Research Square

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Finding the Undiagnosed Juvenile Onset Spondyloarthritis (jSpA) Patient: Does Transient Synovitis of the Hip Help? A Retrospective Cohort Study

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Abstract

Background

The well-known diagnostic delay of juvenile spondyloarthritis (jSpA) is a major clinical problem facing patients, families, and pediatricians today. We conducted a retrospective chart review and follow-up interview study to determine if a cohort of transient synovitis (TS) patients experienced recurrent episodes of chronic joint and lower back pain possibly indicative of subjects with undiagnosed juvenile spondyloarthritis (jSpA) or enthesitis-related arthritis (ERA).

Methods

In this cohort study, baseline demographic and clinical information of all coded TS patients at Children's Hospital of Los Angeles Emergency Department from 2002 to 2022 were collected. Follow-up telephone interview data was obtained on a cohort of these subjects addressing the recurrence of TS, the presence of chronic lower back pain and/or joint pain (lasting > 6 weeks), any physician follow-up for symptoms, and the possibility of a physician diagnosis such as jSpA/ERA, or related conditions.

Results

We enrolled 74 patients (40% of 184 eligible); baseline demographic and clinical features were similar to the unenrolled cohort. Twenty-four patients (32.4%) described recurrence of the initial problem of TS. Chronic lower back pain was reported in 41.7% of the recurrent transient synovitis cohort vs. 0% of the non-transient synovitis cohort ($p < 0.001$). The hips emerged as the most statistically significant involved peripheral joint.

Conclusion

A substantial number of subjects with transient synovitis recurrence revealed symptoms highly suggestive of jSpA/ERA. These findings support the need for additional research to prospectively follow TS cases with a formal rheumatologic assessment to confirm the diagnosis of jSpA or ERA.

Background

Transient synovitis of the hip (TS) is typically viewed as a common self-limited diagnosis that is difficult to study and prognosticate due to its nonspecific symptoms. In fact, recurrences have been noted to occur after many years leading to the question 'why.' [1] Observations by our colleague pediatric rheumatologists at Children's Hospital Los Angeles (CHLA) that multiple episodes of TS had preceded the diagnosis of juvenile-SpA (jSpA) served to heighten our awareness that TS might be acting, in some cases, as a precursor jSpA phenotype. This is coupled with an alarm sounded by jSpA experts in the field through recent reviews and authoritative textbook articles that an unacceptable diagnostic delay occurs in jSpA coupled with data revealing children with juvenile onset SpA share a worse functional outcome

compared to other forms of juvenile chronic arthritis, including higher pain scores and a greater frequency of hip replacement compared to adult-onset SpA.[2–5]

The idea of a study to provide preliminary data that might find the undiagnosed patient with jSpA became a goal for the author/investigators. Therefore, it made sense for us to investigate the possibility, through the mechanism of a retrospective cohort study, of finding data to support the possible evolution from TS to the later development of jSpA. The study reported herein will address the long-term follow-up of a large, well-characterized cohort of TS patients identified from an urban safety-net pediatric hospital in Los Angeles. The main challenge for us was the fact that the presentation of SpA in children differs from that in adults by a case definition revealing a greater prevalence of peripheral enthesitis and arthritis, prominent hip joint involvement, and frequent absence of inflammatory back pain. [2, 5] Thus our questionnaire method was designed to address this concept. We hypothesize that patients who receive a diagnosis of TS as an initial episode may subsequently later in life experience recurrent undiagnosed episodes of chronic joint and back pain possibly indicative of jSpA or enthesitis related arthritis (ERA). Our study was designed to examine this hypothesis.

Methods

After receiving approval from our Human Research Protection Program (HRPP) and Institutional Review Board (IRB: CHLA 23–00214), we identified all cases of TS using ICD-9 and ICD-10 codes (M67.351, M67.352, M67.359, M727.09) for patients seen in our Emergency Department (ED) over a 20-year period (2002–2022). As summarized in Fig. 1, a total of 209 patients were identified; we selected the initial diagnostic-coded visit as the index visit for the beginning of the study period since some patients had subsequent ED visits or hospitalizations. Twenty-five patients were immediately excluded due to an alternate diagnosis made at the time of the initial ED visit. These exclusions included patients with an active infection or septic arthritis as well as those with other conditions known to affect the joint, such as Trisomy 21 and malignancies. Data from the remaining 184 patients were included for subsequent analysis.

Figure 1. Summary of the study recruitment and arrival of the study sub-groups. Eligible participants provided informed consent prior to study enrollment. After enrollment, participants were categorized into predefined subgroups based on recurrence or non-recurrence of transient synovitis as well as occurrence of peripheral joint pain and/or back pain for comparative analyses.

Figure 1. Summary of the Study recruitment and definition of the study sub-groups

Information gathered from the ED visit and its concurrent hospitalization included the patient's age at the time of the ED visit, gender, ethnicity, preceding or associated illnesses, and clinical presentation at time of ED visit. We also collected response to Nonsteroidal Anti-Inflammatory drugs and patient imaging results if these were obtained and recorded.

The study plan involved obtaining verbal phone consent from a patient (over ≥ 18 years of age) or a medical guardian if the patient was under 18 years of age. Formal consent and permission to obtain follow-up medical history was obtained with DocuSign. Clinical information collected included 1) the recurrence and frequency of repeat episodes of transient synovitis symptoms following the index ED visit, 2) occurrence of subsequent lower back pain lasting over six weeks after the initial ED visit, 3) the occurrence of chronic peripheral joint pain in other areas such as the upper extremities, hips, knees, and ankles lasting over six weeks that took place after the initial ED visit. These questions were uniformly administered to all subjects, irrespective of whether they belonged to the recurrence TS group or the non-recurrence TS group. Additionally, the study team inquired whether the patient had been seen and diagnosed by a physician during the follow-up period after the ED visit with conditions such as Juvenile Idiopathic Arthritis (JIA), Enthesitis-Related Arthritis (ERA), Ankylosing Spondylitis (AS), uveitis, or Inflammatory Bowel Disease (IBD), as well as any ongoing treatments for these diagnoses. It is important to note that we did not examine patients or ask them to visit CHLA unless the latter was prompted by their parents or guardians. At that point in the discussion, and when warranted, we suggested a referral to a pediatric rheumatologist.

Statistical Analysis

The distribution of categorical variables was compared across groups using Fisher's exact test, whereas median differences of continuous and ordinal variables were tested via the Wilcoxon rank-sum test.[6] Kaplan-Meier curves were constructed to estimate the survival distribution of the time to follow-up, and comparisons were performed with the log-rank statistic.[7]

Results

From the starting study population of 184 patients, 74 were successfully reached, consented, and participated in follow-up questioning; 110 subjects were unable to be contacted (See Fig. 1 and Table 1). Among the 74 patients contacted, 50 (67.6%) reported no recurrence of the initial episode of TS. In this subgroup, only 4 of 50 patients (8%) experienced subsequent chronic peripheral joint pain; no patient reported the presence of chronic back pain. By comparison, 24 patients (32.4%) described recurrences of the initial problem of TS. Of those who had a recurrence, 18 of 24 (75%) described subsequent chronic lower back and/or peripheral joint pain, while 6 of 24 (25%) reported no chronic pain. The chronic lower back and peripheral joint pain subgroups included 2 patients who had only chronic lower back pain, 8 who had only chronic peripheral joint pain, and 8 who experienced both. The combined lower back and peripheral pain analysis for all subsequent pain categories in the recurrence group (18/24) demonstrated statistical significance compared to the no recurrence group (4/50), with a p-value of < 0.001 across all three categories. As noted in Table 1, of the 8 patients who reported peripheral pain, the hips emerged as the most statistically significant location of pain with a P-value of < 0.001. In comparison, pain was observed in the ankles (p-value = 0.004), lower back (p-value = 0.102), and knees (p-value = 0.001).

Table 1
Characteristics of the No Recurrence versus Recurrence cohorts for contacted patients evaluated for TS symptoms

	No TS Recurrence[a] (N = 50)	TS Recurrence[a] (N = 24)	P-Value
Chronic lower back pain (> 6 weeks)			
No	50 (100.0%)	14 (58.3%)	< 0.001
Yes	0 (0.0%)	10 (41.7%)	
Chronic peripheral joint pain (> 6 weeks)			
No	46 (92.0%)	8 (33.3%)	< 0.001
Yes	4 (8.0%)	16 (66.7%)	
Combined chronic lower back and/or peripheral joint pain (> 6 weeks)			
No	46 (92.0%)	6 (25.0%)	< 0.001
Yes	4 (8.0%)	18 (75.0%)	
Subgroups of combined chronic pain category			
Chronic pain in lower back (> 6 weeks)			
No	50 (100.0%)	22 (91.7%)	0.102
Yes	0 (0.0%)	2 (8.3%)	
Chronic pain in hips (> 6 weeks)			
No	49 (98.0%)	15 (62.5%)	< 0.001
Yes	1 (2.0%)	9 (37.5%)	
Chronic pain in knees (> 6 weeks)			
No	48 (96.0%)	16 (66.7%)	0.001
Yes	2 (4.0%)	8 (33.3%)	
Chronic pain in ankles (> 6 weeks)			
No	49 (98.0%)	18 (75.0%)	0.004
Yes	1 (2.0%)	6 (25.0%)	
[a]Frequency (Percent%); p-value from Fisher's exact test.			

In order to determine if the contacted sample contained an implicit selection bias that could potentially produce a unique outcome, we compared the demographic features and clinical characteristics between the two groups (those enrolled vs. non-enrolled), as illustrated in Table 2. There was no statistically

significant difference in baseline TS features, as well as in time to follow-up time period, between the two groups.

Table 2
Characteristics of study participants

Age at ED[a] visit[a],	**Non-enrolled (N = 110)**	**Enrolled (N = 74)**	**P-Value**
	4.72 (2.76)	**4.54 (2.40)**	**0.879**
Sex[b]			
Female	34 (30.9%)	28 (37.8%)	0.344
Male	76 (58.2%)	46 (62.2%)	
Ethnicity[b]			
Non-Hispanic	34 (30.9%)	21 (33.3%)	1.000
Hispanic	64 (58.2%)	42 (66.7%)	
Unknown	12 (10.9%)		
URI - Viral prodrome[b]			
No	80 (72.7%)	44 (59.5%)	0.078
Yes	30 (27.3%)	30 (40.5%)	
GI - Viral prodrome[b]			
No	100 (90.9%)	71 (95.9%)	0.248
Yes	10 (9.1%)	3 (4.1%)	
Fever at presentation[b]			
No	104 (94.5%)	67 (90.5%)	0.381
Yes	6 (5.5%)	7 (9.5%)	
Viral Syndrome[b]			
No	94 (85.5%)	67 (90.5%)	0.368
Yes	16 (14.5%)	7 (9.5%)	
Time between ED visit and study initiation[a] (years)	5.87 (2.29)	6.18 (2.10)	0.387

[a] Mean (Standard Deviation), years; p-value from a Kruskal-Wallis test

[b] Frequency (Percent%); p-value from Fisher's exact test.

To check for sampling bias, we examined the possibility that subjects who reported recurrent transient symptoms (compared to those who had none) might have been followed for a longer period, hence creating a greater opportunity to experience a recurrence. To analyze this comparison, a Time-to-Event Kaplan-Meier Curve analysis was done (Fig. 2). The median follow-up time was estimated as 6.4 years for no TS recurrent cohort and 7.5 years for recurrent TS cohort. Despite the median separation of one year between the two survival distributions for length of follow-up, the log-rank p-value does not yield statistically significant differences between the two groups.

Discussion

This is a retrospective study reporting the symptoms associated with TS recurrence in 74 pediatric patients who were previously diagnosed with TS from a large quaternary pediatric center. Majority of the patients at the time of TS diagnosis were male, Hispanic, and youthful, ranging from 2 to 7 years old. Approximately one-third of our respondents at the time of follow-up reported experiencing at least one recurrence of the problem that was originally diagnosed with TS at CHLA. We then discovered that of those with a recurrence, 18 of 24 (75%) reported subsequent chronic back pain and/or peripheral joint pain. The combined analysis for all subsequent pain categories demonstrated statistical significance compared to those patients in the no recurrence group, with a p-value of < 0.001 across all three categories. For the 8 patients who reported subsequent peripheral joint pain, the hips emerged as the most statistically significant location of pain, with a p-value of < 0.001. In summary, one-third of patients arising from our initial cohort that we later contacted reported persistent chronic joint symptoms possibly representing the undiagnosed patient with jSpA or ERA.

There is a paucity of reports analyzing either the short-term or the long-term outcome of TS. We are not aware of a similar follow-up study of TS in the USA; previous studies almost all were purposed to collect data on possible Perthes' Disease. A study from Germany reported duration of a hip effusion (3–37 days) in weekly follow-up of 119 patients; within the study period, there were 2 TS recurrences, 11 cases of Perthes' disease, 2 juvenile hip arthritis and one septic hip. [8] A systematic literature review from the Netherlands examining the follow-up of TS in children was conducted by Asche et al. in 2013. These investigators noted that patients with recurrences tended to develop Legg-Calve-Perthes at both long-term and short-term intervals. The possibility of spondyloarthritis (SpA) was not addressed in their report. [9] Pediatric Rheumatologists from 6 centers in Israel performed a retrospective chart review of 39 children diagnosed with 2 or more separate episodes of TS at least 2 months apart. [10] All patients were contacted by telephone 4.2 ± 2.5 years after the first episode. None had developed clinical Perthes' disease or other chronic orthopedic conditions. Three (8%) patients developed a diagnosed chronic rheumatic disease, one with FMF and two with SpA. At follow-up, 26/36 (72%) patients were asymptomatic; however, 10 (28%) reported hip pain following intensive physical effort. Importantly, and in our review of the literature, we were unable to find prior studies that used an objective standard diagnostic approach (imaging, patient examination, laboratory testing for HLA-B27) for the ascertainment of jSpA at the time of follow-up.

In this study we utilized probing and well-thought-out questions, and for consistency we utilized one individual (author AR) to collect the data and provide clarification of what kind of symptoms these patients experienced after the initial TS occurrence. It is important to note that by design, we were unable to diagnose jSpA; we did not obtain imaging, genetic studies, or physical examinations on these patients. We inquired whether these patients were seen by a doctor who would diagnose recurrence of TS or another musculoskeletal diagnosis. Interestingly, no subject or family member reported consulting a physician (either a rheumatologist or a general practitioner) for any of the ongoing musculoskeletal problems.

The main weaknesses of our study due to its design were 1) our inability to establish a diagnosis of jSpA/ERA suggested by the interview findings, and 2) the potential for recall bias in our research subjects. While differential recall between the recurrence and non-recurrence TS groups cannot be excluded, the use of a structured, standardized questionnaire administered by the same interviewer is expected to mitigate recall bias. In addition, the recall periods between the groups were very similar (recurrence TS group is 7.5 years vs. 6.4 years in the non-recurrence TS group (Fig. 2). The strengths of our study design were several, including the large sample size from a single center, the consistency of the diagnosis of TS made by our single-center faculty who work together with many shared QI interactions, and the uniformity of the implementation of the questions by a single individual. We were able to demonstrate a similar demographic and clinical profile between the enrolled and non-enrolled patients to address selection bias. Furthermore, the follow-up periods for enrolled patients were similar between subjects who reported recurrences versus those who reported none.

Conclusions

Our findings disclosed that a substantial number of patients with TS are likely to experience recurrence of the condition. The majority of symptoms were chronic (> 6 weeks) and involving peripheral joints, particularly the hips, and the lower back. With this preliminary information, we can suspect that the recurrence as well as the initial transient synovitis episode itself could possibly be early manifestations of the undiagnosed jSpA patient. We cannot confirm this based on our study design. However, this hypothesis leads us to consider developing a more robust prospective follow-up study to be performed as a next step, provided that subjects are willing to undergo a formal diagnostic process that includes physical examinations, imaging, and HLAB27 testing. In the absence of such a study and recognizing the very preliminary findings we report, it does make sense that a diagnostic follow-up of TS patients could be considered helpful in a research sense. We maintain that our data suggests that a strategy to mitigate the long-term morbidity that can arise from a delayed diagnosis of jSpA/ERA requires additional research efforts.

Abbreviations

Ankylosing Spondylitis (AS), ED
Emergency Department

CHLA
Children’s Hospital of Los Angeles
ERA
Enthesitis-Related Arthritis
FMF
Familial Mediterranean Fever
IBD
Inflammatory Bowel Disease
jSpA
juvenile spondyloarthritis
TS
Transient Synovitis

Declarations

Ethics declaration: This study was approved by the CHLA IRB/ethical Committee (IRB: CHLA 23–00214). Informed consent was provided by all participants prior to start of the study.

M.W. contributed to study design, interpretation of data, editing of manuscript, and final approval.

R.D. contributed to statistical analysis, preparation of tables and Fig. 2 and final approval.

M.C. contributed to interpretation of data, editing of manuscript, preparation of tables, and final approval.

Competing interests:

None

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Author Contribution

A.B. contributed to study design, data acquisition, interpretation of data, draft of manuscript, preparation of figure 1, and final approval.M.W. contributed to study design, interpretation of data, editing of manuscript, and final approval. R.D. contributed to statistical analysis, preparation of tables and figure 2 and final approval.M.C. contributed to interpretation of data, editing of manuscript, preparation of tables, and final approval.

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Data Availability

All data supporting the findings of this study are available within the paper and upon further written request.

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Figures

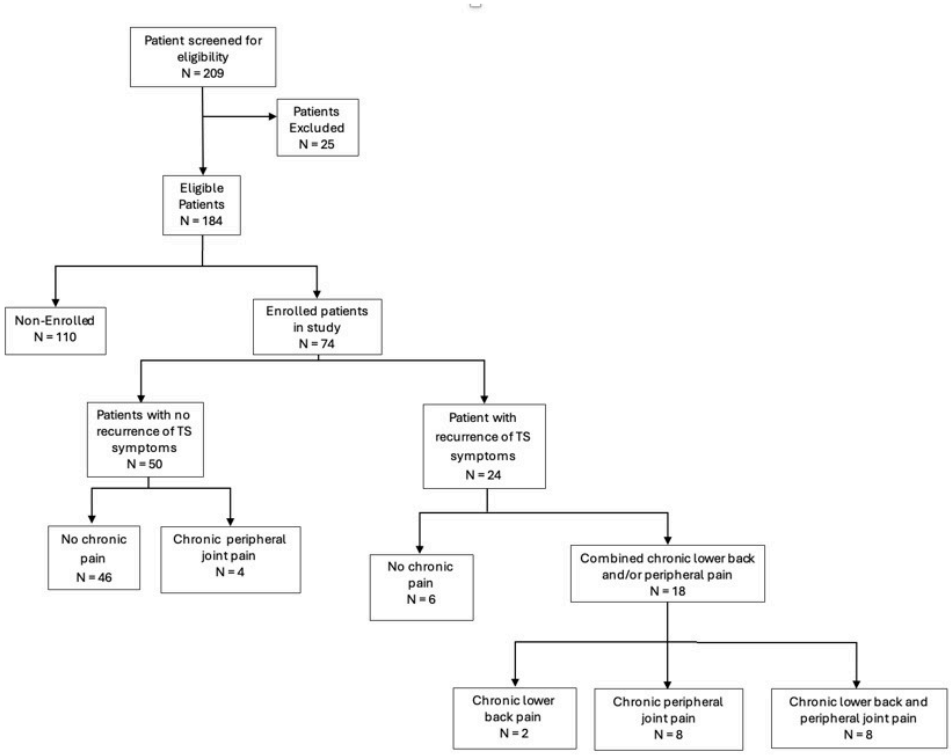


Figure 1: Summary of the Study recruitment and arrival of the study sub-groups.

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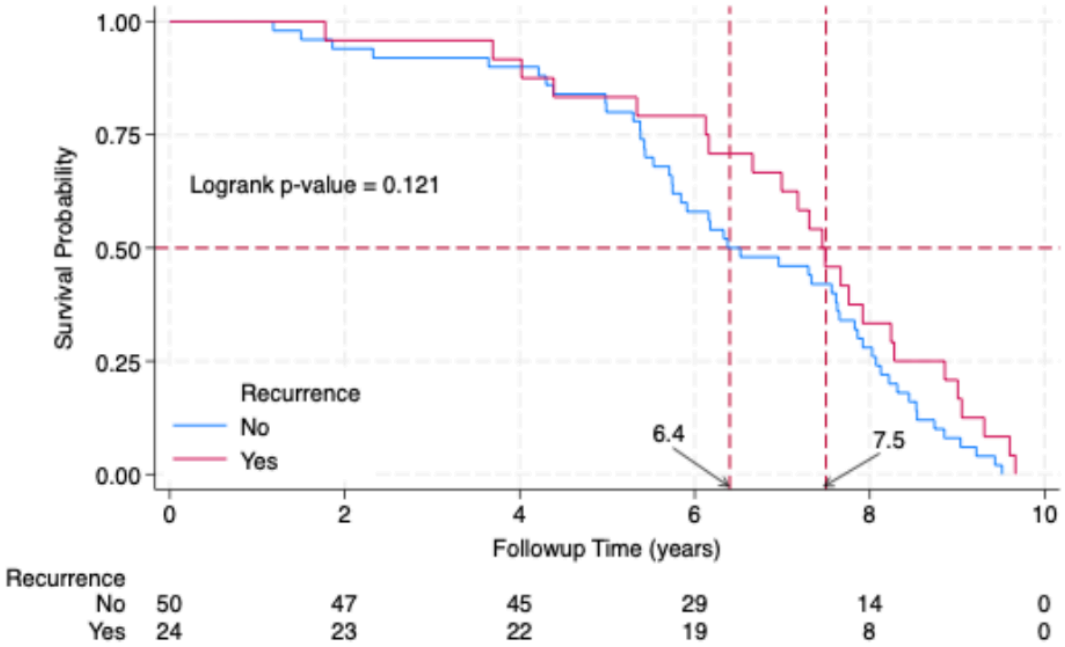


Figure 2: Kaplan-Meier for follow-up time. This illustrates the likelihood (survival probability, S(t)) of a patient follow-up after t years. The median follow-up time in the non-recurrence group is 6.4 years and in the recurrence group 7.5 years. p-value 0.121.

Figure 2

Kaplan-Meier for follow-up time.