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Systemic Onset Juvenile Idiopathic Arthritis: Severity Factors

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Summary

Aim: Systemic Juvenile Idiopathic Arthritis (SJIA) is an autoinflammatory disease with various presentations and unpredictable outcome. he aim of this study is to investigate the factors influencing the response at first intention treatment (non-steroid anti-inflamatory drugs AINS, corticosteroids) and the prognosis of the disease.

Methods: A retrospective study of child with prospective follow-up was used at children Hospital between January 2008 and December 2012. The patients were classified in two groups according to their clinical, paraclinical and radiological signs. Group 1: responders at first-line treatment (AINS, corticosteroid) and group 2: non-responders requiring second and third line treatment.

Results: According to International League Against Rheumatism (ILAR), 46 children's were included. The mean age was 5,81 ± 3,40 years. 23 (50%) among the non-responders of treatment had begin the disease before 5 years old. All the non-responders had polyarticular form straightaway 31 vs 6 (p< 0,001). Fever was constantly present associated at cutaneous eruption in 32 patients (69,6%). Cardiac attack was present in 17,4%. Biological inflammatory syndrome was present in all cases at the diagnosis in the two groups. Thrombocytosis was found in 39 cases (84,7%) whose 30 in group 2 vs 9 in group 1 (p= 0,003). Bone anomalies were found in 18 patients among the non-responders (p= 0,004). The outcome was marked by total remission in 13% in group 1; 56,5% in group 2 made systemic attacks and/or articular whose 30% kept sequelae with articular deformations.

Conclusion: In this study, the severity of SJIA with corticodependance or corticoresistance can be linked at the following factors: polyarticular attacks, thrombocytosis, and bone anomalies.

Keywords: Prognosis; Severity Factors; Systemic Onset Juvenile Idiopathic Arthritis

Introduction

SJIA refers to patients with arthritis of unknown origin and associated with systemic features, and represents one of the categories of Juvenile Idiopathic Arthritis (JIA), a heterogeneous group of diseases with onset before the age of 16 years [1,2]. JIA is one of the most common pediatric chronic diseases, with a prevalence rate varying from 3.8 to 400 cases/100,000 children and a yearly incidence between 1.6 and 23 new cases for 100,000 children [3]. SA is distinguished from other forms of JIA by the presence of systemic symptoms including prolonged and oscillating fever usually inaugural, a transient rash concomitant with fever and other systemic signs [4]. Hence, it features many similarities to autoinflammatory diseases and could be at least partly considered as an autoinflammatory condition [5,6]. Evolution can happen in three main modes: articular and systemic monocyclic, polycyclic with systemic relapses and / or joint and chronic joint with and joint deformity and destruction [7]. Vital prognosis may be initiated due to non- control of the disease in severe forms by the risk of organ damage including heart and kidney as well as the high sensitivity of these children in developing a serious complication of the macrophage activation syndrome. The overall mortality in systemic arthritis is estimated at 2-4 % [8]. Severe forms are also associated with a greater risk of sequels and disabilities due to articular and systemic manifestations. Only a few predicting factors of severe evolution have been individualized (initial poly-arthritis, hip involvement, thrombocytosis, corticosteroid) [9-11]. The goal of this retrospective study describing a population of patients with SAJ followed in pediatrics is to determine the factors influencing the response to treatment of ASJ in Moroccan children.

Patients and Methods

This is a retrospective study that involved children with ASJ collated in pediatric ward 4 (with 53 beds with biotherapy and physiotherapy rooms) and consultation of pediatric rheumatology which drains all cases of rheumatism and systemic chronic inflammatory diseases of children who come to Children's Hospital university hospital Ibn Sina in Rabat between January 2010and December 2015. All records of children with SAJ were analyzed and only those meeting ILAR diagnostic criteria (International League of Associations for Rheumatology) were included [12]. Clinical and laboratory data were collected from patients' medical records. Joint involvement has been used as a criterion diagnosis in the presence of arthritis (oligo or polyarthritis), only patients with arthralgia were excluded from the study. Fever was considered when the temperature exceeded 38.5 with intermittent peaks for more than 2 weeks. The presence of cutaneous, adenomegaly and hepatosplenomegaly was noted. Cardiac involvement was assessed by echocardiography performed routinely on all patients. Biological data collected is: blood count, erythrocyte sedimentation rate, C reactive protein, fibrinogen, urea, creatinine, AST, ALT, anti-nuclear factor, rheumatoid factor.

The evaluation of bone involvement was made by comparative standard radiographs of the affected joints at diagnosis. The different stages of Stein broker were analyzed.

To evaluate severity factors, we divided the patients into 2 groups according to their clinical, laboratory and radiological signs. In group 1: responders to first-line therapy (NSAIDs, corticosteroids) and group 2: non-responders requiring a second treatment and third line (Methotrexate, cyclosporine, biotherapy). Treatment's efficacy was assessed according to Guannini score now called Score of the American College of Rheumatoloy (Pediatric ACR) or sometimes called PRINTO detailed in (Table 1) [13]. Remission is defined by the absence of articular, systemic or biological activity of the disease for at least 6 months [11].

Are taken in compete the 6 followings items
Name of inflammatory articulations (= with joint gonflement linked at active synovitis or articular limitation + pain at mobilization.)
Name of articulations with limitation of mobility (except irreversible ankylosis) functional CHAQ Score EVA (0 to 100 mm) of wel-being of child by parents EVA (0 to 100 mm) of disease activity by doctor Vitesse de sédimentation (VS) at first hour
«Définition of improvement 30% (pédiatric ACR 30) »: at least 30% improvement of 3 at least of 6 score items with much 1 item 30% worsen or more
«improvement pédiatric ACR 50, 70 ou 90 »: at least 50, 70 ou 90% of improvement respectively of at least 3 items with much 1 item 30% worsen or more
« Thrust /relapse of disease » is definite by an aggravation at least 30% of 3 items at least of score (for inflammatory articulations)
Requiring to have at least 2 supplementary articulations and for doctor EVA a progression at least 20/100) with no more than 1 item30% improved or more.
Criteria of response proposed for systemic juvenile arthritis
Response = improvement pediatric ACR 30 + absence of fever linked to disease and rash (7 à 14 days) ± improvement or normalization of biological parameters VS or CRP (absence of consensual definition, suggestion variant of therapeutic essay

Table 1: ACR pédiatric Score or « Giannini score » (9).

Statistical Analysis

Quantitative variables were expressed by their mean and standard deviation when the distribution was normal or by their median and inter- quartile when it was abnormal. Qualitative variables were expressed by their numbers and percentage. Comparisons between groups of quantitative variables with symmetric distribution were conducted by Student's T test. Comparisons between groups of quantitative variables with skewed distributions were made through Wilcoxon test. Comparisons of quantitative variables between groups were performed by Fisher's exact test, as the χ^2 test applicability conditions were not met due to low enrollment. The statistical significance level (p) was set at 0.05.

Results

46 patients including 24 females and 22 males were identified among 220 children followed for JIA in this period, which is 20.9 % of all JIAs. (Table 2) shows our patients' characteristics. The average age was 5.81 ± 3.40 years. Sex ratio was 1.09. The earliestr onset was recorded in a 6 months infant. The median time from diagnosis was 3.5 months [4-10]. Clinical data at diagnosis were dominated by arthritis symptoms, arthritis being the most common reason for consultation (100% of cases) as polyarthritis (82%), oligoarthritis (18%) the most affected joints were: wrists (22.66%), knees (21.33%), ankles (21.33 %). Fever was present constantly associated with a rash in 32 patients (69.6%). Cardiac involvement was present in 8 patients (17.4%). This involvement has been dominated by the pericardial effusion in 66.6 % of cases. Pleural involvement was found in 9% and 47% in lymphoid involvement.

Characteristics		**Values**
		(n = 46)
Age (year)		5, 81 ± 3,40
Age onset(year)		5, 10 ± 2,9
diagnosis delay (month)		3,5 [2-6]
Sex		
	Female	24 (52,2%)

	Male	22 (47,8%)
Polyarthritis		
	Yes	37 (82%)
	No	9 (18 %)
cutaneous anomalies		32 (69,6 %)
visceromegaly		2 (9,4 %)
cardiac anomalies		8 (17, 4 %)
Anemia		
	Hb 10 - 12	23 (50 %)
	Hb < 10	23 (50 %)
Hyperleucocytosis		41 (89, 1%)
Thrombocytosis		39 (84,7%)
ESR		
	20-50	6 (13 %)
	> 50	40 (87 %)
Bone anomalies		
	No	33 (71,7%)
	yes	13 (28,3%)
Treatment		
	AINS	28 (60,9%)
	Corticoids	42 (91,3%)
	Methotrexat	29 (63 %)
	CyclosporinA	12 (26,1 %)
	Biotherapy	08 (17,4 %)
Evolution		
	monocyclic	06 (13 %)
	Attacks	26 (56, 5%)
	Sequelae	14 (30,4 %)
Response at treatment first- line		
	Yes	15 (32,6%)
	No	31 (67,4%)

Table 2: patients characteristics.

A hemophagocytic syndrome was detected in 3 patients (6%). This complication was triggered by a viral infection with cytomegalovirus in one case, the combination of NSAIDs and persistent disease activity in two others. The biological inflammatory syndrome was present in all patients in diagnosis. Nuclear antibodies and rheumatoid serology sought in all patients were negative. Bone involvement was present in 13 patients at diagnosis (28.3%). This was achieved in the form of bone loss in 9 of them, pinching with chondral geodes in 4 patients.

Therapeutic Strategy and Response to Treatment

The combination of NSAIDs with corticosteroids was often necessary to control extra- articular signs. 80.4% of patients received first-line therapy (NSAIDs and / or corticosteroids), including NSAIDs, salicylates were used in 47%, other NSAIDs (diclofenac, arylpropionic derivatives, indole) were used in 60%, however, 42 cases (91.3%) required corticosteroid treatment immediately in the event of cardiac or visceral involvement with important inflammatory syndrome or with the lack of response to NSAIDs. 29 patients (63%) received second-line treatment with methotrexate due to the lack of response to NSAIDs and corticosteroids or in the case of a corticosteroid dependency (inability to reduce steroids below 10 mg / d) or corticosteroid resistance (defined as the inability to achieve remission on corticosteroids), methotrexate was associated with cyclosporin A in 12 of them. 8 patients (17.3 %) required the use of a third-line therapy based biotherapy using only molecules available at this time (etanercept in 5 cases, adalinumab in 1 case and tocilizumab in 7 cases (3 did not respond to etanercept). Complications identified in our study are: Heart problems (17.4%), growth retardation (52%), joint sequelas (30%), macrophage activation syndrome (6%) In order to identify severity predictors factors, responders to first-line treatment were compared to non-responders according to their clinical, paraclinical and evolutionary profile (monocyclic and polycyclic with severe sequela) (Table 3).

Variables	Groupe 1	Groupe 2	Total	P
	n= 15	n= 31	n= 46	
Age(year)	5,60±3,44	5,9±3,43	5,81±3,40	0,767
Age disease onset (year)	5,20±3,55	5±2,6	5,10±2,9	0,870
Diagnosis delay(month)	3 [1,6]	4[2,6]	3,5[2,6]	0,774
Sex Femal	10 (66,7%)	14 (45,2%)	24(52,2%)	0,17
Male	5 (33,3%)	17 (54,8%)	22(47,8%)	
Polyarthritis				<0,001
yes	6(40%)	31(100%)	37(82%)	
No	9(60%)	0	9(18%)	
visceromegaly	1 (2,3%)	5 (5,36%)	2 (9,4 %)	1
Cardiac anomalies	2 (13,3%)	6 (19,4%)	8 (17,4 %)	1
Anemia				0,753
Hb 10-12	7 (46,7%)	16 (51,6%)	23 (50%)	
Hb< 10	8 (53,3%)	15 (48,4%)	23 (50%)	
Hyperleuc ocytosis	12 (80%)	29 (93,5%)	41 (89,1%)	0,311

thrombocytosis	9 (23,1%)	30 (76,9%)	39 (84,7%)	0,003
ESR				0,647
20-50	1 (6,7%)	5 (16,1%)	6 (13%)	
50-100	14 (93,3%)	26 (83,9%)	40 (87%)	
Bone anomalies				0,004
O	15(100%)	18(58,1%)	33 (71,7%)	
1	0(0%)	13(41,9%)	13 (28,3%)	

Table 3: Clinical, biological and radiological Characteristics of responders. At first- line treatment (groupe 1) and non-responders (grouped 2).

On the clinical side, we did not find significant differences with regard to age, sex, early onset, however, all non-responders already had a polyarthritis ($p < 0.001$) Biologically, the VS exceeded 50mm 1st hour in 40 cases (87%), including 26 non-responders with no significant difference, 41 cases (89.1 %) had leukocytosis (average GB 21439), including 29 non-responders ($p = 0.311$). Thrombocytosis was present in 39 patients (84.7 %), average platelet count = 607,818) and 30 did not respond to first-line treatment ($p = 0.003$). Bone involvement was present in 13 patients among non-responders at diagnosis (28.3%) ($p = 0.004$). 6 cases (13 %) among responders to first-line treatment had a monocyclic evolution with remission. Within the non-responders, 26 patients (56.5 %) had systemic relapses and / or joint and among them 14 cases (30.4%) kept a persistent joint damage with sequelae.

In our study, three parameters showed a statistically significant difference in the two groups, polyarthritis involvement ($p < 0.001$), 30 versus 9 thrombocytosis involvements ($p = 0.003$) and the bone involvement 13 versus 0 ($p = 0.004$).

Discussion

Severity factors found in our study with a significant difference were: polyarticular initial damage, thrombocytosis and bone disease. SJIA severity varies from one child to another. These forms are of a highly scalable heterogeneity [14]. Even though SJIA is ranked among the JIA, most experts now agree, considering its clinic, scalable and severity profile, to relate to the group of autoimmune diseases [13]. Significant changes in the understanding of the disease pathogenesis have occurred in recent years [4]. It is radically different from other forms of JIA by the presence, in addition to arthritis, of systemic manifestations in the foreground and a very strong inflammatory response [4].

Some studies have identified predictors factors of poor prognosis such as immediate polyarticular disease with involvement of the hip, persistence of systemic symptoms after 6 months of disease progression, the initial thrombocytosis, and corticosteroid after 6 months or 2 years of disease onset [15], but the prognosis is variable depending on the series. In fact, Lin and Al [16] report that 43 % of children had persistent arthritis over 6 months, and 5 of them kept sequelae with major functional impairment. For Wrang, none of the 12 children with SJIA has developed joint destruction and in Hytsain series, only 3 patients had a destructive arthritis that required a total joint replacement. Shneider and Al [17], noted that the development of joint destruction was closely linked to the persistence of systemic signs and thrombocytosis for at least 6 months of disease onset.

In our study, the initial polyarticular and thrombocytosis were more frequent in non-responders to first-line treatment with corticosteroid or cortico-resistance requiring these patients to use second and third line treatment. Hyperleukocytosis may be an indicator of poor prognosis according to Yuan [18], it was found in 29 of our patients among non-responders but without significant difference. However, the prognosis is largely underpinned by joint damage. Several studies show that a major criterion for poor prognosis is the initial radiation damage [19]. Overall, a third of JIA are present in adulthood bone and joint destruction causing functional impairment [19], however, the assessment of bone disease and joint damage in children with of SJIA is subject to several difficulties. In pediatrics, X-rays are not performed routinely for fear of repeated radiation, the risk of erosion is less important than in adults because of the thickness of the articular cartilage. The four stages of Stein broker, used for a long time (osteoporosis, joint space narrowing, erosions and fusion) can be seen simultaneously; however, the possibility of forming a neocartilage in the case of children may be associated with improvements in the radiological image [20,21].

In our serie, bone involvement was observed in 18 out of 31 children (41.9%) who did not respond to first-line treatment, the long enough diagnosis period in these patients (median 6 months) reflects the relative frequency of bone disease in this study but only two of them had stage 3 and 4 Steinbroker. The type of evolution is another factor that can affect the overall response to treatment, currently, new scores were established to evaluate the activity of SJIA including JADAS score [22]. Lomater and others [23,24] reported that the frequency of remission was 100% in patients with a monocyclic evolution, 37% of those with repeated relapses and 23% when the disease is active. Our data is consistent with Lomater's. The 13% having a monocyclic evolution are currently in full remission.

Conclusion

Significant progress has been made in recent years not only the pathophysiology of JAS but also early indicators of poor prognosis that are better recognized. This work, although limited by its retrospective nature, and the relatively small sample, suggests that polyarticular, thrombocytosis and bone disease may influence the response to first-line treatment and be responsible for active disease in the long term; multicenter studies are however needed to confirm these results.

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