

1. Title

Validation of Juvenile Spondyloarthritis Disease Activity Index (JSPADA) in a prospective cohort of Portuguese patients with juvenile spondyloarthritis.

2. Introduction

The term juvenile spondyloarthritis (SpA) refers to SpA that starts during childhood, until 16 years old. Under the newer International League of Associations for Rheumatology (ILAR) juvenile idiopathic arthritis (JIA) classification (1), most children with juvenile SpA fall into the categories of enthesitis-related arthritis (ERA), psoriatic arthritis, oligoarticular arthritis and undifferentiated arthritis.

Juvenile Arthritis Disease Activity Score (JADAS) is a composite score that have been used for monitoring disease activity in JIA, including patients with juvenile SpA (2). Although patients with juvenile SpA were included in the validation study of the JADAS, they represented a minority of the subjects (less than 1% of 4,363 subjects) (2). This instrument has not been validated in juvenile SpA and does not explicitly account for the unique disease activity features of the condition, such as axial disease and enthesitis. Despite the lack of a composite validated disease activity measure, investigators doing trials in juvenile SpA have traditionally used the ACR Pedi 30/50/70/90 and single measures, such as the active joint count, tender entheses count, physician and parent global disease activity assessments, C-reactive protein level, and the Childhood Health Assessment Questionnaire (CHAQ) (3,4).

Recently, a disease activity assessment tool was developed and validated for use in juvenile SpA, the Juvenile Spondyloarthritis Disease Activity Score (JSPADA) (5). JSPADA is a continuous disease activity measure for children with juvenile SpA that was retrospectively validated in a multicenter cohort of children (5). This index includes 8 items that are equally weighted and based primarily upon physician assessment. It specifically includes measure of axial symptoms and enthesitis, which have been shown to independently

predict poorer outcomes in these conditions (6). Each item is considered to be of equal importance (value =1) and the range of possible scores of JSPADA is 0 to 8, with higher scores indicating higher disease activity.

The JSPADA was originally validated retrospectively. Therefore, it needs to be validated in a prospective cohort. Cutoff values for defining inactive disease, minimal, moderate and high disease activity should also be determined.

3. Objectives

1. To validate the JSPADA in a prospective cohort of Portuguese patients with juvenile SpA.
2. To determine cutoff values of JSPADA for defining inactive disease, minimal, moderate and high disease activity in Juvenile SpA.

4. Methods

Study Design:

This is a multicenter, prospective, observational study, using data from the Rheumatic Diseases Portuguese Register (Reuma.pt).

Population:

Inclusion criteria: patients with less than 16 years with the diagnosis of juvenile SpA according to ASAS criteria registered in Reuma.pt. Patients with enthesitis-related arthritis (ERA), psoriatic arthritis, oligoarticular arthritis and undifferentiated arthritis are most likely to evolve to juvenile SpA. Patients with other diagnosis like inflammatory bowel disease associated arthritis and axial spondyloarthritis, that in the majority of cases are registered as undifferentiated arthritis, will also be included in the analysis. Patients with oligoarticular and undifferentiated JIA who do not evolve to Juvenile SpA will be excluded from the final analysis.

Exclusion criteria: Patients that do not complete the ASAS criteria for axial and peripheral SpA, and patients with other categories of JIA, besides ERA,

psoriatic arthritis, oligoarticular arthritis and undifferentiated arthritis. Patients without available data concerning disease activity measures required for JSPADA calculation will be excluded.

Variables

- We intend to insert in the section of Reuma.pt related to diagnosis of JIA, a new window named juvenile SpA, based on ASAS criteria of SpA, where the physician will register if the patient complete criteria for juvenile SpA. In the JIA categories ERA, psoriatic arthritis, oligoarticular arthritis and undifferentiated arthritis, we will insert 3 new items, needed to calculate JSPADA: 1) morning stiffness (greater than 15 minutes), 2) clinical sacroiliitis (defined as presence of 2 or more of the following: tenderness on examination, positive Patrick's or FABER test and inflammatory back pain) and 3) back mobility as modified Schober's test (less than 15/20 cm) (Table 1).
- We will insert the JAMAR (Juvenile Arthritis Multidimensional Assessment Report) questionnaire, for parent's (when children have less than 12 years old) and for patients (≥ 12 years old) in order to calculate the cutoff values of inactive disease, minimal, moderate and high disease activity in Juvenile Spa.
- A new window in Reuma.pt to register the presence of radiographic sacroiliitis will be inserted.

The following variables will be collected from the Reuma.pt database:

- Demographic characteristics (age, gender, ethnicity)
- Age at disease onset
- Age at diagnosis
- Disease duration
- HLA B27
- Antinuclear antibodies
- Erythrocyte Sedimentation Rate and C-reactive protein
- JADAS
- Number of swollen or tender joints

- Physician Global Assessment (measured on a 10 cm Visual Analog Scale)
- Parent/Patient Global Assessment (measured on a 10 cm Visual Analog Scale)
- Back mobility, as modified Schober's test for children (less than 20 cm).
- CHAQ

Statistical Analysis

For qualitative data, absolute and relative frequencies are presented. In case of quantitative data, mean and standard deviation are presented. Possible missing values will be replaced by imputed data.

For the validation of JSPADA, we will assess the Spearman's correlation between the items of the activity score of all the time-points and the following activity indexes: JADAS27 and BASDAI (when they are not already used to calculate them); as well as the correlation between the changes in the JSPADA score value between time-points, and the variation in the other scores. We will also obtain the discriminant validity by separating the individuals by ACRp response (non-responders/30 responders/50 responders/70 responders). The responsiveness will be evaluated by the Standardized Response Mean.

The 1st quartile of the score distribution and receiver operating characteristics curve analysis against external criteria will be used to obtain the cut-off values separating remission from minimal disease activity. External criteria will be the physician's perception of disease remission, as well as the patient's perception, JADAS27 < 1 in inactive disease, and JAMAR.

All analyses will be performed using Stata IC version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP), and the significance level will be set at 0.05

Expected size sample:

At the end of 2017, according to Reuma.pt Newsletter (2017), there were 663 patients with ERA, psoriatic arthritis, oligoarticular arthritis and undifferentiated arthritis. All of them are potentially eligible for this study, and we expect new patients to be included, once this is prospective study.

5. Expected results and limitations

We expect to fully characterize Portuguese patients with juvenile SpA and to validate JSPADA in Portuguese patients with juvenile SpA. JSPADA items are easily assessed during normal routine care so this tool will be feasible for both clinical care and research. The prospective nature of the study will take a long period (at least a year) to collect data and to write the final report but will be a valuable tool to evaluate disease activity in children with Juvenile Spa.

7. Calendar of Tasks:

	May 2018	July 2018	July 2019	December 2019
- Insert JSPADA in ReumaPt				
- Collet data		✓	✓	
- Final report and publication				✓

8. Proponent

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9. Research Team

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10. Funding and Conflicts of Interest

There are no conflicts of interest or external funding to declare in this study.

11. Bibliography

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Table 1. Juvenile Spondyloarthritis Disease Activity Score (JSPADA) versão Portuguesa

Item	Score* [†]
<p>1. Contagem de articulações ativas: inclui quaisquer articulações atingidas, com um máximo de 10. Não existem pesos diferenciados para as diferentes articulações.</p>	0 articulações= 0
	1-2 articulações= 0.5
	>2 articulações = 1
<p>2. Contagem de entesites ativas: inclui quaisquer entesites atingidas, com um máximo de 10. Não existem pesos diferentes para as diferentes entesites.</p>	0 entesites= 0
	1-2 entesites= 0.5
	>2 entesites= 1
<p>3. Dor: dor referida pelo doente na última semana, registada numa escala visual analógica (0-10).</p>	0= 0
	1-4= 0.5
	5-10= 1
<p>4. VS ou PCR relacionadas com atividade da</p>	normal = 0

Item	Score* [*]
espondilartrite juvenil.	1-2 vezes o normal= 0.5
	>2 vezes o normal= 1
5. Rigidez matinal: rigidez matinal com duração superior a 15 minutos.	Ausente= 0
	Presente= 1
6. Sacroileíte clínica: definida pela presença de 2 ou mais das seguintes: dor à palpação, teste de FABER ou Teste de Patrick positivos e dor lombar inflamatória [#] .	Ausente= 0
	Presente= 1
7. Uveíte: Presença de uveíte (incluindo aguda/sintomática e crónica/assintomática).	Ausente= 0
	Presente= 1
8. Mobilidade lombar: Mobilidade lombar diminuída, definida como teste de Schober modificado < 20 cm.	Normal= 0
	Anormal = 1

Legenda. Items do JSPADA.

* O índice é obtido somando o total em cada item (máximo por item=1).

[#]Não existem critérios validados de dor inflamatória na criança. Neste índice, a definição de doença lombar inflamatória foi adaptado dos critérios ASAS de adultos e

foi definido pela presença de 3 dos seguintes critérios: 1) início insidioso, 2) melhora com exercício, 3) sem melhora com o repouso, 4) dor noturna (com melhora quando se levanta). O intervalo deste índice é de 0 a 8, com pontuações mais elevadas indicando maior atividade da doença.