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The impact of morning stiffness duration on the definition of clinical inactive disease in juvenile idiopathic arthritis

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Abstract

Objective. To investigate the impact of morning stiffness (MS) on parent disease perception in children with juvenile idiopathic arthritis (JIA) with clinical inactive disease (CID).

Methods. 652 visits in which patients fulfilled 2004 or 2011 Wallace criteria for CID were examined. Parent-reported outcomes were compared among patients with no MS or with MS < or ≥ 15 minutes.

Results. Among 652 visits with CID by 2004 criteria, no MS was reported in 554 visits (85%), MS < 15 minutes in 53 (8%), and MS ≥ 15 minutes in 45 (7%). The frequency of altered physical function, health-related quality of life, and well-being, pain and disease activity visual analog scales was proportionally greater from patients without MS to those with longer MS. The frequency of parent subjective rating of disease state as remission was 87.7%, 58% and 27.7% among patients with no MS, MS < 15 minutes and MS ≥ 15 minutes, respectively.

Conclusion. Our results suggest that a change in 2011 CID criteria to require absence of MS should be considered.

Key indexing terms

Juvenile idiopathic arthritis, morning stiffness, remission, pediatric rheumatic diseases

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Short running footline

Morning stiffness in JIA

Conflicts of interest

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Introduction

Morning stiffness (MS) is a major symptom of active disease in children with juvenile idiopathic arthritis (JIA), and may have profound impact on physical function and health-related quality of life (HRQL) (1,2).

In the past two decades there have been remarkable advances in the management of JIA, which comprise the advent of medications that are capable of inducing extended periods of complete disease quiescence. Owing to the key importance of MS on child well-being, it would be important to ascertain whether the achievement of clinical remission is accompanied by its abrogation.

Assessment of MS was not incorporated in the preliminary criteria for clinical inactive disease (CID) in JIA (thereafter called "2004 CID criteria") (3). By these criteria, CID requires the simultaneous presence of: 1) no active joints; 2) absence of systemic symptoms attributable to JIA; 3) absence of active uveitis; 4) normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); and 5) a physician global assessment indicating no disease activity.

A 2011 revision of 2004 CID criteria (thereafter called "2011 CID criteria") specified the definition of inactive uveitis, acknowledged that ESR or CRP can be elevated for reasons unrelated to JIA, and added the presence of MS lasting ≤ 15 minutes (4). This cut-off was based on the belief that MS ≤ 15 min may represent damage from previous active disease or be due to reasons other than active inflammation. However, any cut-off is arbitrary and it is unclear whether a duration of MS ≤ 15 min is equivalent to no MS, particularly when it comes to parent-reported outcomes (PROs).

The present study compared PROs of children with JIA who met 2004 or 2011 CID criteria and had no MS, MS < 15 minutes, or MS ≥ 15 minutes.

Patients and methods

Patient selection. Two datasets including 1208 children with JIA (5), who underwent a total of 3380 visits were examined to identify all visits in which patients fulfilled the 2004 or 2011 criteria for CID. In case a patient met CID criteria in more than 1 visit, only the first visit was retained. The first dataset (named EtICA dataset) included 422 patients treated with etanercept who underwent a single cross-sectional visit (6). The second data set (named Gaslini dataset) was composed of 816 unselected patients followed at authors' center between September 2013 and May 2018.

The study protocol was approved by the Ethics committee of Liguria, Genoa, Italy (session of June 18, 2018, meeting minutes no. 10/2018).

Clinical assessments. At each visit, the caring physician made a standardized joint examination (7) and rated the overall disease activity on a 21-numbered circle visual analog scale (0 = no activity; 10 = maximum activity) (8).

Before physician visit, a parent (or guardian) completed the Italian-language parent proxy-report version of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR (9). This questionnaire incorporates all main PROs, including physical function, HRQL, overall well-being, pain, level of disease activity, MS, subjective assessment of disease status and satisfaction with illness outcome.

Informed consent to original data collections was provided by parent/guardian for all patients.

Assessment of MS. The JAMAR includes a question which asks the parent whether the child had joint stiffness upon waking up over the previous week, and is to be answered as "yes" or "no". If the answer is yes, then the parent is asked how long does MS last by marking one of these

intervals: < 15 minutes; 15-30 minutes; 30-1 hour; 1-2 hours; > 2 hours. For the purposes of the analysis, the time intervals were dichotomized as < 15 minutes or ≥ 15 minutes.

Assessment of inactive disease. The presence of inactive disease was assessed by both the 2004 CID criteria (3) and the 2011 CID criteria (4) (see above). No imputation of missing data was performed. In case both ESR and CRP or ophthalmologic assessment were not available, the disease state was defined as CID is all remaining criteria were met.

Results

A total of 652 visits in which patients met either 2004 or 2011 CID criteria, or both were identified. The main clinical features of these patients are presented in Table 1. As expected, patients in the EtICA dataset, which were all treated with etanercept, had a higher frequency of polyarthritis and extended oligoarthritis than those in the Gaslini dataset, which was composed of patients followed in routine care. They were also older and had longer disease duration than those in the Gaslini dataset. Because the data by level of MS were comparable between the two datasets (see Supplementary Table S1), in the study analyses they were combined.

Among the 652 visits/patients with CID by 2004 or 2011 criteria, no MS was reported in 554 visits (85%), MS < 15 minutes in 53 (8%), and MS ≥ 15 minutes in 45 (7%). All 652 patients met the 2004 CID criteria, which do not include assessment of MS, whereas 45 patients (6.9%) did not meet the 2011 CID criteria because of MS ≥ 15 minutes.

The demographic and clinical features of patients with no MS and MS < 15 or ≥ 15 minutes were comparable (Table 2). As shown in Table 3, patients with MS of any duration had a higher frequency of abnormality of all PROs than patients with no MS. Patients with MS ≥ 15 minutes had a higher frequency of abnormality of most PROs than patients who had MS < 15 minutes.

The frequency of altered PROs by parent-assessed disease state and by presence and duration of MS in in relation to parent-assessed disease state is presented in Supplementary Tables S2, S3 and S4, respectively.

Discussion

We found that 15% of patients meeting the 2004 CID criteria had MS and that 8.1% of patients meeting the 2011 CID criteria had MS < 15 minutes. Patients with MS had worse PROs than those without MS. Most PROs were more impaired in patients with MS ≥ 15 minutes than in patients with MS < 15 minutes. The observed disparities did not depend on differences in disease characteristics and severity. These findings indicate that the presence of MS is associated with worse parent perception of health and disease status of children with JIA who are classified as having CID by formal definitions.

As emphasized previously (10), a major problem with 2004 CID criteria is that they are only based on physician-centered measures and an acute phase reactant and neglect PROs. Integration of patient and parent perspective in the clinical evaluation is important because achievement of CID usually prompts the physician to start decrease or even to discontinue the treatments. Concordance with physician assessment of disease state may facilitate adherence to therapeutic decisions. This limitation was partially amended by inclusion of MS assessment in 2011 CID criteria, which, however, consider MS ≤ 15 minutes compatible with the state of CID.

Our results indicate that most parents may not consider their child's disease in remission in the presence of MS, even of a short duration. It should be acknowledged, however, that 58% of parents of children with MS ≤ 15 minutes still judged their child to be in remission and 85% of them were satisfied with illness outcome. On the other hand, 30% of parents of children with no MS rated the VAS disease activity > 0 and around 12% stated that their child had persistent activity

or disease flare. Thus, although our findings suggest that the 2011 CID criteria should be modified by stating that no MS should be present, studies in different patient populations and prospective validation are needed before considering this change.

Our study should be interpreted in the light of some caveats. Our findings may not be generalizable as all parents and patients lived in Italy. Parent perception of disease burden has been shown to vary across ethnic and cultural environments (11). We did not investigate the influence on parent evaluations of non–disease-related factors, such as depression, coping strategies, anxiety, and family functioning, or persistent pain symptoms independent of joint inflammation. We recognize that requiring absence of MS for the definition of CID does not imply that parent report of brief (e.g. 5 minutes) MS is highly sensitive and specific to detect the degree of activation of the inflammatory process in JIA. In the clinic, it is frequent to see patients who have no inflammatory arthritis whatsoever, yet report brief MS. Likewise, requiring no MS as part of CID would neither prevent patients with brief MS having their treatment “inappropriately” tapered, nor result on patients with 5 minutes of MS, but no clinical evidence of disease activity, having their anti-rheumatic medications “appropriately” switched or increased to “reach the target”.

In conclusion, we found that the presence of MS in JIA patients classified as having CID by formal definitions is associated with worse parent perception of child’s health and disease status. Our observation indicates that the 2011 CID criteria may be preferred over the 2004 version, and that a change in the former criteria to require absence of MS should be considered.

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Table 1. Demographic features and ILAR categories of study patients

	All patients N = 652	EtICA dataset N = 199	Gaslini dataset N = 453	*P*
Females (%)	510 (78.2%)	152 (76.4)	358 (79.0)	0.51
ILAR category (%)				< 0.001
Systemic arthritis	24 (3.7)	4 (2.0)	20 (4.4)	
Persistent oligoarthritis	250 (38.3)	34 (17.1)	216 (47.7)	
RF-negative polyarthritis	130 (19.9)	60 (30.2)	70 (15.5)	
Extended oligoarthritis	185 (28.4)	73 (36.7)	112 (24.7)	
RF-positive polyarthritis	11 (1.7)	6 (3.0)	5 (1.1)	
Psoriatic arthritis	16 (2.5)	8 (4.0)	8 (1.8)	
Enthesitis related arthritis	19 (2.9)	12 (6.0)	7 (1.5)	
Undifferentiated arthritis	17 (2.6)	2 (1.0)	15 (3.3)	
Median [IQR] disease duration, years	4.7 [2.3, 8.7]	7.1 [4.1, 11.1]	3.8 [1.7, 7.4]	< 0.001
Median [IQR] age at visit, years	9.7 [5.4, 13.9]	13.2 [8.4, 16.4]	8.3 [4.6, 12.3]	< 0.001
Median [IQR] age at disease onset, years	2.9 [1.8, 5.9]	3.3 [1.9, 7.4]	2.7 [1.7, 4.8]	0.005

ILAR = International League of Associations of Rheumatology; RF = rheumatoid factor; IQR = interquartile range.

Table 2. Demographic and clinical features by presence and duration of morning stiffness

	Patients meeting 2004 CID criteria			
	Patients meeting 2011 CID criteria			
	No MS	MS < 15 min	MS ≥ 15 min	*P*
	N = 554	N = 53	N = 45	
Females (%)	431 (77.8)	43 (71.1)	36 (80.0)	0.82
ILAR category (%)				0.96
Systemic arthritis	20 (3.6)	2 (3.8)	2 (4.4)	
Persistent oligoarthritis	219 (39.5)	16 (30.2)	15 (33.3)	
RF-negative polyarthritis	153 (27.6)	19 (35.8)	13 (28.9)	
Extended oligoarthritis	109 (19.7)	10 (18.9)	11 (24.4)	
RF-positive polyarthritis	10 (1.8)	0 (0.0)	1 (2.2)	
Psoriatic arthritis	14 (2.5)	1 (1.9)	1 (2.2)	
Enthesitis related arthritis	15 (2.7)	3 (5.7)	1 (2.2)	
Undifferentiated arthritis	14 (2.5)	2 (3.8)	1 (2.2)	
Median [IQR] disease duration, years	4.6 [2.3, 8.8]	3.9 [1.9, 7.3]	6.7 [3.1, 9.1]	0.17
Median [IQR] age at visit, years	9.7 [5.5, 13.8]	8.3 [4.8, 11.8]	10.6 [6.9, 15.2]	0.23
Median [IQR] age at disease onset, years	2.8 [1.7, 5.8]	3.2 [1.9, 5.5]	2.9 [1.9, 7.0]	0.55
Patients with no. tender joints > 0	35 (6.3)	3 (5.7)	5 (11.1)	0.442
Patients with no. restricted joints > 0	111 (20.0)	8 (15.1)	6 (13.3)	0.401

Data are the number (percentage) unless otherwise indicated.

CID = clinical inactive disease; MS = morning stiffness; ILAR = International League of Associations of Rheumatology; RF = rheumatoid factor; IQR = interquartile range.

Table 3. Parent-reported outcomes by presence and duration of morning stiffness

	Patients meeting 2004 CID criteria			
	Patients meeting 2011 CID criteria			
	No MS	MS < 15 min	MS ≥ 15 min	
	N = 554	N = 53	N = 45	
Patients with physical function score[a] > 0	104 (18.8)	24 (45.3)	35 (77.8)	< 0.001
Patients with HRQL PhH score[b] >1 SD above the mean of healthy children	57 (10.4)	22 (42.3)	35 (79.5)	< 0.001
Patients with HRQL PsH score[b] >1 SD above the mean of healthy children	43 (7.9)	11 (21.6)	16 (36.4)	< 0.001
Patients with VAS well-being[c] > 0	208 (37.5)	41 (77.4)	40 (88.9)	< 0.001
Patients with VAS pain[c] > 0	137 (24.7)	38 (71.7)	31 (68.9)	< 0.001
Patients with VAS disease activity[c] > 0	167 (30.1)	43 (81.1)	39 (86.7)	< 0.001
Parent subjective rating of disease status				< 0.001
Remission	476 (87.7)	29 (58.0)	12 (26.7)	
Persistent activity	44 (8.1)	13 (26.0)	18 (40.0)	
Flare	23 (4.2)	8 (16.0)	15 (33.3)	
Parents satisfied with their child's illness outcome	515 (94.3)	45 (84.9)	24 (54.5)	< 0.001

Data are the number (percentage)

CID = clinical inactive disease; MS = morning stiffness; HRQL = health-related quality of life; PhH = Physical Health; PsH = Psychosocial Health; SD = standard deviation; VAS = visual analog scale

[a]Score ranges from 0 (no disability) to 30 (maximum disability)

[b]Score ranges 0–15, higher scores indicate worse HRQL. We previously found that the mean (SD) score of the PhH and PsH subscales in 801 Italian healthy children was 0.8 (1.2) and 1.8 (1.7), respectively (Bertamino M et al. Unpublished observation).

[c]All VAS range from 0 (best) to 10 (worst)