ORIGINAL ARTICLE

CLINICAL PATTERNS OF CHILDREN WITH RHEUMATOLOGICAL DISEASES IN TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA: A RETROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: *Pediatric rheumatologic diseases are heterogeneous group of disorders with different disease manifestations among various populations. There are no reports of studies on pediatric rheumatologic diseases among Ethiopians. We present here in and define the clinical patterns of pediatric rheumatologic diseases encountered at Tikur Anbessa Specialized Hospital, in Addis Ababa University (AAU), Ethiopia.*

Method*: Hospital records of patients with a diagnosis of pediatric rheumatologic diseases with onset at the age of 16 years or less were reviewed between Sept. 2019 and Sept.2020. Diseases were classified based on the international league of associations for rheumatology (ILAR) diagnostic criteria.*

Result*: A total of 52 patients with pediatric rheumatologic disorders of onset at age of 16 years or less were included in the study. The average age at disease onset was 5.9 yrs (range 1-10 years). The average age at first visit to hospital was 9.14 yrs (range:3-12 yrs) and with a female to male ratio of 1.8:1. Rheumatoid factor negative arthritis, 33 %, was the most frequent type of rheumatologic diseases. Systemic onset arthritis was found in 12% of the cases. Systemic Lupus Erythematosus (SLE) was found in 6%, 6% had Henoch-schonlein Purpura and One child had scleroderma. Polyarticular RF +ve 14 %, Oligoarticular JIA 20 %, JDM (juvenile dermatomyositis) 8 % and other vasculitis 2% were other findings. ANA (antinuclear antibody) was found in 25%.*

Conclusion: *Polyarticular rheumatoid factor negative Juvenile Idiopathic arthritis was a predominant type of rheumatological diseases. Timely consideration and diagnosis based on ILAR are recommended to guide care rheumatological diseases. Further studies and training opportunities in the field are recommended to uncover the national burden of the disease.*

Keywords: *Pediatric Rheumatological diseases, Juvenile Idiopathic Arthritis, Systemic Lupus Erythematosus, Comorbid diseases, Addis Ababa University, Rheumatological disorders.*

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BACKGROUND

Reports on the prevalence and incidence of pediatric rheumatologic diseases suggest variability among different ethnic and geographically distinct populations [1-6]. Pediatric rheumatologic diseases are an immune mediated diseases of childhood characterized by inflammation of joints, striated muscles, skin and internal organs. Despite the improvement in treatment outcome and mortality rates among pediatric rheumatologic diseases and treatment related damage remains a major challenge and significantly affect the quality of life of affected individuals [7, 8].

Gene expression profiling studies have identified different immune mechanism in distinct subtypes of the disease, and can help to redefine disease classification criteria. Immunological studies have shown that systemic juvenile idiopathic arthritis is an acquired autoinflammatory disease, and have led to successful studies of both interleukin-1 and interleukin-6 blockade [9]. ANA, Rheumatic factor and HLA testing options should also be offered for such patients [1].

Juvenile Idiopathic Arthritis is the most common childhood rheumatologic disorder with the prevalence of 16-150 per 100,000 children. It is characterized by chronic arthritis of unknown etiology, lasting at least 6 weeks with the onset before 16 years of age [9]. Less resourced countries face a unique set of challenges in caring for children with rheumatologic diseases, which limit the ability to deliver high quality care to patients with JIA and other rheumatologic diseases in children.

There are no studies or reports on the rheumatological disorders from Ethiopia. In this paper, we detail the spectrum and epidemiological subtypes of Pediatric rheumatologic diseases among Ethiopian children seen at a tertiary level hospital. Diagnostic and classification difficulties engendered by limited diagnostic procedures, late presentation to hospital and irregular follow up are highlighted.

METHODS

Study design and settings

This retrospective review of medical records of patients with Pediatric rheumatological diseases was carried out at Tikur Anbessa Specialized Hospital (TASH) from September 2019 to September 2020. TASH is owned by Addis Ababa University and it is a national referral center located in Addis Ababa, Ethiopia. Several Speciality and subspeciality services are provided. Our Rheumatology clinic attended by the Rheumatologist & pediatric attached residents treats 6-10 patients weekly.

Source Population

All Pediatric rheumatologic patients attending follow up at Pediatric rheumatology clinic at TASH.

Study population

All Pediatric rheumatologic patients attending follow up at Pediatric rheumatology

clinic at TASH and whose medical records could be retrieved. Clinical, haematological, immunological, radiological & other relevant findings from the history were obtained from the medical records of study subjects. International league of associations for rheumatology (ILAR) diagnostic criteria was used for classification of the rheumatological diseases. Patients were thus recategorized as systemic arthritis, oligoarthritis, polyarthritis (RF +ve& RF - ve), SLE & others.

Patients who had signs & symptoms of other than rheumatologic diseases such as acute rheumatic fever, septic arthritis, malignancy, HIV infection or metabolic diseases were excluded from the study after careful scrutiny of respective case records. During the recruitment period 58 medical records were reviewed, then 52 cases who fulfilled the inclusion criteria were enrolled in the study.

Ethical considerations

This study was approved by the Pediatrics Department Research and Ethics committee, School of Medicine, Addis Ababa University.

Data collection

Medical records were reviewed and parameters including age at diagnosis, gender, ethnicity, treatment course, joint swelling, fever, rash, ESR, ANA, RF, CRP, systemic manifestations & others. Accordingly, the clinical criteria for probable diagnosis of Pediatric rheumatological diseases were used. Data were collected using structured questionaries.

Medication adherence was assessed with multiple questions developed by the clinic & patients were defined as adherent if they reported taking all doses of their medication in a typical week. Disease activity was assessed on history reported from the caregiver & physician's clinical scale .

Data analysis

Data was analyzed using SPSS (Statistical Package for Social Sciences) version 23 software. Mean & interquartile ranges were used for descriptive statistics for quantitative variables. Frequencies were computed for qualitative variables. For comparison between categorical variables, cross-tabulation with formulation of Fisher's exact (chi square) statistic was used. The two-sided p-value <0.05 were considered to be statistically significant.

RESULTS

This study included 52 Pediatric rheumatological patients. The Pediatric rheumatologic disease subtypes are shown in Table 1. There were 33 girls & 19 boys with a female to male ratio of 1.8:1. The overall average age at disease onset was 5.94 (range :1-10 years) and the majority of the patients presented late with average age at first visit to hospital being 9.14 years (range:3-12 years). Polyarticular Rheumatoid Factor -ve JIA, 33%, was the most frequent type.

Oligoarthritis was found in 20%, while 14% &12% were polyarticular RF +ve & systemic onset JIA, respectively. SLE was found in 6% & only one child ,2%, was determined to have other vasculitis, and 6% (3) children had HSP (Henoch-schonlein Purpura). The majority of oligoarticular JIA had onset in early childhood while a majority of polyarticular JIA had onset in late childhood. Oligoarticular disease affected the lower limbs predominantly. Only one child had Scleroderma.

At presentation the pattern of joint involvement was asymmetric in those with oligoarticular disease & symmetric in polyarticular and systemic onset JIA Fever, rash, eye involvement (acute/chronic uveitis and conjunctivitis), ESR and anaemia were the main noted extra-articular clinical features in JIA cases. Fever of at least two weeks duration was observed in all systemic JIA (See table 1). Clinical remission on medication has been documented in 30 patients out of 38 JIA patients (78.9%) who are still prospectively being followed in the established Pediatric rheumatologic clinic in TASH.

Table-1. Clinical sub types of rheumatological diseases in TASH, Addis Ababa, Ethiopia (no=52)

	Total No (%)	**Female: male ratio**	**Mean age at disease onset (yrs)**	**Age range at onset (yrs)**	**Mean age at presentation (yrs)**	**Age range at presentation (yrs)**
Overall	52(100%)	1.6 :1	5.54	1-10	8.4	2-14
Systemic JIA	6(11.5%)	1:1	4	1-6	6.5	3-10
Polyarticular JIA RF -ve	17 (32.69%)	2.4:1	6	1-10	8	2-14
Polyarticular JIA RF +ve	7(13.45%)	1.3:1	8	5-10	10.6	8-12
Oligoarticular JIA	10 (19.23%)	1:1	5.7	2-10	8	3-12
JDM	4(7.69%)	3:1	7.7	5-10	10	7-12
Reactive arthritis	1(1.92%)	0:1	7	7	7	7
SLE	3(5.76%)	3:0	8.6	8-9	10.3	9-12
HSP	3(5.76%)	2:1	8	7-9	8	7-9
Vasculitis	1(1.92%)	0:1	9	9	10	10

JIA (Juvenile Idiopathic Arthritis), SLE (Systemic lupus erythematosus), HSP (Henoch schonlein purpura), JDM (juvenile dermatomyositis)

Table-2: Clinical profiles of children with rheumatological diseases at presentation TASH, Addis Ababa, Ethiopia (no=52).

	Systemic on set JIA No (%)	**Polyarticular JIA N (%)**	**Oligoarticular JIA No (%)**	**JDM No (%)**	**SLE N (%)**	**HSP N (%)**	**Vasculitis Takayasu No (%)**	**Overall No (%)**
Fever	6(100)	8(33.3)	2(20)	2(50)	3(100)	2(66)	-	25 (48.07)
Rash	3(50)	1(4.2)	1(10)	3(75)	3(100)	3(100)	-	15 (28.84)
ESR	5(83.3)	19(79.2)	7(70)	3(75)	3(100)	2(66.6)	1	36 (69.23)
ANA	1(16.6)	4(16.7)	4(40)	1(25)	3(100)	0	-	13(25)
RF	2(33.3)	7(29.2)	1(10)	1(25)	1(33.3)	0	-	10 (19.23)
Arthritis	6(100)	24(100)	10(100)	3(75)	2(66.6)	1(33.3)	-	45 (86.53)
X-ray	4(66.6)	18(75)	7(70)	2(50)	2(66.6)	1(33.3)	1	41 (78.84)
Ex.Art.	6(100)	10(41.7)	7(70)	4(100)	3(100)	3(100)	1	38 (73.07)
Eye	2(33.3)	2(8.3)	2(20)	0	0	0	-	7(13.46)
Infections	3(50)	3(12.5)	3(30)	2(50)	3(66.6)	2(66.6)	-	17 (32.69)

Table 3: Comorbid diseases found in children with various rheumatologic diseases TASH, Addis Ababa, Ethiopia (no=52)

No	System Involved	No.of patients	Specific diseases
1	CARDIOVASCULAR	5	common AV canal, PHPN, dilated CMP, TOF, CRHD
2	INFECTIOUS:	6	Septic arthritis, disseminated tuberculosis, pneumonia, hepatitis
3	SYNDROMES:	2	down, Marfan
4	DRUG RELATED	3	drug induced hepatitis, fungal infections
5	HEMATOLOGIC	6	Transient neutropenia, severe anaemia, chronic Idiopathic thrombocytopenic Purpura (ITP)
6	DERMATOLOGIC	4	Seborrheic dermatitis, fungal infections, erythema nodosum
7	RAYNAUDS PHENOMENON	1	Raynaud's Phenomenon
8	OCULAR:	7	conjunctivitis, ectopia lentis, strabismus, bilateral uveitis
9	SKELETAL	3	Pectus carinatum, cervical ankylosis, kyphoscoliosis
10	RENAL:	3	Lupus nephritis, stage 2 chronic kidney diseases (CKD), Hypertension (HPN)
11	MALNUTRITION:	3	Severe Acute Malnutrition (SAM)
12	NEUROLOGIC:	3	Flaccid paralysis, hemiparesis, fascial palsy
13	ENDOCRINE	2	hypothyroidism, hypoparathyroidism
14	EFFUSIONS	2	Pulmonary pericardial

AV (atrioventricular), PHPN (pulmonary hypertension), CMP (cardiomyopathy), TOF (tetralogy of fallot), CRHD (chronic rheumatic heart diseases)

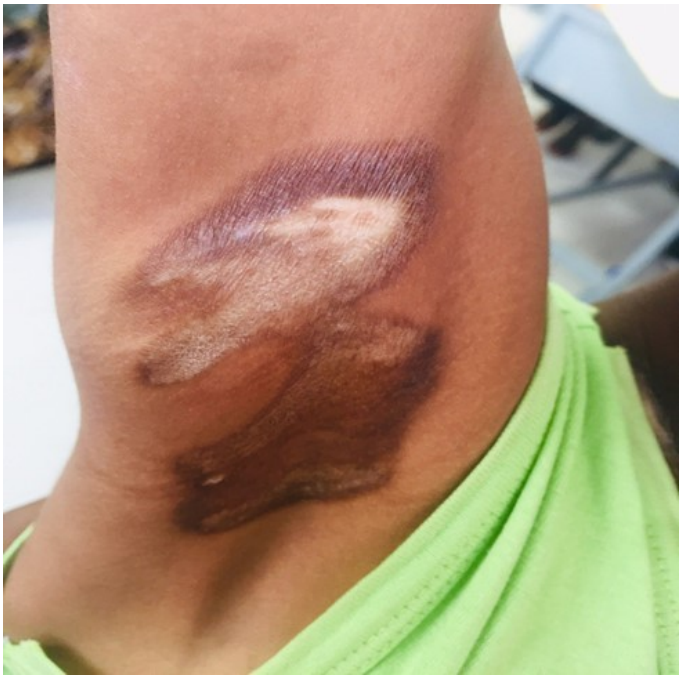

Fig-1 Scleroderma in a 6 yrs old child (with family permission)

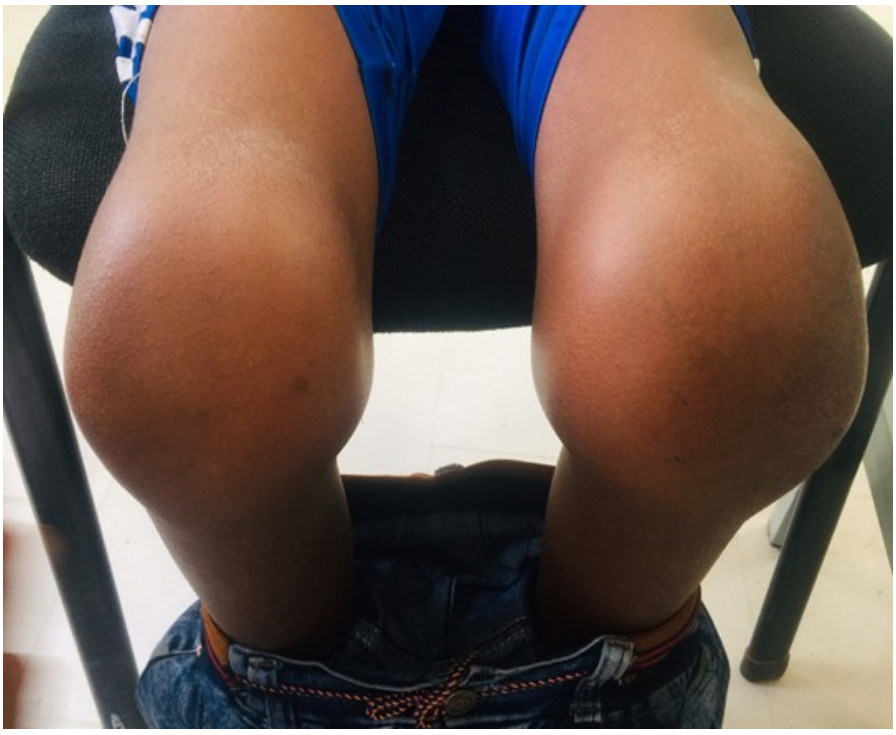

Fig-2 Oligoarticular JIA in an 8-yr- old child (with family permission).

PATIENT CLINICAL OUTCOMES

The majority of documented JIA children in remission 18 out of 30 (60%) were with polyarticular RF (-ve) disease. Four of the patients in remission were polyarticular RF +ve disease. Three of the patients with HSP also improved & two of the SLE patients being followed up in the established Pediatric rheumatologic clinic were also in clinical remission.

All the three of the SLE patients were females and 3 of the 4 JDM (Juvenile Dermatomyositis) patients were females. Creatinine Kinase (CK) was elevated in 3 of the 4 JDM patients. Muscle biopsy was performed in 2 (50%) of these patients and showed characteristic features including perifascicular atrophy, fiber degeneration& perivascular inflammation consistent with JDM.

Our retrospective observational study of patients included 34 with Juvenile Idiopathic Arthritis (JIA),3 with SLE,6 with Systemic onset JIA, 4 with JDM & 3 patients with HSP. Patients were 2-14 years old at presentation (mean 9.14 years) and 64 % were females.

Diagnoses included Polyarticular RF -ve JIA 33%, oligoarticular JIA 20%, Polyarticular RF +ve JIA 14 %, Systemic Onset JIA 12 %, JDM 8 %, SLE 6 %, HSP 6 % and other vasculitis 2 %. Mean age at disease onset was 5.3 years.

Three SLE patients (6%) were included in the study: one was from Oromia, one from Amhara and one from Addis Ababa. Organ involvement distribution was: renal involvement in one patient, cardiac one and chronic ITP & bleeding in one patient, skin involvement in 2 patients & arthritis in 2 patients. Antidouble stranded DNA antibody was found in one patient. Most of the patients were screened with CBC, ESR, RF, ANA& X-RAY. X-RAY of joints revealed that 41 (79%) patients had abnormal joint findings including periarticular osteoporosis, effusions& proximal & distal phalangeal erosions.

Twenty-eight had comorbid diseases associated with their rheumatologic manifestations (Table 3). Most of the patients were investigated with ANA, RF etc. Among the clinical features observed 45 of them 86 % had arthritis. Twenty-five of them (48 %) had fever. ANA was positive in 13 (25 %) of patients. RF was positive in only 10 (19 %) of patients. Infections were observed in 17 (32.6 %) of patients. Extra-articular manifestations were observed in as many of the clinical features of the patients (76 %).

The majority of patients in this series 36 (72 %) of the 52 patients coming to follow up had clinical remission on medication. In demographics by age distribution in years the median age was 9 yrs (95% CI: 8-9; SD is 2.97); the mean duration of follow up in yrs was 3.5 yr. (95% CI, 3 - 4; SD, 1.42)

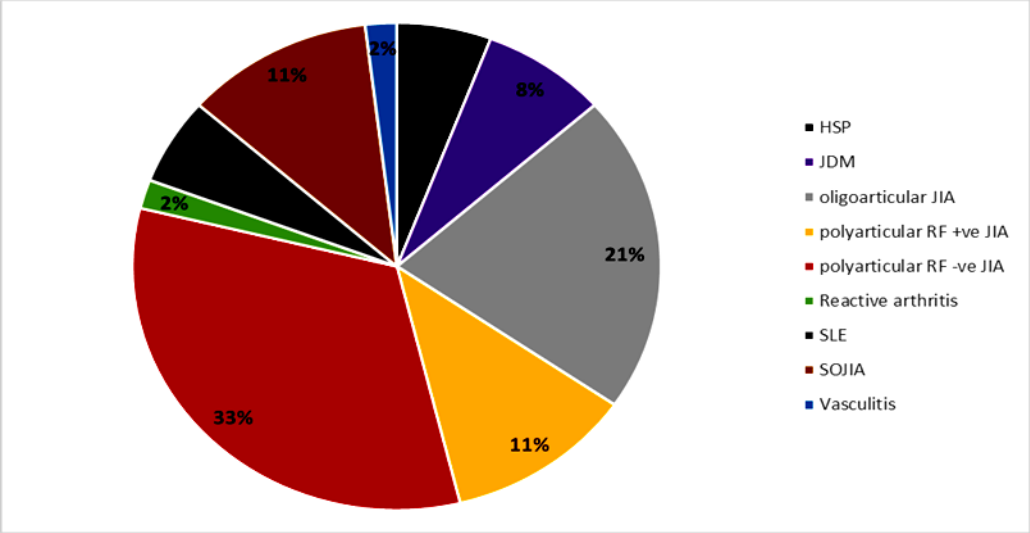

Fig -3 Clinical subtypes of rheumatological diseases

Table-4 Determinants of disease activity in children with rheumatological diseases TASH, Addis Ababa, Ethiopia (no=52)

Characteristics		**Rheumatology Subtype**				**Total**	**Pearson X^2**	**P-Value**
		Oligoarticular JIA	Polyarticular RF –ve JIA	Polyarticular RF +ve JIA	Other			
Gender	Female	6	12	4	11	33		
	Male	4	5	3	7	19	0.59	0.899
Total		10	17	7	18	52		
Residence	A. A	3	6	4	12	25		
	Out of A.A	7	11	3	6	27	5.14	0.16
Total		10	17	7	18	52		
Response for treatment	Improved	7	11	2	14	34		
	Not Improved	3	6	5	1	18	5.5	0.14
Total		10	17	7	18	52		
Joint disability, damage	No	10	6	2	16	34		
	Present	0	11	5	2	18	20.68	0.001
Total		10	17	7	18	52		

In the above table: Joint disability was associated with the type of rheumatological disease (P-value =0.001) while gender, residence, response to treatment didn't show any association with the type of rheumatological disease.

DISCUSSION

Our study on the Pediatric rheumatological disorders is the first to report the disease profile in Ethiopia. We have used the ILAR classification criteria for disease classification. The overall average age at disease onset was 5.94 years (range :1-10 years) and the majority of the patients presented late with average age at first visit to hospital being 9.14 years (range:3-12 years). Polyarticular JIA is the major documented form of rheumatological disorders. The heterogeneity in nomenclature of the disease ,the lack of diagnostic tests & the differences in diagnostic criteria have made it difficult to understand fundamental epidemiological comparisons such as incidence ,prevalence & clinical manifestations.The current international league of associations for rheumatology (ILAR) JIA classifications is contributing to a more uniform nomenclature & nosology, and thus improving comparative disease diagnosis & epidemiology across countries & ethnic populations[1,5].

We chose to adopt the ILAR classification criteria for this study. This study covered a total period of 2 years & has yielded 52 cases of pediatric rheumatology diseases cases. The prevalence of polyarticular sero negative disease (33% in this study) is among the highest reported worldwide, f followed by oligoarticular disease (20 % in this study), the most common subtype described in studies from Europe & North America (6,7). This finding is in keeping with other studies from the developing world UK (20), where evidence for a lower incidence of oligoarticular disease has been noted (7-13). The noted difference could be related to the study setting, and health seeking behaviour. Genetics could also play in this.

The gender distribution in our study were almost comparable. Caucasian studies documented a higher female occurrence, almost five times higher in females. Social and cultural rather than biological reasons may lie behind this observation. It is highly likely that so called 'milder ' cases of JIA cases might never reach a tertiary care facility in many developing world settings. In developed world children with pediatric rheumatologic diseases will usually be reviewed in a hospital setting and have access to diagnostic and therapeutic facilities not yet available in most parts of our country.

It is apparent that differences in prevalence of pediatric rheumatologic diseases in Ethiopia from those reported in the industrialized west may simply be the result of a selection bias imposed by a dearth pediatric rheumatology service and expertise. In this context it is of interest that in true community-based studies in the developing world the prevalence of oligoarticular disease matches or exceeds that of polyarticular disease (14-19).

In Caucasian& Indian studies the majority of subjects ERA(Enthesitis related arthritis) are B27 positive & the prevalence of ERA is much higher than our study & this is likely due to the virtual absence of the B27 gene study in our country .The extra-articular features were as expected,apart from the poor ophthalmic outcomes in those with chronic uveitis .As pediatric rheumatology knowledge increases amongst doctors & other care providers in Ethiopia leading to the application of standard diagnostic & classification criteria , prevalent cases are likely to continue to resemble those reported elsewhere. Clinicians working in parts of Ethiopia where rheumatological services are non-existent or rudimentary face enormous challenges. These include a wide differential diagnostic list and a limited arsenal of diagnostic procedures to aid them in reaching a definitive diagnosis.

Limited training in pediatric rheumatology and working in an environment burdened with infectious diseases , their differential diagnostic list is frequently limited to possible infectious causes for rheumatological problems .Distinguishing common rheumatic fever from rarer pediatric rheumatologic subtypes is one example and unless clinicians are well trained to recognize the distinctive features of the two conditions, they will have doubts about diagnosing pediatric rheumatologic diseases[3,4] .

TABLE 5: Epidemiological comparison of JIA in developing and developed countries [UK (20); SA, (21)]

	Ethiopia	**South Africa**	**UK**
No in studied series	34	78	572
Systemic JIA (%)	13.7	7.7	14.7
Polyarticular JIA RF –ve (%)	45.5	14	19.5
Polyarticular JIA RF +ve (%)	18.1	26.9	5.2
Oligoarticular JIA (%)	22.7	26	43.7
Eye involvement	15.9	-	20
ANA positivity (%)	20.4	4.48	33

In our setup milder pediatric rheumatologic patients are not referred to our clinic and be attributed to trauma or thought to be infective & children with persistent or more severe joint symptoms may be subjected to unnecessary long term steroid treatment with its ugly complications. Therefore, increasing training & awareness of pediatric rheumatologic diseases among clinicians in Ethiopia should lead to improvement in reporting & adherence to the standard diagnostic criteria & early referral to our pediatric rheumatological clinic and prompt treatment with a better prognosis of the disease.

A better understanding of the epidemiology and reports of clinical outcomes of Juvenile Dermatomyositis (JDM) is engendered by scarce data from the country. Delay in diagnosis of JDM may be the consequence of lack of access to clinicians skilled in diagnosing & managing JDM & similar conditions; and lack of access to diagnostic facilities such as EMG & muscle biopsy [8]. Future efforts should be directed at validating efficacy of methotrexate in pediatrics and adverse events and many candidate predictors should be investigated. Recently a review was published about genetic predictors of MTX (methotrexate) efficacy & toxicity in pediatric rheumatological diseases (22).

Approximately 1/3 of our patients report imperfect adherence to medications which is similar to other reported adherence rates among pediatric patients with chronic illnesses. The most common reasons provided for missing medications was forgetfulness, cost of medications & cost to follow up (23) This cohort of subjects include pediatric SLE patients with a female predominance of 100%. Our study had several limitations including a small sample size and retrospective approach. Additionally, lack of comprehensive record and history documentation for several subjects.

CONCLUSSION AND RECOMMENDATIONS

All categories of pediatric rheumatologic diseases were identified in Ethiopian children. Polyarticular RF -ve disease was the most common presentation. Late presentation coupled with the scarcity of specialized health services are issues with major implications for patient care and productivity.

Furthermore, there was persistent clinically active disease in a large proportion of this cohort (50%), putting them at risk of further disease complications. Establishment of a prospective cohort in future could be useful in providing better quality data for better outcome assessments in line with currently accepted international guidelines. Better trainings opportunities in the field will help earlier diagnosis and assist in generation of data for advocacy in the care for such patients.

ABREVIATIONS

JIA -Juvenile Idiopathic Arthritis

ILAR -International League of Associations for Rheumatology

ESR - Erythrocyte Sedimentation Rate

ANA -Antinuclear Antibody

ADSDNA Ab- Antidouble Stranded DNA Antibody

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