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Medical pathways of children with juvenile idiopathic arthritis before referral to pediatric rheumatology centers

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ABSTRACT

Objective: A better understanding about the referral pathway of patients suffering from juvenile idiopathic arthritis (JIA) is required. The aim of this study was to describe and analyze time from onset of symptoms to first pediatric rheumatology (PR) visit and the referral pathway of children with incident JIA in two French competence centers.

Methods: From October 2009 to October 2017, new JIA patients were registered in the “Auvergne-Loire cohort on JIA”. We collected referral pathway, symptom onset, biological and clinical data at first assessment in PR department.

Results: In all, 111 children were included. Median time to first PR visit was 3.3 months [interquartile range (IQR) 1.3, 10.7] with a significant difference between JIA subtypes. After exclusion of systemic JIA, older age at onset of symptoms, and presence of enthesitis or joint pain were significantly associated with a longer time to first PR visit, while joint swelling or limping, abnormal ESR or CRP were associated with a shorter time. The median number of health care practitioners met was 3 [IQR 3, 4]. Orthopedists referred children to a PR center in 64% of cases, pediatricians in 50%, emergency care practitioners in 27% and general practitioners in 25%. Although non-systemic JIAs are not an emergency, 45% were referred to the emergency room.

Conclusion: Time to first PR visit is rather short compared to other countries but remains too long. Pediatric rheumatologists should offer primary care providers basic training on JIA and fast direct access to PR departments if JIA is suspected.

Key words: juvenile idiopathic arthritis, pediatric rheumatology, referral pathway, access to care

1. Introduction

Juvenile idiopathic arthritis (JIA) is considered as a rare disease(1) (prevalence in France 15.7(2) to 19.8/100 000(3)). However it is the most common form of chronic arthritis in children and may well be underdiagnosed(4). It is defined as an inflammatory joint disease persisting longer than 6 weeks in children under 16 years old and after exclusion of all other causes of arthritis. Severe painless uveitis can be associated(5).

Studies demonstrate that there is a “window of opportunity” early in the disease course to alter the natural history of the disease process(6)(7). Early medical intervention comprising disease-modifying anti-rheumatic drugs, and in the past decade biologic agents, has dramatically decreased the risk of joint and/or ocular damage and improved the children’s quality of life (8)(9)(10)(11). Prompt referral to an experienced pediatric rheumatology (PR) center is crucial to start proper management and avert a period of undertreated disease. There are no international guidelines on time to referral, but the British Society for Paediatric and Adolescent Rheumatology Standards of Care advocates that every child with suspected JIA should be assessed by a PR team within 10 weeks of symptom onset(12).

However, in Europe, despite facilitated access to health care, children with JIA are referred to PR centers with significant delay(13)(14). The reasons are many: some are related to the disease itself, with a frequent insidious onset with painless subclinical swellings and multiple flares and spontaneous remission. In addition, after the first medical appointment the disease is usually undiagnosed, the child is referred to a specialist other than a pediatric rheumatologist (PRst): the referral pathway until final diagnosis can be very long, and include unneeded procedures(14).

Given this “window of opportunity”, strong efforts are required to identify in each country the components of time to first PR visit and shorten it. In France, in 2001 the “Société

francophone pour les maladies inflammatoires et la rhumatologie pédiatrique” (SOFREMIP) was created to promote research and training in PR in France and to foster exchange with other research societies(15). In 2004 the French National Plan for Rare Diseases has been implemented to structure diagnosis and care in rare diseases countrywide(16). Regarding PR, it has organized a network comprising 2 reference centers and 31 competence centers (including our two centers) throughout the country(17)(13). Only one monocentric study has previously assessed the time to diagnosis in 67 JIA patients in France. Data were collected in a center of reference in Paris, the capital of France, a densely populated metropolitan area(18) with the highest medical density in the country(19). Moreover, the study did not present in detail for the whole cohort the chronology of referral by healthcare provider (HCP) subspecialty (i.e. which HCP subspecialty referred to which one) to identify any misreferrals. Finally no predictive factors influencing time to diagnosis were found, probably owing to the small population (13).

The aim of this study was to describe and analyze the time from onset of symptoms to first PR visit, and the referral pathway of children with incident JIA in two French competence centers in PR encompassing large rural areas(20).

2. Methods

This retrospective cohort study is based on the prospective observatory “Auvergne-Loire cohort on JIA” including all patients of Clermont-Ferrand University Hospital and Saint-Etienne University Hospital (France) diagnosed with JIA from October 2009 to October 2017.

The database was approved (ref DR-2014-220) by the French board of data registry: Commission Nationale de l'Informatique et des Libertés.

2.1. Data collection

At enrolment, the following data were collected by the PRst: age, sex, dwelling place, date of symptom onset (if parents had forgotten the exact date, the first day of the month was retained), date of first visit with a PRst, date of diagnosis, clinical history: joint pain, joint swelling, morning stiffness, limping. Clinical examination findings at first visit were also collected: physician's global assessment of the disease activity (using a 1–10 scale), active joint count, presence of enthesitis, psoriasis or uveitis; and laboratory features: erythrocyte sedimentation rate (ESR) at one hour, C reactive protein (CRP), anti-nuclear antibody (ANA), presence of rheumatoid factor (RF) or HLAB27. The diagnostic pathway was also described: the specialty of each healthcare provider (HCP) met for JIA related symptoms and the timing, the presence of invasive investigations, immobilization or the use of antibiotics.

2.2. Definitions

Time to first PR visit was defined as the time from the onset of symptoms to the first visit to a PR center. Time to diagnosis was defined as the time from the onset of symptoms to the diagnosis.

Each JIA patient was classified according to the International League of Associations for Rheumatology criteria based on number of joints involved, associated symptoms and laboratory features (21).

Number of active joints was defined using the JADAS 71 score(22). Involved joints were classified as large joints (i.e. shoulder, elbow, hip, knee and ankle); small joints or spinal involvement(23).

CRP was considered elevated when its value exceeded 10 mg/L(24), ESR when its value exceeded 20 minutes at the first hour(22), and ANA when titers exceeded 160.

HCP specialty was classified as pediatric rheumatologist (PRst), general pediatrician (ped), general practitioner (GP), emergency care practitioner, orthopedic surgeon (ortho) and other.

The distance from parent's dwelling place to the pediatric rheumatology center was calculated using an Internet-based route calculator, URL: <https://fr.mappy.com>.

2.3. Statistical analysis

No sample size estimation was performed. Moreover, the multivariable analyses were carried out according to rules-of-thumb reported in the literature concerning the minimum number of subjects required to conduct multiple regression analyses(25). Secondary analyses were exploratory, given a particular focus to the magnitude of differences, in addition to inferential statistical tests expressed using p-values.

Statistical analysis was performed using Stata software (version 13; StataCorp, College Station, Texas, USA). All tests were two-sided, with a Type I error set at 0.05. Categorical parameters were expressed as frequencies and associated percentages and continuous data as mean (standard deviation (SD)) or as median [interquartile range: IQR], according to statistical distribution. Primary analysis was estimated using the Kaplan-Meier approach, and comparisons were made using the log-rank statistic in univariate analysis. Multivariable analysis was then performed using the Cox proportional hazards model, considering covariates determined according to univariate results, to clinical relevance and avoiding multicollinearity. Age at diagnosis, enthesitis, swelling, limping and ESR were selected. The proportional hazard hypothesis was verified using Schoenfeld's test and plotting residuals. The results were expressed as hazard ratios (HR) and 95% confidence interval (CI). In this

context, $HR = 1$ indicates an equal likelihood of first PR visit in the presence of the variable in question compared to its absence, while $HR > 1$ indicates an increased likelihood (shorter time), and $HR < 1$ indicates a reduced likelihood (longer time). Furthermore, association between number of health care practitioners met and time to first PR visit was assessed with Spearman's rank correlation coefficient.

3. Results

3.1. Characteristics at first PR visit

One hundred and eleven patients were included (Table 1). The mean age at symptom onset was 7.9 (SD 4.3). The most frequent JIA subtype was oligoarticular (oJIA) (33%). At first PR assessment, all the patients had active disease (physician's global assessment 4 [IQR 3, 7]). Almost all the children (94%) had large joint involvement, 52 (47%) had small joint involvement and 11 (11%) had spinal involvement. There was no documentation of macrophage activation syndrome.

3.2. Symptom duration

Median time to first PR visit was 3.3 months [IQR 1.3, 10.7]. Fifty children (45%) were assessed by a PRst within 10 weeks after onset of symptoms. The shortest time to PR visit was for children presenting with sJIA (median 0.5 months [IQR 0.3, 0.9]), and the longest in those presenting with ERA (median 11.4 months [IQR 4, 24]).

3.3. Referral pathway

During the referral pathway, pain was the most often reported symptom (78%), followed by swelling (43%) and limping (38%). Many patients underwent unneeded procedures: plaster or traction (13%), antibiotherapy (13%) and invasive procedures (7%) including arthroscopies, bone biopsies and electromyogram.

A median of 3 HCPs [IQR 3, 4] were involved prior to the first PR assessment with a maximum of 6. No correlation was found between time to first PR visit and number of HCPs met ($r = -0.02$, $p = 0.83$).

Figure 1a describes the first three HCPs involved in the diagnostic pathway of patients after exclusion of sJIA: GPs, emergency care practitioners and peds were the most frequently involved as first HCP. The GP was the main first HCP, who mostly referred the child to an emergency care practitioner (31%) and less often to a PRst (26%). As first HCP, the emergency care practitioner referred most often to an ortho (50%) and very seldom to a PRst (6%), whereas the ped referred more than half of the children (57%) to a PRst.

Figure 1b describes for sJIA patients the first three HCPs involved in the diagnostic pathway: GPs and emergency care practitioners were the most frequently met as first HCP. The GP was the main first HCP, who mostly referred the child to an emergency care practitioner (50%). As first HCP, the emergency care practitioner referred to a ped (100%). Orthos were not involved in the referral pathway.

Figure 2 describes the patient's referral by subspecialty. GPs and emergency care practitioners were those most frequently met (respectively 31% and 27% the cases). However, the HCP who referred most frequently to PRst was the ortho (63%), the ped (50%), the emergency care practitioner (27%) and the GP (25%).

3.4. Predictive factors of time to first PR visit

The time to first PR visit of sJIA patients was the shortest ($p < 0.001$) and only 10% of these children met the criteria of delay to referral(12) so we decided to exclude them from this analysis; 101 patients were thus included. As shown in Table 2, higher age at diagnosis/onset, presence of enthesitis or pain, and appointment with an ortho during the referral pathway, were significantly associated with a longer time before the first PR visit. By contrast, undifferentiated JIA and oJIA patients were more likely to have shorter time before the first PR visit than ERA, as were patients with a history of limping or swelling, or with positive CRP, ESR or ANA. Although emergencies were involved for many patients, referral to the emergency department does not seem to be associated with the time before the first PR visit (HR 0.88 (95% CI: 0.57, 1.35)).

The median journey distance to the PR center was 26 km [IQR 11, 92] with a maximum of 247 km, and there was no association between this distance and time to first PR visit (HR 1 (95% CI: 0.99, 1.01)).

In multivariable analysis, ESR > 20 mm/h (HR 1.75 (95% CI: 1.11; 2.77)) and age at diagnosis (HR 0.92 (95% CI: 0.87; 0.98)) remained an independent factor associated with total symptom duration (Figure 3).

4. Discussion

As described in other studies, children with JIA have a long and intricate journey from the onset of the disease to the first assessment by a PRst. In the present study, the median time to first PR visit was fairly short (3.3 months) compared to the other studies: 3 months in France(13) and Germany(26), 3.8 months in Canada(27), 5.5 months in the UK(28), 10

months in the United Arab Emirates(29). This heterogeneity reflects differences between national health care organizations. In our cohort only 45% of the children met the British guidelines(12) and only 22% of the ERA patients. Here again, promptness of referral was slightly better than previously described: in a study in the UK only 26% patients were seen in a PR center before 10 weeks after symptom onset(30). This may owe something to the French national campaign for rare diseases which has also been set up to reduce diagnostic delay in rare diseases(16)(17). The time to first PR visit was the shortest for the sJIA as already reported in other studies in which the classical features observed in sJIA such as fever, deep asthenia, swelling and rash were associated with a prompt assessment by the HCP and referral to a PRst (13)(27)(28). This is important because among all JIA subtypes, sJIA is associated with the worse short-term prognosis owing to life-threatening events such as macrophage activation syndrome or pericarditis(31). In our study and as reported by Aoust *et al.*(13), GP and emergency care practitioners were the first HCPs met in 90% of the cases, and in our cohort, orthos were never involved in the referral pathway of sJIA patients. Conversely, the time to first PR visit was the longest for ERA. In our study, according to Shiff *et al.*(27) and Adib *et al.*(32), the presence of enthesitis led to a longer time to first PR visit, whereas a history of limping, and positivity of the CRP or ESR induced a shorter time to referral. However, this is the first study that finds a statistical significance between a longer time lag before the first PR visit and an older age at diagnosis, at disease onset or in the presence of pain; and a shorter time lag in the presence of swelling or positivity of ANA. Thus a subtle presentation of JIA with indolent symptoms such as enthesitis without swelling, transitional early morning stiffness, well-preserved function and normality of biological analysis, as frequently described in ERA, causes misreading of JIA symptoms both by family and HCPs(33).

Overall, the GP referred more patients to the emergency care practitioner than to the PRst and during their pathway, 45% of our non-systemic JIA cases were referred to the emergency room even though these patients did not meet the criteria of a real emergency. It can therefore be supposed that the care provider referred the child to the emergency department not for a real suspicion of emergency but as a starter for referral to the PRst. As advocated in the UK, we must develop and promote a proper “fast track” service for children with suspected musculoskeletal disease, with an assessment by the PRst within 4 weeks after reception of the referral letter(12).

As we described previously, the emergency care practitioner was a major actor in the referral pathway but in 79% of the cases he did not refer children to a PRst. The emergency care practitioner has a specific training in dealing with emergencies, and so faced with a child presenting joint pain or swelling, he may more readily suspect septic arthritis, trauma, malignancy or transient synovitis than JIA and most frequently refers the patient to the ortho. However his presence in the referral pathway does not increase the time to the first PR visit.

The presence of an ortho during the referral pathway was significantly associated with a longer time of referral to the PRst. In other studies(26)(30), authors state that this is possibly due to lack of knowledge about JIA among orthos. However, in our study, the ortho referred most frequently to a PRst, the number of children who had invasive procedures was lower than in the literature (7% *versus* 19%)(30) and the rate of antibiotics use was high (13%), but below that previously reported (28%)(13). Thus the time to get an appointment with an ortho could explain the overall increased time to the first PR visit.

The ped was seldom involved in the referral pathway (14%), but when involved, referred the child directly to the PRst in half the cases. This is less than reported in a German(26) and a British(30) study in which a ped was the referral in respectively 49% and 56% the cases. This

difference may reflect the French Health care organization: in France there is only 1 ped for 7000 children(34), against a European average of 1/1707(35). Previous studies(36)(37) reported that peds feel more comfortable than GPs in managing the diagnosis of JIA patients and refer patients to PRst earlier.

In Germany, the distance between the parent's dwelling place and the PR center affected the time to referral. Authors assumed that the farther the primary physicians are from the university hospital, the less access they have to the educational services for autoimmune disease(26). In the present study, the median distance to PR center was the shortest in the literature (26 km *versus* 38.2 km in Canada(27) and 38.8 km in Germany(26)) and had no effect on time to first PR assessment. The earlier French study(13) found no correlation with the distance of the parent's dwelling place. We would have liked to compare this distance with ours but no value was reported in the article. In this study the time to diagnosis was here again fairly short (median time 3 months), which could reflect the efficacy of the national campaign for rare diseases countrywide, in both reference and competence centers(17).

This study has some limitations. Our population came from a particular region of France, with possibly some specific features: a part of France place encompassing large rural areas(20) with a low demographic density(18). However our results do not differ from those already reported in a different French area(13) but to get a countrywide overview, a national study would clearly be useful. The date of symptom onset was declared by the parents, so a memory bias cannot be excluded. We did not collect the date of the first appointment with an HCP, but in a previous study in Canada(38), children with rheumatic disease saw an HCP in a median time of two weeks after the onset of symptoms, and the median time to first PR visit was 24 weeks: the time lag before referral was more likely due to the health care system's organization than to a long time before recourse to HCP. We did not collect the date of the referral letter from the referring physician to evaluate whether there was a time lag between

referral and assessment by the PRst. We did not include non-physician HCPs (physiotherapists, nurses, chiropractors and naturopaths) or advice from close acquaintances, who can probably play a major role in the referral pathway(33). Finally, we did not know the level of parental education or socio-economic status, which might influence time to referral, with a prompter response in families with a higher level of education (27)(39)(32).

This study conducted in two competence centers in PR confirmed that in France the time to the first PR visit is fairly short compared to other countries but remains too long, especially for ERA patients. We also highlight that despite not meeting real emergency criteria, too many non-systemic JIA patients are sent to the emergency room. PRst should accordingly offer the primary care providers and especially emergency care practitioner basic training to improve their awareness of JIA. PRst should also organize and promote a proper fast track referral service with a prompt assessment by the PRst after reception of the referral letter.

The authors declare that they have no competing interest.

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Figure 1. Diagnostic pathway depending on the first practitioner: number of patients seen by the first two specialists before the PRst

1a: Diagnostic pathway of the cohort after exclusion of sJIA patients (n=101)

Example: 68 children saw the GP as first HCP, among whom 21 saw the ECP as second HCP, and then only 5 saw a PRst as a third specialist.

1b: Diagnostic pathway of sJIA patients (n=10)

Example: 6 children saw the GP as first HCP, among whom 3 saw the ECP as second HCP, and then only 2 saw a PRst as a third specialist.

ECP: emergency care practitioner; GP: general practitioner; HCP: health care provider; ortho: orthopedic surgeon; ‘other’ includes adult rheumatologist, pediatric hematologist, rehabilitation physician and sport medicine physician; ped: general pediatrician; PRst: pediatric rheumatologist

Figure 2. Patient’s referral by subspecialty

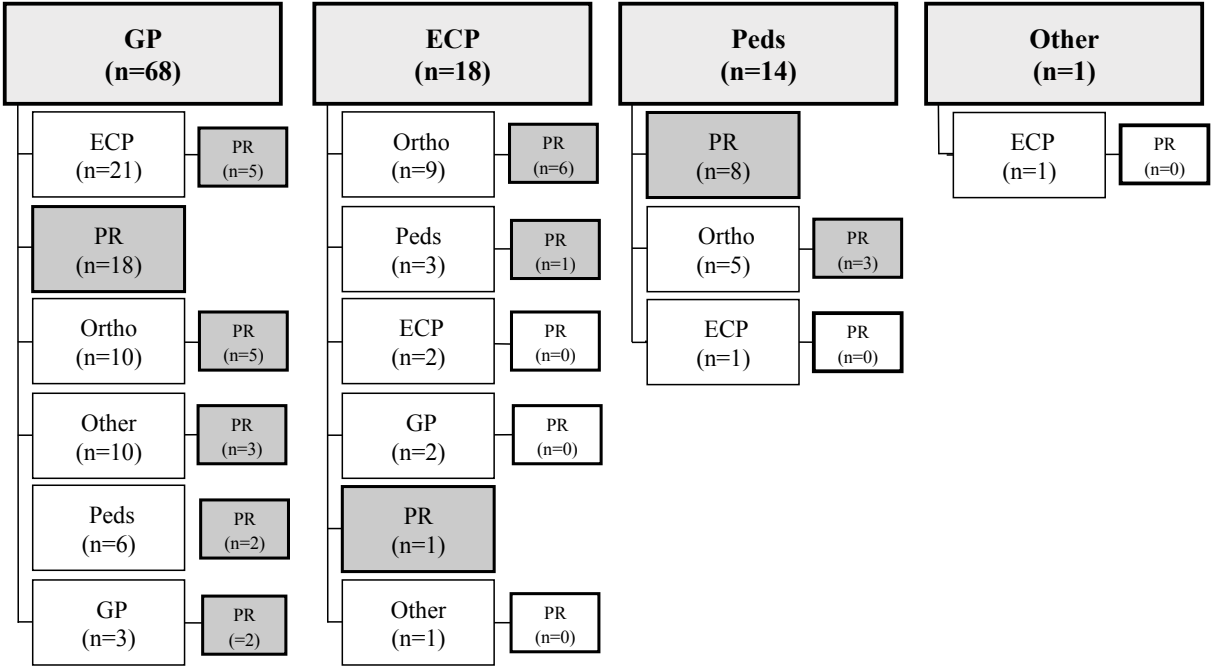
Example: Overall during the referral pathway, the GP was seen in 31 % the cases. He sent patients to a PRst in 25% the cases, to an ECP in 34% of cases ,to an ortho in 13% the cases and to a ped in 11 % the cases.

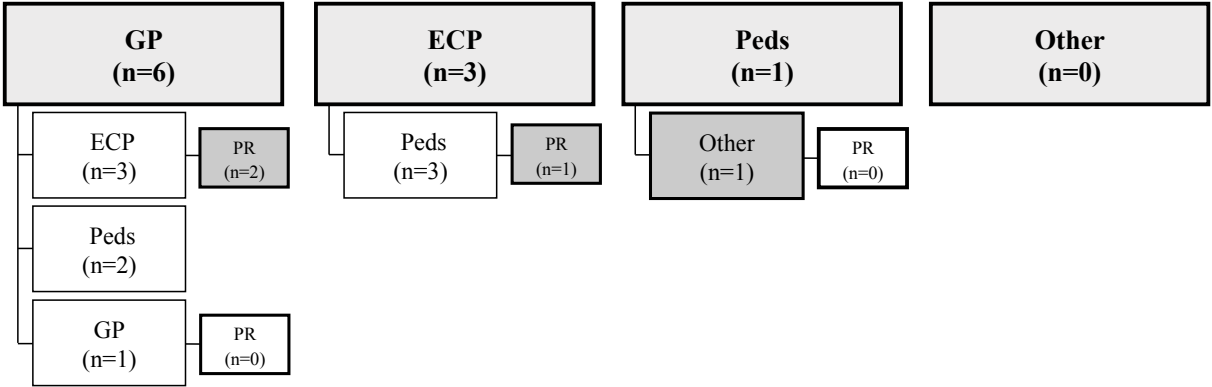
ECP: emergency care practitioner; GP: general practitioner; ortho: orthopedic surgeon; 'Other' includes adult rheumatologist, pediatric hematologist, rehabilitation physician and sport medicine physician; ped: general pediatrician; PRst: pediatric rheumatologist

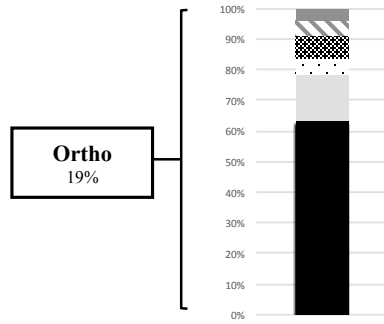
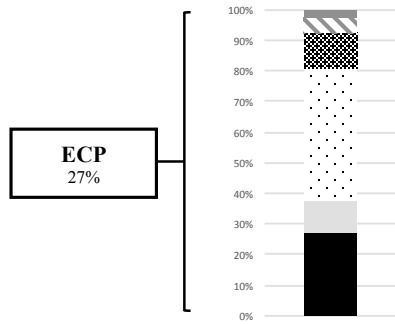
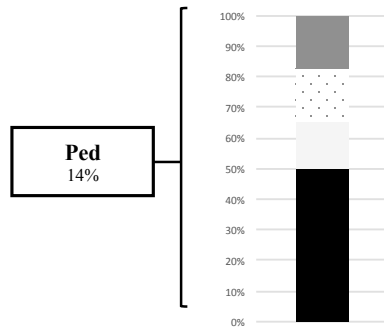
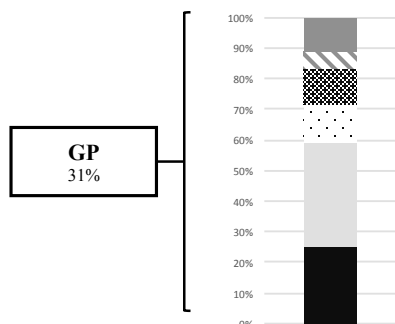
Figure 3. Multivariate analysis of predictive factors of time to first PR visit ($n = 101$ after exclusion of sJIA)

HR = 1 indicates an equal likelihood of a short time to first PR visit in the presence of the variable in question compared to its absence. HR > 1 indicates an increased likelihood of a short time to first PR visit. HR < 1 indicates a reduced likelihood of a short time to PR visit.

ESR: erythrocyte sedimentation rate in mm/hour, HR: hazard ratio, CI: confidence interval







- Other
- ▤ GP
- ▨ Peds
- ⋯ Ortho
- ECP
- PRst

	HR	95% CI	p-value
Age at diagnosis	0.921	[0.867 ; 0.978]	0.007
Enthesitis	0.593	[0.335 ; 1.051]	0.073
ESR>20	1.752	[1.106 ; 2.774]	0.017
Swelling	1.260	[0.815 ; 1.948]	0.299
Limping	0.930	[0.566 ; 1.527]	0.773

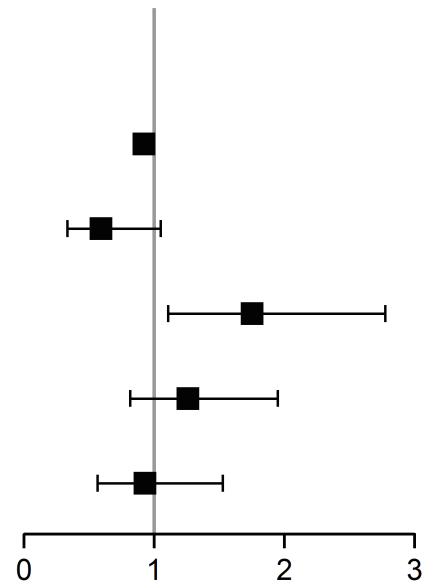


Table 1: Patient's characteristics at 1st PR visit

	Whole cohort (n=111)	oJIA (n=37)	pJIA (n=23)	sJIA (n=10)	ERA (n=23)	PsA (n=5)	UndJIA (n=13)
Age (years)	8.6 (4.6)	4.4 (3.0)	10.3 (4.0)	6.9 (5)	12.1 (2.2)	11.7 (3.3)	11.8 (2.6)
Age at onset (years)	7.9 (4.3)	3.9 (2.7)	9.6 (3.6)	6.8 (5.0)	10.6 (1.8)	10.9 (3.2)	11.1 (2.4)
Sex male	34 (31%)	4 (11%)	3 (13%)	5 (50%)	16 (70%)	2 (40%)	4 (31%)
Physician's global assessment of the disease activity (0 to 10)	4.0 [3.0, 7.0]	3.0 [3.0, 5.0]	7.0 [4.0, 8.0]	8.0 [7.0, 8.5]	4.0 [3.0, 6.0]	6.0 [4.5, 7.5]	4.0 [3.0, 5.0]
Musculoskeletal features							
<i>Number of active joints</i>	3.0 [1.0, 6.0]	1.0 [1.0, 2.0]	8.0 [6.0, 11.0]	4.0 [2.0, 5.0]	3.0 [1.0, 5.0]	2.0 [1.0, 6.0]	3.0 [2.0, 5.0]
<i>Enthesitis</i>	23 (21%)	0 (0%)	0 (0%)	0 (0%)	18 (78%)	3 (60%)	2 (15%)
<i>Psoriasis</i>	6 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (60%)	3 (23%)
<i>Uveitis</i>	2 (2%)	2 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Positive ANA	48 (50%)	29 (78%)	10 (46%)	1 (17%)	3 (19%)	2 (40%)	3 (27%)
Positive HLA-B27	21 (23%)	3 (8%)	1 (4%)	0 (0%)	11 (48%)	0 (0%)	6 (46%)
CRP (mg/L)	6.0 [0.0, 35.0]	6.2 [0.8, 17.0]	9.8 [0.4, 37.0]	148.0 [100.0, 205.0]	0.4 [0, 8,8]	0.0 [0.0, 0.0]	4.2 [0, 41.0]
ESR (mm/h)	24.0 [8.0, 36.0]	24.0 [11.0, 34.0]	29.0 [21.0, 46.0]	78.0 [50.0, 92.0]	10.0 [5.0, 25.0]	6.0 [5.0, 24.0]	16.5 [7.0, 33.0]
Time to first PR visit (months)	3.3 [1.4, 10.7]	2.8 [1.4, 7.2]	3.5 [1.9, 14.2]	0.5 [0.3, 0.9]	11.4 [4.0, 24.0]	10.5 [5.1, 10.7]	2.0 [1.3, 6.0]
Time to first PR visit < 10 weeks	50 (45%)	18 (49%)	9 (39%)	9 (90%)	5 (22%)	1 (20%)	8 (62%)
Time to first PR visit >1 year	25 (23%)	4 (11%)	6 (26%)	0 (0%)	11 (48%)	1 (20%)	3 (23%)

Number of HCPs met before the pediatric rheumatologist	3.0 [3.0-4.0]	4.0 [2.0-4.0]	3.0 [2.0-4.0]	4.0 [3.0-4.0]	4.0 [3.0-5.0]	3.0 [3.0-3.0]	3.0 [2.0-4.0]
Distance from patient's dwelling place to the PR center (km)	26.0 [11.0, 92.0]	51.0 [13.5, 118.0]	25.0 [9.0, 81.0]	35.0 [15.0, 71.0]	32.0 [10.0, 86.0]	26.0 [25.0, 44.8]	17.5 [13.0, 38.0]

Data are presented as frequencies (associated percentages), mean (standard deviation) or as median [interquartile range] JIA: juvenile idiopathic arthritis; oJIA: oligoarticular JIA; pJIA: polyarticular JIA; sJIA: systemic JIA; ERA: enthesitis related arthritis; PsA: Psoriatic arthritis; UndJIA: undifferentiated JIA; ANA: antinuclear autoantibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate, HCP: health care provider, PR: pediatric rheumatology

Table 2. Predictive factors of time to first PR visit (n = 101 after exclusion of sJIA)

	HR	95% CI	p-value
Sex male	0.673	0.434 ; 1.043	NS
Age at diagnosis	0.898	0.857 ; 0.942	<0.001
Age at onset	0.933	0.886 ; 0.982	<0.01
JIA subtype			
ERA	REF		
UndJIA	2.597	1.279 ; 5.271	<0.01
oJIA	2.402	1.386 ; 4.160	<0.01
pJIA	1.820	0.999; 3.315	NS
PsoJIA	1.878	0.695 ; 5.070	NS
Number of active joints	0.994	0.939 ; 1.051	NS
Physician's global assessment of the disease activity	1.069	0.967 ; 1.181	NS
Large joint involvement	0.516	0.235 ; 1.134	NS
Small joint involvement	1.222	0.824 ; 1.813	NS
Axial involvement	0.536	0.267 ; 1.073	NS
Enthesitis	0.403	0.245 ; 0.661	<0.001
Psoriasis	1.380	0.598 ; 3.183	NS
History of pain	0.594	0.366 ; 0.963	<0.05
History of limping	1.539	1.019 ; 2.323	<0.05
History of swelling	1.810	1.210 ; 2.707	<0.01
History of stiffness	1.155	0.629 ; 2.120	NS
Distance from the PR center	1.000	0.996 ; 1.003	NS
Distance			
0-24 km	REF		
25-49 km	1.554	0.906 ; 2.667	NS
≥50 km	1.015	0.645 ; 1.598	NS
CRP >10 mg/L	1.713	1.095 ; 2.677	<0.05
ESR >20 mm/h	1.959	1.262 ; 3.042	<0.01
AAN ≥160	1.961	1.273 ; 3.020	<0.01
ECP met during the referral pathway	0.878	0.571; 1.349	NS
Orthopedic surgeon met during the referral pathway	0.616	0.411 ; 0.922	<0.05

HR = 1 indicates an equal likelihood of a short time to first PR visit in the presence of the variable in question compared to its absence. HR > 1 indicates an increased likelihood of a short time to first PR visit. HR < 1 indicates a reduced likelihood of a short time to PR visit. JIA: juvenile idiopathic arthritis; oJIA: oligoarticular JIA; pJIA: polyarticular JIA; sJIA: systemic JIA; ERA: enthesitis-related arthritis; PsA: psoriatic arthritis; UndJIA: undifferentiated JIA; ANA: antinuclear autoantibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate, PR: pediatric rheumatology, CI: confidence interval