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The Role of Age in Delays to Rheumatological Care in Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To investigate the relationship between age and symptom duration at initial presentation to pediatric rheumatology for juvenile idiopathic arthritis (JIA).

Methods. In children and young people (CYP) enrolled in the Childhood Arthritis Prospective Study prior to March 2018, an association between age at presentation (< 5, 5–11, and > 11 yrs) and symptom duration was tested by multivariable linear regression.

Results. In 1577 CYP, 5- to 11-year-olds took 3.2 months longer and > 11-year-olds 6.9 months longer to reach pediatric rheumatology than < 5-year-olds.

Conclusion. Adolescents take longer to reach pediatric rheumatology, potentially affecting their longer-term outcomes given the window of opportunity for JIA treatment.

Key Indexing Terms: adolescent rheumatology, age, juvenile idiopathic arthritis, pediatric rheumatology, symptom duration

The "window of opportunity" for treating children and young people (CYP) with juvenile idiopathic arthritis (JIA) suggests that earlier treatment results in better outcomes,[1] including greater treatment response to methotrexate[2] and etanercept. In addition, earlier control of disease limits the length of time CYP spend in pain or with functional limitations associated with active disease.[3]

To gain early treatment for JIA, both the early seeking of primary healthcare and prompt onward referral to rheumatology services are vital. In the UK, Standards of Care published by the British Society for Paediatric and Adolescent Rheumatology suggest a maximum time period of 10 weeks from symptom onset and 4 weeks from referral to be seen at pediatric rheumatology.[4] However, a previous UK study in 1066 CYP with JIA diagnosed between 2001 and 2011 revealed that these standards are not being met and did not improve over time, with only 20% of CYP with JIA seen within pediatric rheumatology services within 10 weeks of symptom onset and 50–60% within 4 weeks of referral.[5]

Barriers to timely referral to pediatric rheumatology are multifactorial.[6] The heterogeneous signs and symptoms of JIA, coupled with limited training and resources relating to pediatric rheumatology in community settings, may hinder referral rates.[6,7] While severe signs of systemic disease may facilitate prompt referrals,[6,7] multiple signs and symptoms of JIA may not be initially evident or may be attributed to normal development. In younger children, the abnormal gait of an unsteady child may mask true gait disturbances or joint limitations, which may take many years to fully manifest.[8] In contrast, in adolescent medicine, generic symptoms associated with JIA, such as fatigue, are documented in up to 40% of healthy teenagers.[9] The primary feature of JIA—joint pain—may be indistinguishable from the "growing pains" experienced in adolescence during periods of rapid bone growth.[10] These factors may influence care seeking by both parents and adolescents themselves.

The aim of the current study was to investigate the association between age at JIA onset and the length of time from symptom onset to first appointment at pediatric rheumatology.

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METHODS

Study population. CYP with a physician diagnosis of JIA were included in the study if recruited to the Childhood Arthritis Prospective Study (CAPS), a UK multicenter inception cohort of childhood-onset arthritides, between January 2001 and March 2018. CYP were excluded if no date of birth had been recorded during the study. Ethical approval for CAPS was gained from the Northwest Multicentre Ethics Committee (REC/02/8/104, IRAS 184042). Written informed consent was gained from guardians of the CYP included, with assent provided from the CYP themselves where appropriate.

Data collection. Data for this study were collected at initial presentation to pediatric rheumatology, and demographic, disease-related, and medication data, and referral source were extracted from medical case notes by study nurses. Disease-related information included the date of symptom onset, as recorded by the family. Where > 11 years old, CYP were asked to complete the Childhood Health Assessment Questionnaire (CHAQ),[11] which incorporates two 100-mm visual analog scores for pain and patient/parent global evaluation of well-being (PGE). Where CYP were < 11 years at initial presentation, guardians were asked to complete the CHAQ as proxies.

Age categorization. Age at initial presentation was calculated using the participant's date of birth and the date of initial presentation to pediatric rheumatology. This variable was categorized according to UK preschool, primary, and senior school education age groups: < 5 years, 5–11 years, and > 11 years, respectively.

Outcomes. The primary outcome was symptom duration between initial symptom onset and initial presentation to pediatric rheumatology.

Statistical analysis. Outcomes were compared descriptively between CYP within the different age categories, with statistical significance assessed by Kruskall-Wallis and chi-square tests. Subsequently, a multivariable linear regression model explored any association between age category and symptom duration at initial presentation. The multivariable model adjusted for International League Against Rheumatism (ILAR) category, ethnicity, gender, pain, and the JIA core outcome variables (active joint count, limited joint count, physician global assessment of disease activity, PGE, functional ability, erythrocyte sedimentation rate [ESR]),[12] to assess whether age was an independent predictor of symptom duration to pediatric rheumatology, regardless of disease severity. Secondary analyses mitigated for "previtial time bias," whereby older age groups have had opportunity for longer symptom durations than the younger children have been alive for. An initial secondary analysis log-transformed symptom duration to minimize the effects of large outliers, with a further secondary analysis limiting symptom duration to a maximum of 3 years, wherein there was a minimum participant age of 3 years to be included in the model.

RESULTS

Patient cohort. A total of 1746 CYP had been recruited to CAPS prior to March 2018. Of these, 153 did not have JIA and a further 16 had no date of birth recorded, leaving 1577 for the study. The majority of CYP were female (65%) and had oligoarthritis (52%).

Age distribution. There were roughly equal numbers of CYP in each age category, with 536 CYP < 5 years (34%), 543 CYP 5–11 years (34%), and 498 CYP > 11 years (32%) at initial presentation to pediatric rheumatology (Table 1). A greater proportion of children aged < 5 years had been referred from accident and emergency (A&E) departments (< 5, 5–11, > 11 yrs: 8%, 7%, 5%, respectively) and pediatricians (49%, 41%, 37%, respectively), with a greater proportion of CYP aged 5–11 years and > 11 years referred from general practice clinics (11%, 22%, 21%, respectively; Table 1).

Association between age and symptom duration. Across the cohort, 26% of CYP had their first pediatric rheumatology appointment within 10 weeks of symptom onset. This percentage was higher for the CYP aged < 5 years (35%) than for CYP aged 5–11 years (25%) or > 11 years (17%).

In univariable analysis, compared with CYP who were aged < 5 years at initial presentation to pediatric rheumatology, those aged between 5–11 years took an average of 4.6 (95% CI 2.9–6.3) months longer and those aged > 11 years took 7.1 months (95% CI 5.3–8.8) longer to reach pediatric rheumatology (Table 2).

After adjusting for demographic and disease characteristics, age at presentation was still significantly associated with longer symptom duration. Compared with CYP aged < 5 years, those aged between 5–11 years took an average of 3.2 (95% CI 0.5–5.9) months longer and those > 11 years took 6.9 (95% CI 4.0–9.8) months longer to reach pediatric rheumatology (Figure 1, Table 2). In secondary analyses, both restricting age and symptom duration as well as log-transforming symptom duration produced similar results to the primary analysis: increased symptom duration for older age categories (Supplementary Tables 1–2, available with the online version of this article).

One-fifth of overall symptom duration at initial pediatric rheumatology appointment was accounted for from the time of final referral. This period contributed to longer symptom durations for older age groups (median < 5 yrs: 0.7 months; 5–11 yrs: 1.0 month; > 11 yrs: 1.2 months; $P < 0.001$; Table 1).

DISCUSSION

The importance of early diagnosis and treatment of JIA is well established, particularly in light of the window of opportunity for early effective treatment.[1] Our current study reports that, even after adjusting for disease severity and ILAR category, school-aged CYP with JIA take longer to reach pediatric rheumatology clinics after symptom onset than preschool children, with the longest symptom duration in CYP of senior school age. In addition, the current study confirms existing associations between age at diagnosis and clinical factors such as ILAR category, ESR, and patient-reported pain and PGE.

The window of opportunity in JIA represents a period of time in which treatment may facilitate optimal outcomes.[13] Shorter time between symptom onset to commencing treatment has been associated with better outcomes.[2,14,15,16,17] In the present study, after adjusting for disease severity, primary school–aged children took approximately 3 extra months and senior school–aged adolescents approximately 7 extra months to reach pediatric rheumatology, compared with preschool-aged children. In JIA, where peaks of incidence are between ages 0–4 years and 9–14 years,[18] the longer symptom duration in adolescence represents a substantial unmet need for timely healthcare seeking and referral to pediatric rheumatology.

Before accounting for age, several ILAR categories were associated with symptom duration at pediatric rheumatology. Compared with oligoarthritis, CYP with systemic JIA had shorter symptom durations, as expected, since these CYP are systematically unwell. Those with enthesitis-related JIA had longer symptom durations before reaching pediatric rheumatology. As

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Table 1. Characteristics of CYP of different ages at initial presentation to pediatric rheumatology

	% Available	Median (IQR) or n (%) Within Age Groups			Univariable *P**
		< 5 Yrs	5–11 Yrs	> 11 Yrs	
n		536 (34)	543 (34)	498 (32)	
Symptom duration at initial presentation, months	87	**3.4 (1.8–6.3)**	**4.9 (2.3–9.0)**	**6.6 (3.3–13.5)**	**< 0.001**
Months from final referral to pediatric rheumatology appointment	90	**0.7 (0.3–1.5)**	**1.0 (0.4–1.9)**	**1.2 (0.6–2.1)**	**< 0.001**
Demographics					
Female gender	100	**409 (76)**	**319 (59)**	**292 (59)**	**< 0.001**
White ethnicity	96	419 (82)	418 (80)	375 (77)	0.28
ILAR category					
Systemic	94	**35 (7)**	**38 (7)**	**27 (6)**	**< 0.001**
Oligoarthritis		**336 (63)**	**295 (54)**	**195 (39)**	
RF-negative polyarthritis		**96 (19)**	**108 (21)**	**66 (14)**	
RF-positive polyarthritis		**7 (1)**	**11 (2)**	**33 (7)**	
Enthesitis-related		**0 (0)**	**15 (3)**	**59 (13)**	
Psoriatic arthritis		**15 (3)**	**21 (4)**	**48 (10)**	
Undifferentiated		**47 (9)**	**55 (11)**	**70 (15)**	
Clinical characteristics					
Active joint count	87	**2 (1–4)**	**2 (1–5)**	**2 (1–6)**	**0.04**
Limited joint count	87	1 (1–3)	1 (1–4)	2 (1–5)	0.15
PGA, cm	64	1.6 (0.8–5.0)	2.6 (1.2–4.7)	3.0 (1.5–5.0)	0.08
PGE, cm	65	**2.2 (0.5–5.0)**	**2.0 (0.4–5.0)**	**3.2 (1.0–5.1)**	**0.006**
CHAQ score	60	0.8 (0.3–1.5)	0.7 (0.1–1.4)	0.6 (0.1–1.8)	0.05
ESR, mm/h	69	**25 (10–51)**	**21 (7–49)**	**15 (5–45)**	**0.009**
Pain, cm	65	**2.5 (0.5–5.5)**	**2.5 (0.6–5.7)**	**3.9 (1.4–6.2)**	**0.003**
Referral source					
A&E	71	**32 (8)**	**26 (7)**	**17 (5)**	**< 0.001**
General practice		**41 (11)**	**86 (22)**	**74 (21)**	
Orthopedic surgery		**97 (25)**	**91 (23)**	**92 (27)**	
Pediatrician		**188 (49)**	**160 (41)**	**129 (37)**	
Physiotherapist		**2 (1)**	**2 (1)**	**6 (2)**	
Other		**21 (6)**	**29 (7)**	**29 (8)**	

* Chi-square or Kruskall-Wallis test. Values in bold are statistically significant. A&E: accident and emergency department; CHAQ: Childhood Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; ILAR: International League Against Rheumatism; PGA: physician global assessment of disease activity; PGE: patient/parent global assessment of well-being; RF: rheumatoid factor.

corroborated in the current study, ILAR categories are known to associate with different age groups, with younger children more commonly presenting with oligoarthritis, and adolescents with enthesitis-related JIA.[19] After adjusting for age, only 1 ILAR category had significantly different symptom durations compared with oligoarthritis: undifferentiated JIA. That associations between other ILAR categories and symptom duration to pediatric rheumatology attenuate when age is accounted for suggest that age plays a primary role, beyond disease manifestations, on presentation to primary care or onward referral to pediatric rheumatology care.

It is likely that CYP with similar disease manifestations across ages initially present to medical care, and are referred through different pathways, with different levels of urgency. In the current study, a greater proportion of adolescents were referred from general practice and younger children from A&E. This may reflect greater presentation of adolescents at general practice, where younger children, such as those with systemic JIA (who have systemic disease) or oligoarthritis (whose differential diagnoses may include septic arthritis), may enter clinical care through A&E,[5] facilitating earlier, and potentially faster, referrals. A combination of holding within these services and additional referrals to services such as pediatrics or orthopedics further delays specialist pediatric rheumatology care.

As adolescents take greater independence regarding their own health and their families have less direct care of their bodies, clinical care may be sought later than their younger peers due to a number of factors. First, the generalized signs and symptoms of JIA may be interpreted as growing pains,[10] or the fatigue common in adolescence.[20] In addition, adolescents are known to engage less with the health service than their younger or older peers.[21] Although several educational campaigns, often through schools or social media, have targeted adolescents and young adults on topics surrounding common mental health problems in addition to physical ailments,[22,23] awareness of rare diseases such as JIA is limited in the public sphere.[24] Compounding these issues, adolescents report dissatisfaction with primary care once received, particularly in terms of short consultation times, lack of continuity of care, and a perceived lack of interest or skill in emotional healthcare.[25] Specific training in adolescent medicine

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Table 2. Univariable and multivariable associations with symptom duration (months) to pediatric rheumatology.

	Univariable	Multivariable	
	Coefficient (95% CI)	Coefficient (95% CI)	*P*
Age at pediatric rheumatology, yrs			
< 5	Ref.	Ref.	
5–11	**4.6 (2.9–6.3)**	**3.2 (0.5–5.9)**	**0.02**
> 11	**7.1 (5.3–8.8)**	**6.9 (4.0–9.8)**	**< 0.001**
Demographics			
Female gender	−0.9 (−2.4 to 0.6)	0.8 (−1.6 to 3.3)	0.53
White ethnicity	0.8 (−1.6 to 3.1)	−0.3 (−3.9 to 3.4)	0.88
ILAR category			
Systemic	**−5.1 (−8.0 to −2.2)**	−0.6 (−5.7 to 4.4)	0.80
Oligoarthritis	Ref.	Ref.	
RF-negative polyarthritis	1.6 (−0.3 to 3.4)	2.2 (−0.9 to 5.2)	0.16
RF-positive polyarthritis	3.1 (−0.8 to 7.0)	4.5 (−1.8 to 10.7)	0.16
Enthesitis-related	**3.9 (0.7–7.1)**	−1.5 (−7.3 to 4.3)	0.61
Psoriatic arthritis	2.3 (−0.6 to 5.2)	2.8 (−1.5 to 7.2)	0.20
Undifferentiated	0.2 (−3.0 to 3.4)	**6.1 (0.6–11.5)**	**0.03**
Clinical characteristics			
Active joint count	**0.1 (0.0–0.2)**	0.0 (−0.3 to 0.2)	0.66
Limited joint count	**0.2 (0.1–0.3)**	0.1 (−0.1 to 0.4)	0.28
PGA, cm	−0.2 (−0.5 to 0.2)	−0.2 (−0.7 to 0.3)	0.43
PGE, cm	0.2 (−0.1 to 0.5)	0.0 (−0.6 to 0.6)	0.99
CHAQ score	0.6 (−0.5 to 1.6)	1.7 (−0.3 to 3.7)	0.09
ESR, mm/h	**−0.1 (−0.1 to −0.1)**	**−0.1 (−0.1 to 0.0)**	**< 0.001**
Pain, cm	0.2 (−0.1 to 0.4)	0.1 (−0.5 to 0.6)	0.85

Values in bold are statistically significant. CHAQ: Childhood Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; ILAR: International League Against Rheumatism; PGA: physician global assessment of disease activity; PGE: patient/parent global assessment of well-being; RF: rheumatoid factor.

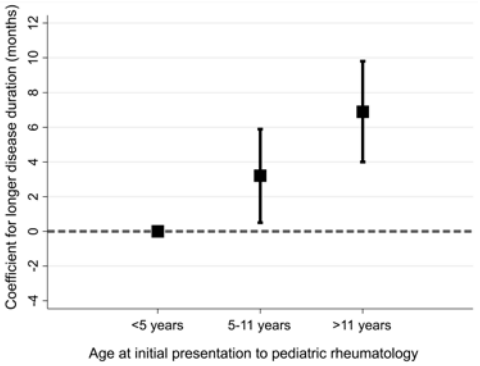

Figure 1. Coefficients for symptom duration prior to initial presentation according to age category. Associations are independent of gender, ethnicity, ILAR category, the JIA core outcome variables and pain. ILAR: International League Against Rheumatism; JIA: juvenile idiopathic arthritis.

is therefore needed across all settings, and particularly in primary care, A&E, and orthopedics; additional outreach activity is also needed in educational settings, both for teachers and adolescents themselves. Further, pediatric rheumatology training is needed across settings, since little time is devoted specifically to pediatric rheumatology during general practitioner training.

This cohort allowed the assessment of the association between age and symptom duration across a well-powered, diverse population of JIA, with every ILAR category represented. The vast data collection by CAPS also allowed for the assessment of associations independent of multiple demographic and clinical factors.

The current study had access only to final referral source to pediatric rheumatology. This study could not assess the sequence or timing of referrals between primary care and final referral source to pediatric rheumatology. Therefore, it was unclear whether the majority of symptom duration to pediatric rheumatology was accounted for before seeking any healthcare, or whether it was accounted for after initial referral from primary care. While the majority of CYP with JIA saw a pediatric rheumatology specialist within a year of symptom onset, data had a highly right-skewed distribution, with many years between symptom onset and presentation at pediatric rheumatology in some cases. Our present study modeled several secondary analyses to demonstrate that despite these skewed data and inability for particularly young children to have these long disease durations (prevital time bias), adolescents consistently had longer symptom duration than younger children at initial presentation to pediatric rheumatology. However, longer-term analyses are needed to determine whether clinical outcome is affected by these longer symptom durations.

A minority of CYP with JIA are seen at pediatric rheumatology within 10 weeks following symptom onset. Even after adjusting for disease severity, older CYP with JIA take longer to see a pediatric rheumatologist after symptom onset than their

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younger peers. Compared with preschool-aged children, primary school–aged children take 3 months longer, and senior school–aged adolescents 7 months longer. This potentially affects the effective treatment of JIA in older CYP within the window of opportunity. Further work is needed to build engagement with adolescents in seeking care and in recognizing pediatric rheumatological conditions in primary practice.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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