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 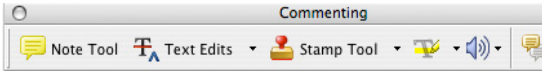

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 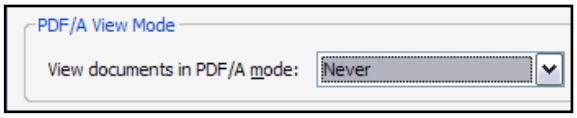

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 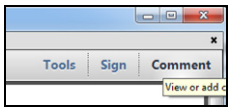

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 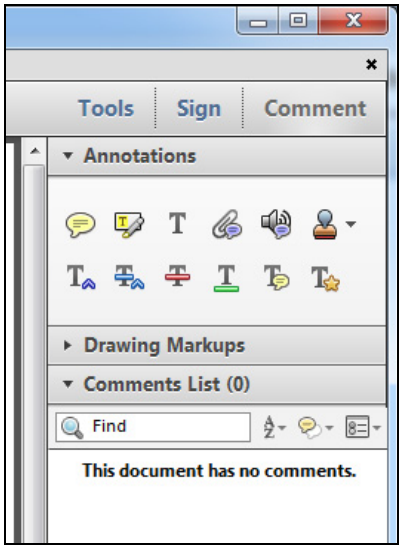
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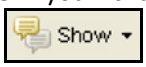
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
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Developing a Predictive Score for Chronic Arthritis among a Cohort of Children with Musculoskeletal Complaints—The Chronic Arthritis Score Study

Marco Cattalini, MD[1], Ilaria Parissenti, MD[1], Elena Tononcelli, MD[1], Francesca Lancini, MD[2], Luca Cantarini, MD, PhD[3], and Antonella Meini, MD, PhD[1]

Objective To explore if features obtained from a carefully taken medical history can be predictors of the final diagnosis in children with musculoskeletal complaints.

Study design We collected detailed clinical information on 178 children referred to our Pediatric Immunology and Rheumatology Unit by their primary care pediatrician for musculoskeletal complaints; a univariate logistic analysis was performed to identify variables correlated with the diagnosis of chronic arthritis. The variables identified were combined in a linear score that indicates the probability for a patient with musculoskeletal pain to receive the diagnosis of chronic arthritis.

Results The joint swelling pattern ($P < .0001$), the precipitating factors of pain ($P = .001$), the duration of morning stiffness ($P < .0001$) and the frequency of pain ($P < .0001$), were found to be independently correlated with the diagnosis of chronic arthritis and were used to develop a diagnostic score. This score had a sensitivity of 90.9% and specificity of 95.3%.

Conclusions We developed a score that could be useful in the daily clinical routine to correctly direct the differential diagnosis in a child with musculoskeletal complaints, rationalizing time and resources necessary to reach a definitive diagnosis. *(J Pediatr 2015;■:■-■).*

Musculoskeletal pain is one of the most common complaints in the pediatric population and affects between 10% and 20% of children.[1,2] It is one of the leading causes of office visits among pediatricians and one of the most common reasons why these children are referred to a rheumatologist.[3-5]

The differential diagnosis of children with musculoskeletal symptoms may cover a wide range of diseases,[6-10] with a variable spectrum of severity, from benign conditions, such as "growing pains," to potentially fatal disorders, such as leukemia.[11-13] Musculoskeletal pain may contribute to the clinical presentation of various rheumatic diseases, such as juvenile idiopathic arthritis (JIA), systemic lupus erythematosus, and Henoch-Schönlein purpura.[8,9] However, isolated pain is, in most cases, secondary to a noninflammatory condition, including orthopedic diseases (trauma, Osgood-Schlatter disease, Legg-Calvé-Perthes disease), hypermobility, "growing pains," and postural disorders.[1,12,14]

In this context, a careful review of the clinical history, together with a detailed physical evaluation, are helpful tools when approaching children with musculoskeletal pain, enabling the diagnosis of majority of cases.[7,15]

In this study, we analyzed the clinical presentation of children referred for musculoskeletal complaints by their primary care pediatrician to our Pediatric Immunology and Rheumatology Unit. Our aims were to explore if features obtained by a careful medical history can predict the final diagnosis and to identify which features would be more predictive of chronic arthritis.

Methods

We enrolled all patients who were referred to our Immunology and Rheumatology Unit for musculoskeletal complaints between June 2012 and December 2013. Only children referred by their primary care pediatrician were enrolled, and children referred from other specialists or facilities (ie, adult rheumatologists, other pediatric subspecialists, emergency department, and other pediatric clinics) were excluded. At the time of the first evaluation, we obtained the patient and family medical history, focusing on the pain frequency and pattern, precipitating factors of pain, joint swelling pattern, stiffness, and constitutional symptoms. All data were

ANA	Antinuclear antibodies
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
JIA	Juvenile idiopathic arthritis
RF	Rheumatoid factor

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entered into a database, together with demographic information and, when available, specific laboratory tests performed before our evaluation, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibodies (ANA), and rheumatoid factor (RF).

Once recruited, all patients were followed until a final diagnosis was confirmed. According to the final diagnosis, we categorized each patient to 3 groups: chronic arthritis, infectious-related arthritis (including acute rheumatic fever and reactive arthritis) and noninflammatory disorders (ie, orthopedic disorders, benign hypermobility syndrome, and postural defects). All the data recorded were taken during routine visits, and patients were followed as per normal clinical practice. No study-specific procedures were undertaken. Consent was obtained from all parents/guardians of the children to record the data.

Statistical Analyses

We used Fisher exact test to analyze the distribution of the variables recorded in the database within the three groups. We considered a P value of $<.05$ as statistically significant. We used a leave-one-out cross-validation to select the variables associated with the diagnosis of chronic arthritis; we then performed a logistic regression, using these features as independent variables and the probability of having chronic arthritis as the dependent variable, in order to build a model that could indicate the probability for a patient with musculoskeletal pain to receive the diagnosis of chronic arthritis.

Results

A total of 178 patients were recruited, 95 (53%) females and 83 (47%) males. Mean age was 8.5 ± 3.6 years. The 3 subpopulations did not differ in age at onset, and in children with chronic arthritis, there was a higher percentage of females (72%), compared with the other subpopulations ($P = .0145$).

Thirty-six patients had chronic arthritis (20% of the population), of whom 26 were females and 10 males, with a mean age at onset of 8.2 ± 4.1 years. All patients had JIA according to the International League of Associations for Rheumatology criteria[16-18]; 28 patients had infection-related arthritis (16% of the population) of whom 10 were females and 18 males, with a mean age at onset of 8 ± 3.8 years. Furthermore, 114 patients had noninflammatory disorders (64% of the population) of whom 59 were females and 55 males (48%), mean age at onset was 8.7 ± 3.5 years. Further information on the initial and final diagnosis is provided in Table I. We performed a Fisher exact test, in order to describe the distribution of the recorded variables within the three groups (Table II).

Joint pain was recorded in 163 out of the 178 (92%) patients. The group of patients with chronic arthritis showed a dichotomic pain distribution (persistent pain vs absence of pain), and the 2 other groups showed a more heterogeneous distribution of pain characteristics. By the Fisher exact text both the constant presence (56%) and absence of pain (36%) were associated with the diagnosis of chronic ($P < .0001$ and $P < .0001$, respectively). The presence of recurrent pain with more than 1 episode per month was significantly associated ($P < .0001$) with ~~children with~~ noninflammatory disorders.

Evening/night pain was more frequently reported by the patients with noninflammatory disorders (48% of these patients) ($P < .0001$). This characteristic was not found in any of the patients who received a diagnosis of chronic arthritis or infections-related arthritis. The presence of morning pain was observed in a higher percentage (26%) of patients with chronic arthritis compared with the 2 other groups (4% and 7% of children, respectively; $P < .009$).

The analysis of precipitating factors of pain identified features associated with each of the categories: rest in 68% of patients with chronic arthritis ($P = .001$), a prior infection in 79% of children with infection-related arthritis ($P < .0001$), and activity in 46% of patients with noninflammatory disorders ($P < .0001$). None of the patients who experienced pain only after activity received a diagnosis of chronic arthritis.

Eighty-three percent of children with chronic arthritis had daily persistent joint swelling in 1 or more joints ($P < .0001$). By contrast, in the other groups, the clinical presentation at

Table I. Initial diagnostic suspicion by the referring physician and final diagnosis

	Chronic arthritis 36 patients (20%)		Infection-related arthritis 28 patients (16%)		Noninflammatory disorders 114 patients (64%)	
Diagnostic suspicion	Arthritis	27	Arthritis	12	Arthritis	11
	Joint pain	5	Joint pain	8	Joint pain	93
	Joint swelling	4	Joint swelling	3	Joint swelling	3
			Limp	1	Limp	7
			Acute rheumatic fever	4		
Final diagnosis	Systemic arthritis	1	Acute rheumatic fever	7	Postural abnormalities†	53
	Oligoarthritis	22	Poststreptococcal reactive arthritis	5	Benign joint hypermobility syndrome	9
	Polyarthritis	7	Parvovirus B19 infection	1	Orthopedic disorders‡	13
	Psoriatic arthritis	2	Posttubercolosis infection	1	Growing pains	39
	Enthesitis-related arthritis	4	Post upper respiratory or gastrointestinal tract infection*	14		

*Including transient synovitis of the hip.
†At least one of the following: cervical kyphosis (1), thoracic kyphosis (9), hyper-lordosis (10); nonstructural scoliosis (12); increased femoral anteversion (9); genu-varus (5), genu-valgus (8), patella femoral malalignment (2); flat feet (6), planovalgus feet (8); generalized joint hypermobility (Beighton score >4 with negative Brighton criteria: 14).
‡Structural scoliosis (3); Osgood-Schlatter disease (4); Hoffa syndrome (2); Sever disease; Perthes' disease (1); posttraumatic injury (3).

Table II. Clinical features statistically associated with the diagnostic groups

	Chronic arthritis (% of patients)	Infection-related arthritis (% of patients)	Noninflammatory disorders (% of patients)	*P* value
Pain frequency				
Persistent	56[1]	29	15	<.0001[1]
1/mo	8	18	64	n.s.
<1/mo	0	14	13	n.s.
Single Episode	0	32	8	n.s.
Absent	36[2]	7	0	<.0001[2]
Precipitating factors				
Aspecific	68	18	46	n.s.
Injury	4	0	4	n.s.
Infection	0	79[3]	2	<.0001[3]
Activity	0	0	43[4]	<.0001[4]
Rest	28[5]	3	5	.013[5]
Joint swelling				
Persistent	83[6]	18	3	<.001[6]
>1/mo	0	0	2	n.s.
<1/mo	0	0	1	n.s.
Single Episode	3	28	4	n.s.
Absent	14	54[7]	90[7]	<.002[7]
Morning stiffness				
Present	55[8]	11	14	<.0001[8]
None	45	89	86	n.s.

onset was characterized in most cases by the absence of joint swelling (54% of children with infection-related arthritis and 90% of children with noninflammatory disorders). A thorough joint examination allowed us to clarify that the persistent joint swelling reported by the parents of 4 children with noninflammatory disorders (2 patients with Osgood-Schlatter disease and 2 with Hoffa syndrome) actually was swelling in extra-articular structures.

Morning stiffness was reported more frequently in patients with chronic arthritis (55% of patients) compared with the other 2 groups (11% and 14%) ($P < .0001$). Among children with chronic arthritis who suffered from morning stiffness, this symptom usually lasted for less than 1 hour (33%).

The presence of fever in 39% of children with infection-related arthritis was statistically significant ($P < .0001$). Fever was recorded in a lower percentage of patients among the other 2 groups (8% of patients with JIA and 1% of children with noninflammatory disorders). All remaining features (fatigue, weight loss, sleep disorders, and muscle pain) were not significantly associated with any one of the diagnostic groups.

Acute Phase Reactants

These variables were not statistically associated with any of the 3 groups. Among patients with chronic arthritis elevated ESR and CRP values, (36%) were found in those with polyarticular or systemic JIA, and normal in patients with other forms of JIA. Most of the patients with noninflammatory disorders (89%) had normal ESR and CRP values ($P < .0001$).

The presence of ANA positivity, regardless of the titer, was statistically associated with chronic arthritis ($P < .05$). Positive ANA, especially at titer between 1:160 and 1:640, was found in 26% of the patients from the other 2 groups. Two patients with JIA were RF positive. Three patients with noninflammatory diseases had an initial positive RF that turned negative in subsequent evaluations.

Fifty-three percent of the patients with chronic arthritis reported a first or second-degree relative affected by an autoimmune disease compared with 32% of children from the other 2 groups ($P = .034$); 29% of children with JIA and 22% from the other groups had family history of rheumatic diseases (not significant).

We identified 4 variables statistically associated with the final diagnosis of chronic arthritis. Joint swelling pattern (b_1), precipitating factors of pain (b_2), morning stiffness duration (b_3), and pain frequency (b_4). We then build up a regression logistic model, evaluating the distribution of each one of the 4 variables, with their respective characteristics (as independent variables), in the population of patients with chronic arthritis (dependent variable). This led to a numeric coefficient ("x" = log of the OR) that expressed the impact each variable had on the final diagnosis (Table III). The logistic regression formula (called the chronic arthritis score) was [T3]

$$y = k + b_1x_1 + b_2x_2 + b_3x_3 + b_4x_4$$

where y is logit $(P) = \ln (P/1 - P)$; k is a coefficient (=15.735) returned by the model; x_1 is the coefficient corresponding to the specific joint swelling pattern (b_1); x_2 is the coefficient

Table III. The CASco* (regression logistic model obtained with the study)

	Characteristics	"x" coefficient
Joint swelling (b1)	No joint swelling	0
	Single episode	1.654
	Less than 1 episode/mo	0.318
	More than 1 episode/mo	−2.194
	Persistent	5.324
Precipitating factors (b2)	Rest	−18.202
	Activity	−37.892
	Infection	−42.145
	Trauma	−44.859
	Nonspecific	−20.731
Morning stiffness (b3)	No morning stiffness	0
	Less than 1 h	0.484
	More than 1 h	1.992
Pain frequency (b4)	No pain	0
	Single episode	−15.358
	Less than 1 episode/mo	−14.284
	More than 1 episode/mo	0.635
	Persistent	3.148

CASco, chronic arthritis score.

*For example we can consider 2 different case scenarios: the first of a child with recurrent joint pain with more than 1 episode/month ($x_4 = 0.635$), no clear precipitating factors ($x_2 = -20.731$), and without joint swelling ($x_1 = 0$) or morning stiffness ($x_3 = 0$). In this case, the application of the CASco will be: $y = 15.735 + 0 - 20.731 + 0 + 0.635$, with the result $y = -4.36$ that correspond in the logit transformation table with a probability of 1.5%. The second case scenario will be of a patient with persistent joint swelling ($x_1 = 5.324$) and morning stiffness of less than one hour ($x_3 = 0.484$), without joint pain ($x_4 = 0$), or a known precipitating factor ($x_2 = -20.731$). In this case, the formula will be: $y = 16.735 + 5.324 - 20.731 + 0.484 + 0$ obtaining a value of $y = 0.812$, giving a probability of 69.5%. The primary care physician would probably develop different diagnostic strategies for the 2 cases.

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corresponding to the specific precipitating factors (b_2); x_3 is the coefficient corresponding to the morning stiffness pattern (b_3); and x_4 is the coefficient corresponding to the pain frequency pattern (b_4). Applying the "logit transformation table," the y value can be converted to the probability of the patient receiving a final diagnosis of chronic arthritis (Tables III and IV). This score had a sensitivity of 90.9% and a specificity of 95.3% of predicting chronic arthritis in our cohort.

Discussion

Chronic or recurrent musculoskeletal pain is a common complaint in children, accounting for between 6% and 10% of office visits in different countries.[1,2] Primary care physician are usually consulted first, but between 6% and 22% of these children are then referred to other medical or surgical specialists.[3-5] A tool that will help physicians to rationalize the approach to musculoskeletal pain in children may have an impact on health care utilization.[3]

Among the 178 patients referred to our clinic with musculoskeletal complaints, chronic arthritis was the final diagnosis in the minority of cases. The main diagnosis was of noninflammatory disorders, in concordance with previous reports.[1,2,10] All the children with chronic arthritis satisfied the International League of Associations for Rheumatology criteria for JIA.[16,17] This result could be seen as a potential drawback in the study, limiting the application of the score just to JIA. Still, we should consider that clinical characteristics of the different forms of chronic arthritis are overlapping, no matter the underlying disease, therefore, we believe our results may be applied to children with chronic arthritis in general.[19-21]

Of note, 12 patients from our cohort were diagnosed as having streptococcal-related arthritis (ie, acute rheumatic fever or poststreptococcal arthritis). This number is quite high, given the estimated prevalence of acute rheumatic fever in developed countries. Patients with chronic arthritis from our cohort typically experienced constant pain, or no pain at all, and not intermittent joint pain. The incidence of persistent joint pain was surprisingly high in our chronic arthritis population because pain usually is not the dominating symptom in the majority of patients with JIA. Isolated joint pain was found in some studies to have a very poor predictive value for rheumatic conditions, although in those studies, the distribution of pain over time was not specifically addressed.[1,15] The high incidence of pain in our cohort could be partially due to the fact that in younger nonverbal children limping or joint stiffness may be interpreted by the parents as pain. Given the pathophysiology of pain in chronic arthritis, it is likely that, if present, pain would be persistent, rather than recurrent.[19,21,22] Other characteristics of pain were informative for the final diagnosis: evening/night pain was statistically associated with a diagnosis of noninflammatory disorders, and there was a correlation between morning pain and chronic arthritis. Again, this is in accordance with the presumed pathophysiology of pain in those conditions because pain in noninflammatory diseases is typically elicited by activity, therefore, it usually occurs at the end of the day. This is obvious for "growing pains" and orthopedic conditions, but also for postural abnormalities: in the majority of cases children with postural abnormalities had nonspecific muscle and joint pain; therefore, it is reasonable to presume the pain was secondary to the variable coexistence of muscle contractures (for example in those with bad spinal alignment) and joint/bone pain from altered load distribution (for example in those with flat foot).

The presence of constant swelling and morning stiffness was, as it could be expected, a characteristic of our patients with chronic arthritis, and its absence was highly indicative of a noninflammatory condition.

The lack of association with constitutional symptoms or elevated inflammatory markers with a specific diagnosis is probably a result of the selected population, where the majority of patients had noninflammatory conditions. Only few patients had systemic or poly/articular JIA, and none had neoplastic diseases, conditions in which constitutional symptoms and elevated inflammatory markers are more prevalent. The ANA determination is often used by pediatricians as a "screening" test to rule out a rheumatic disease. Our study confirmed the association between high title ANA positivity and chronic arthritis.[22,23] Indeed, we observed a high rate of ANA-positive patients in our population, probably reflecting the high prevalence of oligoarticular JIA (the category known to have higher prevalence of ANA) among the chronic arthritis group. Still, there was a large proportion of patients with JIA and negative ANA, as there were some patients with postinfection arthritis or noninflammatory musculoskeletal

Table IV. Logit transformation table

P	Logit (P)	P	Logit (P)	P	Logit (P)	P	Logit (P)
.01	−4.5951	.26	−1.0460	.51	0.0400	.76	1.1527
.02	−3.8918	.27	−0.9946	.52	0.0800	.77	1.2083
.03	−3.4761	.28	−0.9445	.53	0.1201	.78	1.2657
.04	−3.1781	.29	−0.8954	.54	0.1603	.79	1.3249
.05	−2.9444	.30	−0.8473	.55	0.2007	.80	1.3863
.06	−2.7515	.31	−0.8001	.56	0.2412	.81	1.4500
.07	−2.5867	.32	−0.7538	.57	0.2819	.82	1.5163
.08	−2.4423	.33	−0.7082	.58	0.3228	.83	1.5856
.09	−2.3136	.34	−0.6633	.59	0.3640	.84	1.6582
.10	−2.1972	.35	−0.6190	.60	0.4055	.85	1.7346
.11	−2.0907	.36	−0.5754	.61	0.4473	.86	1.8153
.12	−1.9924	.37	−0.5322	.62	0.4895	.87	1.9010
.13	−1.9010	.38	−0.4895	.63	0.5322	.88	1.9924
.14	−1.8153	.39	−0.4473	.64	0.5754	.89	2.0907
.15	−1.7346	.40	−0.4055	.65	0.6190	.90	2.1972
.16	−1.6582	.41	−0.3640	.66	0.6633	.91	2.3136
.17	−1.5856	.42	−0.3228	.67	0.7082	.92	2.4423
.18	−1.5163	.43	−0.2819	.68	0.7538	.93	2.5867
.19	−1.4500	.44	−0.2412	.69	0.8001	.94	2.7515
.20	−1.3863	.45	−0.2007	.70	0.8473	.95	2.9444
.21	−1.3249	.46	−0.1603	.71	0.8954	.96	3.1781
.22	−1.2657	.47	−0.1201	.72	0.9445	.97	3.4761
.23	−1.2083	.48	−0.0800	.73	0.9946	.98	3.8918
.24	−1.1527	.49	−0.0400	.74	1.0460	.99	4.5951
.25	−1.0986	.50	0.0000	.75	1.0986		

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pain with positive ANA. Our study, therefore, confirms that ANA should not be used as a "screening" test for rheumatic conditions.[24-26] The low percentage of patients with chronic arthritis and RF positivity is in agreement with the low predictive value of this test in children with musculoskeletal complaints.[20,27,28]

In the second part of the study, we attempted to identify the features more specifically associated with chronic arthritis. These features included the presence of persistent joint swelling, rest as a precipitating factor for pain, the presence of morning stiffness, and the persistence of pain. We then developed a logistic regression model and formula to calculate the weight of each one of these features on the final diagnosis of chronic arthritis. This formula may help determine the probability that children with musculoskeletal pain will be diagnosed with chronic arthritis.

The main limitation of this study is that it was conducted in a single center with a particular diagnostic distribution, with a high prevalence of postural defects and streptococcal-related arthritis and lack of patients with pain amplification syndromes. These differences may partially depend on the approach local physicians ~~refer~~ a patient with musculoskeletal pain. Indeed, it has been published that in US and United Kingdom, pediatric rheumatologist are often the last of a series of specialists to be consulted for such cases, and it seems from our region, pediatric rheumatologist are the first to be consulted.[29-31] It is reasonable to presume that we see many children with musculoskeletal pain attributable to noninflammatory conditions because we are the first specialists to be consulted; however, in other countries, these patients are seen by other specialists first without the need of further rheumatologic evaluations. Even though this may limit the application of our score to other pediatric rheumatology clinics, we believe it will be useful for pediatricians because our population was very heterogeneous, not only including patients with true inflammatory diseases. Further studies, possibly with a multicenter design, will help to prevent this bias and to validate the score.

Another limitation is that the study relies on information obtained by patients and parents that may be biased by different factors, such as age of the patients, education level, etc. However, this was the ~~main~~ way to obtain information on the period of time preceding our evaluation.

Our study confirms that the minority of children with musculoskeletal pain have a chronic inflammatory condition. The application of the chronic arthritis score may be a useful tool for primary care physicians investigating children with musculoskeletal complaints. The rationalization of resources may reduce investigations that are both time- and money-consuming for patients as well as for the health care system. ■

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