Arthritis in children: comparison of clinical and biological characteristics of septic arthritis and juvenile idiopathic arthritis

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ABSTRACT

Aim Childhood arthritis arises from several causes. The aim of this observational study is to compare the clinical and biological features and short-term outcome of different types of arthritis because they have different treatment and prognoses.

Methods Children <16 years of age hospitalised in a French tertiary care centre for a first episode of arthritis lasting for less than 6 weeks who underwent joint aspiration were retrospectively included. We performed non-parametrical tests to compare groups (septic arthritis (SA), juvenile idiopathic arthritis (JIA) and arthritis with no definitive diagnosis). The time before apyrexia or C reactive protein (CRP) <10 mg/L was analysed using the Kaplan-Meier method.

Results We studied 125 children with a sex ratio (M/F) of 1.1 and a median age of 2.2 years (range 0.3 to 14.6). SA was associated with a lower age at onset (1.5 years, IQR 1.2–3.0 vs 3.6 years, IQR 2.2–5.6), shorter duration of symptoms before diagnosis (2 days, IQR 1–4 vs 7 days, IQR 1–19) and higher synovial white blood cell count ($147 \text{ cells} \times 10^3/\text{mm}^3$, IQR 71–227, vs $51 \text{ cells} \times 10^3/\text{mm}^3$, IQR 12–113), than JIA. Apyrexia occurred later in children with JIA (40% after 2 days, 95% CI 17% to 75%) than children with SA (82%, 95% CI 68% to 92%), as did CRP <10 mg/L (18% at 7 days, 95% CI 6.3% to 29.6% vs 82.1%, 95% CI 76.1% to 89.7%, $p=0.01$).

Conclusions There were no sufficiently reliable predictors for differentiating between SA and JIA at onset. The outcomes were different; JIA should be considered in cases of poor disease evolution after antibiotic treatment and joint aspiration.

INTRODUCTION

Septic arthritis (SA) usually occurs in children as a complication of bacteraemia. Arthritis may also be caused by transient synovitis, juvenile idiopathic arthritis (JIA), reactive arthritis or other inflammatory diseases.

We previously reported that SA was the most frequent aetiology in children hospitalised for arthritis, followed by JIA; a further 40% was of unknown cause.¹ Early differential diagnosis between SA and JIA is essential, since children with SA require urgent treatment associating surgical joint drainage and intravenous antibiotics to avoid infectious complications.^{2–6} In opposition, children with JIA are usually referred to a specialist to

What is already known on this topic?

- ▶ In a previous study, septic arthritis (SA) was the most frequent cause of arthritis among hospitalised children, followed by arthritis of unknown cause and JIA.
- ▶ Children with SA require early diagnosis and hospital treatment so that septicaemia, growth problems and joint damage can be avoided.
- ▶ A delay before the appropriate treatment of juvenile idiopathic arthritis (JIA) may result in additional disease progression and increased joint erosion and disability.

What this study adds?

- ▶ There are no sufficiently reliable predictors for differentiating between SA and JIA at onset.
- ▶ Joint aspiration is needed for microbiological methods and to diagnose SA when a child has monoarthritis for less than 6 weeks.
- ▶ JIA should be considered in cases of poor disease evolution after antibiotic treatment and joint aspiration.

initiate specific treatment, including non-steroidal anti-inflammatory drugs and/or intra-articular glucocorticoid injections and/or biological therapeutics.^{7–10} Joint drainage and immobilisation may delay appropriate treatment of JIA if it is misdiagnosed, resulting in additional disease progression and increased joint erosion and disability.^{11–14}

The gold standard for the diagnosis of SA is isolation of the causative agent from joint fluid or blood, but this is not always possible.^{15 16} JIA corresponds to an arthritis of unknown aetiology that persists for at least 6 weeks.¹⁷ During the 1st weeks of disease, differentiation between JIA and SA can be challenging, especially for cases of culture-negative monoarthritis.¹⁸ Many diagnostic criteria have been developed to differentiate between transient synovitis and SA,^{19–23} but no such criteria have been determined to distinguish JIA from SA.

In this study, we compared the characteristics of children with arthritis who underwent joint

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aspiration who were divided into three groups: SA, JIA and arthritis with no definitive diagnosis.

METHODS

Study population

Children hospitalised in a French tertiary referral centre for paediatric orthopaedics and rheumatology and who underwent joint aspiration for a first episode of arthritis were retrospectively included. The French National Hospital Discharge Database (Le Programme de Médicalisation des Systèmes d'Information) was used to identify children with a diagnosis of

arthritis according to the International Classification of Diseases-Tenth Revision.²⁴ Diagnosis was defined as the association of joint pain and/or functional disability with clinical and/or radiological joint effusion. Children hospitalised between 1 January 2008 and 31 December 2009 were screened using specific inclusion criteria. We expected a very low number of inflammatory arthritis cases. Therefore, we also screened children who were followed for JIA in the same centre who were recorded in the CEMARA (Centres Maladies rares) database, a French information system which stores records of patients with rare diseases.²⁵

Figure 1 Flow chart for inclusion in children. CEMARA, Centres Maladies rares; JIA, juvenile idiopathic arthritis; SA, septic arthritis; PMSI, Le Programme de Médicalisation des Systèmes d'Information.

Children with the following criteria were included: (1) under the age of 16 years; (2) hospitalised for a first episode of arthritis; (3) onset of symptoms less than 6 weeks prior to hospitalisation; (4) underwent surgical joint aspiration at diagnosis.

We excluded children younger than 3 months, children with documented sepsis and secondary arthritis, associated osteomyelitis, associated fracture, underlying foreign body, prior anti-inflammatory treatment, or underlying conditions (sickle-cell anaemia, immunosuppression including renal failure and immunosuppressive therapy).

Management

All children with joint effusion associated with fever, high C reactive protein (CRP) levels or high white blood cell (WBC) counts, were suspected to have SA and underwent joint aspiration, performed by a paediatric orthopaedic surgeon under general anaesthesia. In Paris and the Ile-de-France region, the orthopaedic departments of the three paediatric tertiary hospitals are the major centres involved in management of children with bone and joint diseases. The hospital involved in this study is one of those three.

In France, all children with paediatric rheumatic diseases (PRDs) are referred for their medical care in clinical centres (regional competence centres and national reference centres) engaged in the research and clinical care of children with PRD (<http://www.cerhumip.fr>). The hospital involved in this study is one of the two national reference centres for JIA.

Microbiological methods

A blood sample was stored in an aerobic blood culture phial before the surgical procedure. Aspirated joint fluid was immediately stored in aerobic blood culture bottles following the intervention. The blood culture phials were incubated in a continually monitored instrument (BacT/Alert 3D; BioMérieux) and no blind subcultures were performed. The remainder of the joint fluid sample was sent to the laboratory for Gram staining, cell counting and immediate inoculation onto Columbia blood agar (incubated in anaerobic conditions), chocolate agar (incubated in CO₂-enriched air) and brain-heart broth. Aliquots (100–200 mm³) were stored at –80°C for DNA extraction. Blood culture bottles and the other media were incubated for 5 days and 10 days, respectively. Bacterial identification was based on their biochemical characteristics. *Kingella kingae* DNA was detected in joint fluid by a real-time PCR-based method for samples from children under 6 years old, as previously described.²⁶ In cases of negative blood or joint culture and negative *K. kingae* real-time PCR, universal rRNA 16S PCR was systematically performed.

Diagnostic classification

SA was defined as arthritis associated with bacteria detected in blood or synovial fluid by culture or molecular methods, as described above.

Cases were classified as JIA based on the diagnosis of the paediatric rheumatologist. This diagnosis presumably followed the International League of Associations for Rheumatology (ILAR) classification for JIA: arthritis of unknown aetiology that begins before the 16th birthday and persists for at least 6 weeks.¹⁷

Arthritis that did not fulfil the criteria for SA, JIA or other well established diagnoses (haemarthrosis, Kawasaki disease, villonodular synovitis and chronic recurrent multifocal osteitis) were classified as 'Arthritis with no definitive diagnosis'.

Table 1 Diagnoses of children included in the study

Group	Diagnoses	n	Per cent	Included in the comparison
Group 1: SA (n=63)	▶ <i>Kingella kingae</i>	50	79.4	Yes
	▶ <i>Staphylococcus aureus</i>	5	7.9	
	▶ Group A <i>Streptococcus</i>	4	6.3	
	▶ <i>Streptococcus pneumoniae</i>	2	3.2	
	▶ <i>Haemophilus</i> sp	1	1.6	
	▶ Serogroup B <i>Neisseria meningitidis</i>	1	1.6	
Group 2: No definitive diagnosis* (n=45)	▶ Children diagnosed as having a SA with negative culture of synovial fluid	37	82.2	Yes
	▶ Children undiagnosed and cured without any antibiotic treatment	6	13.3	
	▶ Children diagnosed as having a reactive arthritis without any positive serology	2	4.5	
Group 3: JIA (n=17)	▶ Oligoarticular JIA	6	35.3	Yes
	▶ Psoriatic JIA	2	11.8	
	▶ Systemic JIA	6	35.3	
	▶ Enthesitis-related arthritis	3	17.6	
Other diagnoses (n=6)	▶ Kawasaki disease	2	33.3	No
	▶ Haemarthrosis	2	33.3	
	▶ Villonodular synovitis	1	16.7	
	▶ Chronic recurrent multifocal osteitis	1	16.7	
Unclassifiable (n=2)	▶ <i>K. kingae</i> arthritis with subsequent JIA	1	50.0	No
	▶ <i>N. meningitidis</i> arthritis with subsequent reactive arthritis	1	50.0	

*Arthritis with no definitive diagnosis: Arthritis that did not fulfil the criteria for SA, JIA or other well established diagnoses.
JIA, juvenile idiopathic arthritis; SA, septic arthritis.

Study variables

We retrospectively recorded demographic and clinical characteristics on a standardised form. Depending on the number of joints initially involved, we distinguished monoarthritis, oligoarthritis (involving two to four joints) and polyarthritis (involving five or more joints).

Statistical analysis

Categorical variables were described as frequencies and compared between the three groups using the χ^2 test or Fisher's exact test. Continuous variables were described by the median and compared using non-parametrical tests (Kruskal-Wallis test). The LOWESS (locally weighted scatterplot smoothing) curve was used to picture the C reactive protein for the three groups, using a local polynomial of first degree and linear weight function. The time before apyrexia for children with initial fever, and time before obtaining a CRP <10 mg/L were estimated using the Kaplan-Meier method and compared between groups using the log-rank test. A p value <0.05 was considered to be significant (two-sided). Statistical analyses were performed using SAS statistical software (V9.3; SAS institute).

RESULTS

Study population

A total of 133 children was included in the study (figure 1). The median age at onset was 2.2 years (IQR 1.3–4.1).

We compared the following three groups: children with SA (n=63), JIA (n=17) and arthritis with no definitive diagnosis (n=45). Two children were unclassifiable because they had

Table 2 Initial clinical characteristics of children with SA, JIA and arthritis with no definitive diagnosis

Variable	According to group			p Value	Total n=125
	Group 1: SA (n=63)	Group 2: No definitive diagnosis* (n=45)	Group 3: JIA (n=17)		
Age at diagnosis (years)					
Median (IQR)	1.5 (1.2–3.0)	3.1 (1.7–5.5)	3.6 (2.2–5.6)	<0.001	2.2 (1.3–4.1)
Min–Max	0.8–13.7	0.3–14.6	1.5–12.2		0.3–14.6
Male, % (n)	50.8 (32)	55.6 (25)	47.1 (8)	0.83	52.0 (65)
Onset in autumn or winter, % (n)	49.2 (31)	33.3 (15)	56.3 (9)	0.15	44.4 (55)
Number of affected joints, % (n)					
Monarthritis	100 (63)	91.1 (41)	82.4 (14)	<0.01	94.4 (118)
Oligoarthritis (2–4 joints)	0 (0)	8.9 (4)	17.6 (3)		5.6 (7)
Polyarthritis (≥5 joints)	0	0	0		0
Affected joints, % (n)					
Knee	57.2 (36)	37.8 (17)	64.7 (11)	0.30	51.2 (64)
Hip	23.8 (15)	44.4 (20)	23.5 (4)		31.2 (39)
Ankle	9.5 (6)	6.7 (3)	5.9 (1)		8.0 (10)
Other joints	9.5 (6)	11.1 (5)	5.9 (1)		9.6 (12)
Family history of inflammatory disease, % (n)	3.0 (1)	8.3 (2)	26.7 (4)	0.03	9.7 (7)
Missing data	N=30	N=21	N=2		N=53
Duration of fever prior to admission					
Median (IQR)	2 (1–3)	1 (0–3)	1 (0–7)	0.44	1 (0–4)
Min–Max	0–8	0–11	0–24		0–24
Duration of local symptoms prior to admission					
Median (IQR)	2 (1–4)	2 (1–4)	7 (1–19)	0.04	2 (1–5)
Min–Max	1–14	1–15	1–30		1–30
Duration of symptoms prior to admission (local or fever),					
Median (IQR)	3 (1–4)	3 (1–5)	7 (2–19)	0.06	3 (1–5)
Min–Max	0–14	1–15	1–30		0–30
Temperature at admission					
Median (IQR)	37.6 (37.0–38.4)	37.4 (36.9–37.9)	37.3 (36.7–37.7)	0.17	37.4 (36.9–38.2)
Min–Max	36.0–40.0	36.0–39.4	36.4–39.3		36.0–40.0
Duration of hospital stay					
Median (IQR)	7 (5–8)	6 (5–7)	11 (6–12)	0.05	7 (5–8)
Min–Max	1–14†	1–32	2–32		1–32

Arthritis with no definitive diagnosis: Arthritis that did not fulfil the criteria for SA, JIA or other well established diagnoses.

†The child with SA and a hospital stay of 1 day was transferred to another hospital.

JIA, juvenile idiopathic arthritis; SA, septic arthritis.

both: a history of SA and inflammatory disease (table 1). Details of the different subgroups and the pathogens found in SA are reported in the table 1.

Demographic and clinical characteristics

Children with SA were significantly younger than those of the JIA or ‘no definitive diagnosis’ groups ($p<0.001$) and presented exclusively with monarthritis (table 2). JIA was associated with a higher frequency of family history of inflammatory disease ($p=0.03$) and a longer duration of local symptoms prior to admission ($p=0.04$), than the other two groups.

Biological characteristics

Fibrinogen was lower in the ‘no definitive diagnosis’ group than in the other two groups ($p=0.03$; table 3). Platelet counts were higher in JIA than in the other two groups ($p=0.01$). CRP, WBC and neutrophil counts were not significantly different between the groups. Median synovial WBC counts were higher for SA than those for JIA and arthritis without a definitive diagnosis ($p<0.001$, figure 2). Synovial WBC counts were above

50 000 cells/mm³ in 86.2% of SA, 31.6% of arthritis with no definitive diagnosis and 50.0% of JIA ($p<0.001$).

Management and short-term outcomes

All children with SA were treated by intravenous antibiotic therapy, compared with the other groups (87%); $p<0.01$. Treatment with anti-inflammatory drugs was initiated for all children with JIA, during the first hospitalisation (59%) or after (41%). The median time between joint aspiration and the initiation of this treatment was 11 days (IQR 5–35).

Children with JIA had the longest hospital stay (table 2). Kaplan-Meier estimates of the time between joint drainage and apyrexia was higher for the JIA group than the other two groups ($p<0.001$); Kaplan-Meier estimates of the probability of apyrexia at 2 days were 40% for JIA (95% CI 17% to 75%), 82% for SA (95% CI 68% to 92%) and 88% for arthritis with no definitive diagnosis (95% CI 72% to 97%).

Figure 3 presents the evolution of CRP levels. The Kaplan-Meier estimate of median time from joint aspiration to CRP <10 mg/L was 7 days (95% CI 6 to 7). Kaplan-Meier estimates of obtaining CRP <10 mg/L were 7% (95% CI 5% to

Table 3 Biological characteristics of children with SA, JIA and arthritis with no definitive diagnosis at onset

Variable	According to group			p Value	Total (n=125)
	Group 1: SA (n=63)	Group 2: No definitive diagnosis* (n=45)	Group 3: JIA (n=17)		
CRP (mg/L)					
Median (min–max)	39 (5–246)	33 (5–205)	35 (5–134)	0.14	36 (5–246)
IQR	21–76	12–50	22–70		20–69
Missing value	N=0	N=1	N=1		N=1
Fibrinogen (g/L)					
Median (min–max)	5.73 (3.52–8.44)	5.04 (2.92–10.3)	5.61 (3.10–11.49)	0.03	5.52 (2.92–11.49)
IQR	5.04–6.81	4.28–6.00	4.90–6.10		4.74–6.48
Missing value	N=7	N=3	N=2		N=12
WBC counts ($\times 10^9/L$)					
Median (min–max)	12.1 (7.8–30.7)	11.9 (6.1–22.6)	11.7 (7.5–21.0)	0.53	11.9 (6.1–30.7)
IQR	9.8–15.5	8.8–14.7	10.0–15.0		9.7–15.0
Missing value	N=3	N=2	N=0		
Neutrophil counts ($\times 10^9/L$)					
Median (min–max)	5.9 (2.0–22.7)	6.5 (1.7–16.6)	7.1 (4.1–15.3)	0.53	6.5 (1.7–22.7)
IQR	4.0–9.5	4.0–8.8	5.4–10.2		4.3–9.5
Missing value	N=28	N=19	N=4		N=51
Haemoglobin (g/dL)					
Median (min–max)	11.5 (9.9–14.4)	11.6 (9.4–13.5)	11.0 (9.5–13.2)	0.19	11.6 (9.4–14.4)
IQR	10.9–12.1	10.8–12.3	10.6–11.7		10.8–12.2
Missing value	N=9	N=3	N=0		N=12
Platelets ($\times 10^9/L$)					
Median (min–max)	346 (163–702)	356 (154–560)	460 (288–591)	0.01	360 (154–702)
IQR	284–421	262–409	364–522		284–457
Missing value	N=7	N=3	N=2		N=12
Synovial WBC counts ($\times 10^3$ cells/mm ³)					
Median (min–max)	147 (10–2790)	10 (0–1000)	51 (6–1110)	<0.001	71 (0–2790)
IQR	71–227	1–59	12–113		11–209
Missing value	N=34	N=23	N=9		N=66
Synovial WBC counts $>50 \times 10^3$ cells/mm ³ , % (n)	86.2 (25)	31.6 (6)	50.0 (4)	<0.001	59.3 (35)

Arthritis with no definitive diagnosis: Arthritis that did not fulfil the criteria for SA, JIA or other well established diagnoses.
CRP, C reactive protein; JIA, juvenile idiopathic arthritis; SA, septic arthritis; WBC, white blood cell.

10%) after 3 days and 66% (95% CI 57% to 69%) after 7 days. It was lowest in the JIA group ($p < 0.01$): after 7 days, it was estimated to be 18.0% for JIA (95% CI 6% to 30%), 62% for arthritis with no definitive diagnosis (95% CI 52% to 73%) and 82% for SA (95% CI 76% to 90%).

During the hospitalisation, 58.8% of children with JIA ($n=10$) presented with extra-articular symptoms (erythematous rash or macrophage activation syndrome).

DISCUSSION

During childhood, arthritis may be caused by transient synovitis, SA, JIA and other inflammatory diseases. In a previous study of children hospitalised for a first episode of arthritis, we found that SA was the most frequent cause (43%) followed by JIA (8%). To our knowledge, no previous study has compared the characteristics of SA, JIA and arthritis of unknown cause in children. In this study, we compared the clinical and biological features and short-term outcome in children with first arthritis. We selected children who underwent joint aspiration to provide a gold standard for SA diagnosis.

The age at onset was significantly lower for children with SA than for those with JIA. Indeed, SA is more frequent in children younger than 3 years^{1 27 28} while 95% of *K. kingae* arthritis occurs before the age of 2 years.^{29–31} In contrast, the median age for the onset of JIA in France is 4.7 years for girls and

7.2 years for boys.³² The duration of local symptoms was longer in children with JIA, who presented with less severe symptoms and whose parents waited longer before consultation. Fever was not significantly different between the two conditions; thus fever is not able to discriminate between SA and JIA as already shown in a meta-analysis in adults.³³ Polyarthritis is commonly due to JIA.^{1 27 28 34} No polyarthritis cases were included in this study, probably because children who underwent joint aspiration were selected.

CRP has been described as a sensitive predictor of SA^{35–37} but our results suggest that it might not be sufficiently specific to distinguish between JIA and SA. High levels of synovial fluid WBC count have also been described as a predictor of SA.³⁴ Our results showed a significant difference between the synovial WBC counts and platelet enumeration of JIA and SA, but with a large overlap zone. Four of the eight children with JIA had synovial WBC counts higher than $50\,000/\text{mm}^3$. This is in agreement with a previous study that described three cases of JIA with synovial WBC counts higher than $80\,000/\text{mm}^3$.³⁸

Kaplan-Meier estimates of the median time between drainage and apyrexia or for CRP to return to normal values were shorter for SA than for JIA. The persistence of fever or abnormal inflammation markers could therefore favour the diagnosis of JIA along with extra-articular symptoms.

Figure 2 Distribution of synovial white blood cell (WBC) counts in children with septic arthritis, juvenile idiopathic arthritis (JIA) and arthritis with no definitive diagnosis (arthritis with no established association with infection that did not fulfil the classification criteria for JIA or other well established diagnoses).

Figure 3 LOWESS (locally weighted scatterplot smoothing) curves of C reactive protein (CRP) in children with septic arthritis, juvenile idiopathic arthritis (JIA) and arthritis with no definitive diagnosis (arthritis with no established association with infection that did not fulfil the classification criteria for JIA or other well established diagnoses).

We describe an important group designated as arthritis with no definitive diagnosis, which represents 40.4% of the first episodes of arthritis requiring hospitalisation between 2008 and 2009 in our centre.¹ These patients present with some characteristics. The median age at diagnosis (3.1 years) for this group was greater than that for children with SA but closer than that for JIA. The fibrinogen and synovial WBC counts were lower than those for children with SA. A previous study reported less severe symptoms of longer duration for culture-negative compared with culture-positive arthritis.³⁹ This suggests that culture-negative arthritis described in the literature may not be due to SA, or may be associated with pathogens that are less aggressive than classic ones. With the development of current molecular techniques, the proportion of culture-negative arthritis has decreased.^{26 29 40} There are still many cases of culture-negative arthritis. The ability to distinguish SA from other aetiologies will require further work. In our study, the

median follow-up time was relatively short (4.5 months). A longer follow-up should improve the accuracy of the diagnosis.

Our study has several limitations. The low number of children in the JIA group and a selection bias prevented us from distinguishing between children with SA and those with JIA. Indeed, the inclusion of only children who underwent joint aspiration may have selected patients with JIA with more serious symptoms and, therefore, those more similar to patients with SA. Moreover, children with JIA were included over a larger period than children with SA, and evolution of medical practices may have influenced the short-term evolution. Furthermore, this was a retrospective study and there was a large amount of missing data; for example, a family history of inflammatory disease was more frequently reported for children with JIA, but this was probably due to a reporting bias. Likewise, we looked for information on prior use of antibiotics but this was missing in more than 50% of the medical records. Otherwise, we were not able to describe precisely the short-term progression of the disease, and we did not have any information on long-term progression. Finally, the monocentre type of the study and the selection of children hospitalised in a tertiary children hospital decrease the generalisability of our results.

In conclusion, we did not find any sufficiently reliable clinical or biological predictors for differentiating between SA and JIA at onset. Joint aspiration remains necessary when a child has arthritis for less than 6 weeks, especially a monoarthritis. The short-term outcomes were different depending on the type of arthritis; JIA must be considered if there is a poor evolution after antibiotic treatment and joint aspiration. Clearly, the diagnosis of arthritis in children needs to be improved. A prospective study would be useful to avoid missing data and a reporting bias, and to more systematically define the diagnosis.

Contributors Study concept and design: CAu, AF and ML; acquisition of data: CAu, AB, MD and SB; analysis and interpretation of data: CAu, RB, BI, CJ-D, AF, SB, CAI and ML; drafting of the manuscript: CAu, RB and ML; revision of the manuscript: CAu, RB, BI, AB, MD, CJ-D, AF, SB, CAI and ML; statistical analysis: CAu and CAI.

Competing interests None declared.

Ethics approval The study was approved by the Institutional Review Board of Paris-North Hospitals, Paris 7 University, AP-HP (IRB no. 2013-84, 17 September 2013) and the French national data protection agency (Commission nationale de l'informatique et des libertés).

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