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Concise report

Prospective validation of the Juvenile Spondyloarthritis Disease Activity Index in children with enthesitis-related arthritis

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Abstract

Objective. To measure disease activity in children with enthesitis-related arthritis the Juvenile Spondyloarthritis Disease Activity Index (JSpADA) was developed and retrospectively validated. We prospectively validated JSpADA and also assessed performance of adult SpA scores.

Methods. Children with enthesitis-related arthritis (ILAR criteria) less than 18 years of age were enrolled. Baseline characteristics and different disease activity measures (JSpADA, BASDAI, Ankylosing Spondylitis Disease Activity Score-ESR, juvenile arthritis DAS-10 joints), and Childhood HAQ, physician global assessment and patient global assessment were recorded at baseline. In some children follow-up was also done.

Results. The mean (S.D.) age of 127 children (116 boys) was 14.3 (2.4) years and disease duration was 36.9 (3) months. Ninety of 104 (86.5%) children were HLA-B27 positive. JSpADA showed high correlation with physician global assessment ($r = 0.87$; $P < 0.0001$), patient global assessment ($r = 0.80$, $P < 0.0001$), juvenile arthritis DAS-10 joints ($r = 0.89$; $P < 0.0001$) and Childhood HAQ ($r = 0.83$, $P < 0.0001$). The JSpADA scores showed good internal consistency, discriminative validity and sensitivity to change. In 15% of children back mobility could not be tested due to active arthritis in lower limbs. The 7-variable JSpADA excluding back mobility performed as well as the original JSpADA. Adult scores showed good construct validity, discriminative capacity and sensitivity to change, and had good correlation with JSpADA (BASDAI, $r = 0.84$; Ankylosing Spondylitis Disease Activity Score-ESR, $r = 0.84$).

Conclusion. JSpADA is a valid score for measuring disease activity in enthesitis-related arthritis. Adult scores also performed well. Excluding back mobility needs to be assessed in future to improve JSpADA performance.

Key words: juvenile spondyloarthritis, enthesitis-related arthritis, Juvenile Spondyloarthritis Disease Activity Index, BASDAI, ASDAS-ESR, JADAS-10, Childhood-HAQ

Rheumatology key messages

- Juvenile Spondyloarthritis Disease Activity Index is a valid score to measure disease activity in enthesitis-related arthritis.
- Exclusion of back mobility from Juvenile Spondyloarthritis Disease Activity Index may increase its applicability.
- Ankylosing Spondyloarthritis Disease Activity Score and BASDAI also perform well in enthesitis-related arthritis.

Introduction

SpA are a group of disorders that present with inflammatory back pain, enthesitis, sacroiliitis and HLA-B27 association. Enthesitis-related arthritis (ERA) in the classification for JIA as proposed by the ILAR mainly represents the Juvenile SpA (JSpA) category in children [1]. ERA differs from adult SpA in having a higher prevalence of peripheral arthritis and enthesitis and lower prevalence of axial disease. Patients have worse functional outcomes and more severe disease than adult AS [2]. ERA is the most common subtype of JIA in most Indian series [3].

Among all categories of JIA, children with ERA have higher pain intensity, worse health status and lower likelihood of sustaining inactive disease [4]. More than half of the children with JSpA continue to have active disease at the end of 4 years, while only a quarter achieve drug-free remission [5].

DAS for JIA such as that juvenile arthritis DAS (JADAS) disregard axial disease and enthesitis, which are common in ERA. In adults, DAS such as the BASDAI and

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CLINICAL SCIENCE

Ankylosing Spondyloarthritis Disease Activity Score (ASDAS) are routinely used in the clinic. Owing to differences in clinical presentation, ERA warrants a separate instrument that focuses on the key features of the disease. In response to this unmet need, the Juvenile Spondyloarthritis Disease Activity Index (JSpADA) was recently developed [6] (supplementary Table S1, available at *Rheumatology* online). The score was validated in a retrospective multicentre cohort in which it showed good discriminative ability, responsiveness to change and correlations with JADAS and Childhood HAQ (CHAQ).

ACR recommendations for development and validation of response criteria include validation in prospective clinical trials [7]. In the absence of major ongoing clinical trials in JSpA, the viable alternative was validation in a prospective cohort, which we have undertaken in this study. In addition, we have assessed the performance of adult scores.

Methods

Patients

Consecutive children with ERA (ILAR criteria) <18 years of age, seen in the outpatient clinic at Sanjay Gandhi Postgraduate Institute of Medical Sciences, a tertiary care hospital in North India, during the study period (February 2016 to February 2017) were included in the study. Ethical approval was obtained from the institutional ethics committee of Sanjay Gandhi Post-graduate Institute of Medical Sciences Lucknow (2016-26-DM-EXP). Written informed consent was obtained from parents or legal guardians.

Clinical details

Demographic and clinical parameters were recorded. Patients were asked to fill the validated local language BASDAI and CHAQ [8]. Physician global assessment (PGA) and patient global assessment (PtGA) were recorded on visual analogue scale of 1–10. Active disease was defined as PGA $\geqslant 1$. Individual components of all the scores were recorded at the time of assessment and the actual scores, viz. BASDAI, ASDAS-ESR, CHAQ, JADAS-10 and JSpADA, were calculated later to avoid their effect on PGA. The CHAQ measures the effect of disease on the child's function, with a questionnaire grading various daily activities. The JADAS-10 is modified from the adult DAS, focusing on active joint count (capped at 10 joints), PGA, PtGA and ESR. BASDAI and ASDAS are both validated to measure disease activity in adult SpA. BASDAI is a patient-reported measure (0–10 scale) that has questions on pain, stiffness and fatigue. ASDAS-ESR has three questions from BASDAI, patient's rating of global disease activity and ESR. To study sensitivity to change a repeat assessment was done after >2 months in a subset of patients.

Laboratory and imaging methods

HLA-B27 typing was done on DNA extracted from peripheral blood using PCR. ESR was measured by Westergren's method. An anterio-posterior radiograph of the pelvis was done to assess sacroiliitis.

Statistical methods

The construct validity of JSpADA was assessed by correlating its score with PGA, PtGA, JADAS-10 and CHAQ using Spearman's rank correlation. Discriminative capacity was tested by comparing mean JSpADA scores between patients with active disease and inactive disease. Internal consistency was tested by deriving Cronbach's α coefficient. Sensitivity to change was checked by standardized response mean and comparing mean change in JSpADA between those who improved and those who worsened. Correlation of adult SpA score with other activity measures and PGA was done using Spearman's rank correlation.

Results

Patient characteristics

We screened 138 patients with ERA of whom 127 (116 boys) agreed to participate in the study. Mean (S.D.) age was 14.3 (2.42) years and mean disease duration was 36.9 (3) months. Four children had disease duration of <6 months. Inflammatory back pain ever was present in 85 while peripheral arthritis was seen in 115 (Table 1). Arthritis of hip joint was seen in 16 patients (12.5%). Ninety of 104 (86.5%) children were HLA-B27 positive. The majority (107 patients) had active disease. Follow-up visits were recorded in 32 patients at mean (S.D.) time of 98 (48) days.

Table 1 Characteristics of patients with enthesitis-related arthritis (n = 127)

Characteristic	Values
Age, mean (S.D.), years	14.3 (2.42)
Boys:girls	116:11
Duration of disease[a], mean (S.D.), months	36.9 (3)
HLA-B27, *n* (%)	90/104 (86.5)
Radiographic sacroiliitis, *n* (%)	50/116 (43)
Inflammatory back pain, *n* (%)	85 (66.9)
Peripheral arthritis, *n* (%)	115 (90.55)
Treatment (*n*)	
NSAIDs	91
Methotrexate	20
Sulphasalazine	8
Leflunomide	1
JSpADA[b], mean (S.D.)	2.8 (1.8)
JADAS-10, mean (S.D.)	12.36 (8.6)
ASDAS-ESR, mean (S.D.)	2.99 (1.2)
CHAQ, mean (S.D.)	0.77 (0.7)
BASDAI, mean (S.D.)	3.03 (2.4)

[a]There were four children with duration of disease <6 months. [b]$n = 108$. JSpADA: Juvenile Spondyloarthritis Disease Activity; JADAS-10: juvenile arthritis DAS-10; ASDAS-ESR: Ankylosing Spondylitis Disease Activity Score-ESR; CHAQ: Childhood HAQ.

We could not test back mobility in 19 patients owing to active lower limb arthritis. Excluding these, 137 visits on 108 children were analysed.

Mean JSpADA score was similar between those who had radiographic sacroiliitis and those who did not (3.34 *vs* 2.28, $P = 0.15$). JSpADA scores showed no correlation with age or duration of disease. Mean JSpADA score was similar in boys and girls (3.05 *vs* 2.9, $P = 0.86$).

Construct validity

JSpADA score showed high correlation with PGA ($r = 0.87$, $P < 0.0001$) and PtGA ($r = 0.80$, $P < 0.0001$). It also showed high correlation with JADAS-10 ($r = 0.89$, $P < 0.0001$) and CHAQ ($r = 0.83$, $P < 0.0001$).

Discriminative capacity

Mean (S.D.) JSpADA score at visits with active disease ($n = 107$) was 3.23 (1.4) and inactive disease (PGA <1; $n = 30$) was 0.35 (0.5) ($P < 0.0001$). When the JADAS-10 cut-off for polyarticular JIA (inactive <0.7) was used mean JSpADA score was higher in active ($n = 112$) as compared with inactive ($n = 25$) disease (3.06 (1.5) *vs* 0.13 (0.35), $P < 0.001$). When the JADAS-10 cut-off for JIA (inactive <1) was used mean JSpADA score was higher in active ($n = 115$) as compared with inactive ($n = 22$) disease (3.06 (1.5) *vs* 0.18 (0.36), $P < 0.001$) [9].

Sensitivity to change

Out of 32 patients who had second visits, 3 could not be tested for back mobility and so were excluded from the analysis. Of the remaining 29 patients, 8 showed no change in disease activity, 15 had improvement and 6 had worsening. Mean change in JSpADA among those who improved as compared with those who worsened was significantly different (−2.1 (1.3) *vs* +1.5 (1.3), $P < 0.0001$). Standardized response mean was 0.48.

Internal consistency

Cronbach's α between JSpADA score and peripheral disease (arthritis, enthesitis, morning stiffness, patient assessment of pain and ESR) and axial disease (clinical sacroiliitis and back mobility) was 0.95 and 0.63, respectively. Only one patient had uveitis and so was not included in the analysis.

Performance of 7-variable JSpADA

As we could not measure back mobility in 19 children and only 16 children had abnormal back mobility, we analysed the performance characteristics of JSpADA without inclusion of back mobility. In 137 patient visits, 7-variable JSpADA showed good correlation with PGA ($r = 0.86$, $P < 0.0001$), PtGA ($r = 0.794$, $P < 0.001$), JADAS-10 ($r = 0.88$, $P < 0.001$), ASDAS-ESR ($r = 0.87$, $P < 0.001$), BASDAI ($r = 0.84$, $P < 0.001$) and CHAQ ($r = 0.80$, $P < 0.001$).

Performance of JADAS-10 and adult SpA scores

JADAS-10, BASDAI and ASDAS-ESR showed good construct validity, discriminative capacity and sensitivity to change (Table 2 and supplementary Table S2, available at *Rheumatology* online). JSpADA had good correlation with ASDAS-ESR ($r = 0.89$) and BASDAI ($r = 0.84$).

Discussion

We validated the JSpADA score in a single-centre prospective cohort of children with ERA and compared its performance with scores routinely used in adult SpA and JIA. Our cohort had some differences as compared with the cohort that was used in initial validation of the score: a higher male to female ratio, older age at assessment, more axial involvement, radiographic sacroiliitis and higher HLA-B27 positivity [6]. These differences suggest that our cohort of ERA resembled adult SpA. Possible reasons are late referrals to a tertiary care centre, social practices of providing health care to a male child more

Table 2 Comparison in performance of JSpADA with other disease activity measures in children with enthesitis-related arthritis

Validity domains	JSpADA	JADAS-10	BASDAI	ASDAS-ESR
Content validity (*r* value)				
PGA	0.87	0.93	0.80	0.85
PtGA	0.80	0.85	0.82	0.81
CHAQ	0.83	0.79	0.74	0.79
Pain	0.64	0.78	0.79	0.74
ESR	0.54	0.63	0.36	0.70
Discriminative capacity: ability to discriminate active and inactive disease	Yes	Yes	Yes	Yes
Sensitivity to change	Yes	Yes	Yes	Yes
Standardized response mean	0.48	0.36	0.52	0.47

PGA: physician global assessment; PtGA: patient global assessment; CHAQ: Childhood HAQ; JSpADA: Juvenile Spondyloarthritis Disease Activity Score; JADAS-10: juvenile arthritis DAS-10 joints; ASDAS-ESR: Ankylosing Spondylitis Disease Activity Score-ESR.

than a female child and more severe phenotype in India. A higher rate of HLA-B27 positivity has been shown previously in ERA patients from India [10].

Construct validity was determined by convergent validation, assessing relationships of JSpADA with three different instruments measuring similar constructs. JSpADA correlated well with other scores of disease activity in children such as JADAS-10, as well as with tools assessing function such as CHAQ. Correlation with CHAQ and PGA was stronger than that seen in the original validation study and this could be related to higher disease activity in our cohort.

Discriminative validity and responsiveness to change was assessed with the external criterion being PGA to determine active or inactive disease. The score differed significantly in those who improved *vs* those who worsened, suggesting good responsiveness to change. The high Cronbach's α of >0.9 denotes that the score has excellent reliability for peripheral disease. Even in the initial validation study Cronbach's α was 0.66 for total score, whereas it was 0.70 for peripheral disease alone [6]. This may be related to lower prevalence of axial disease in children with ERA.

Adult scores performed well in this study. JSpADA correlated well with BASDAI and ASDAS. BASDAI has been validated in children with ERA where it showed good correlation with joint count and CHAQ but not with enthesitis [11, 12]. However, both these studies had cohorts with a high prevalence of axial involvement. The advantage of JSpADA over BASDAI is the inclusion of enthesitis, arthritis and objective findings, as the reliability of entirely patient-related outcomes in children seems circumspect [13]. ASDAS has not been formally validated in ERA in any previous study.

Hip disease is common in JSpA patients and affects mobility and quality of life [14]. Patients with hip arthritis had higher CHAQ scores. JSpADA did not correlate with CHAQ, PGA or PtGA in these patients (data not shown). While the sample size of patients with hip arthritis in this study is small and precludes drawing conclusions, it will be interesting to assess performance after attributing higher weight to hip involvement in future studies.

To test back mobility, the child has to stand, which may be difficult in those with active lower limb arthritis. In almost 15% of children included in study, back mobility could not be tested. Exclusion of back mobility from score did not affect performance of the score. Whether the 7-variable score increases applicability to majority of patients needs to be tested in a larger cohort. Similarly, active uveitis is a relatively rare manifestation of ERA as was seen in our cohort; the value of uveitis in the score needs to be re-evaluated.

By validating the score in a prospective cohort, it was ensured that appropriate data were available for all subjects. The strengths of our study are a homogeneous population, recording of individual items and calculation of scores later to avoid bias in PGA. Limitations include small sample size, lack of information on time taken for doing JSpADA in the routine clinic setting and follow-up only in a subset of patients.

The JSpADA is an easy-to-perform instrument as all parameters can be easily assessed on routine clinical visits. About 40% of patients with juvenile SpA progress to AS in 10 years [15]. It would be useful in future to assess whether the same score can be used to follow up these patients into adulthood, thus obviating the need to change over to separate adult scores.

Thus to conclude, JSpADA is a good score for measuring disease activity in ERA. Potential areas of future study include: looking into exclusion of back mobility, to possibly improve its performance and applicability to all children, and assessment of time taken in a routine clinic. Finally, validation of the score in a prospective controlled trial will confirm its usefulness in a more structured environment.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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