowledge in addition to poor awareness reflected by improper handling of the cases; most children were kept on long-acting benzathine penicillin although having chronic arthritis and unjustified usage of oral prednisolone

in suboptimal doses which may provide a partial response to the patient and at the same time masks the typical picture of the disease resulting in delayed referral and delayed diagnosis. The same situation was reported in India [7, 9, 24] and Africa [21].

10. The high cost and unavailability of DMARDs, immunosuppressive drugs and biologics [21] in addition to the misbelief that these drugs are used only in malignancy; these factors helping family refusal even if their child is not responding to steroids. This attitude results from poor health education in our areas.

A pediatric rheumatology service faces emergencies and mortality cases. MAS, lupus crisis, vasculitis with major organ manifestations, Kawasaki shock syndrome, and septic arthritis were some of the emergencies encountered [9]. In our study, the mortality rate was 5.4%; this result was much less than the result reported by Olaosebikan et al, where mortality rate was 10.5% of PRD cases [21]. In Africa, as reported by Henrickson M, where MSK disease does not form a primary health priority in comparison to infectious diseases. It only comprises 0.1% of mortality among children 5-14 years of age [33].

Our study is considered a preliminary data as the sample was limited to the cases diagnosed or referred for rheumatology opinion in pediatric rheumatology clinic in Al-Mukalla hospital. Suspected rheumatic cases treated in other hospitals or private clinics were not included in this study.

In conclusion, pediatric rheumatology is a relevant and an important speciality in Hadhramout/Yemen with increasing frequency of different PRDs. Childhood musculoskeletal pain is still a dilemma among specialists and general practitioners. This work may increase the awareness of specialists and general practitioners for early diagnosis and referral to avoid long-term morbidity, mortality, and disability.

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