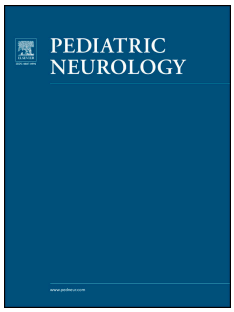

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Development and preliminary validation of an Electromyography-scoring protocol for the assessment and grading of muscle involvement in patients with juvenile idiopathic inflammatory myopathies

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ABSTRACT

Introduction: We performed a pilot study in order to investigate the feasibility of an Electromyography (EMG)-scoring protocol for the assessment of disease activity in juvenile idiopathic inflammatory myopathies (JIIM).

Methods: Children with JIIM followed up in a tertiary level care center underwent standardized clinical, laboratory and EMG assessment. An EMG-scoring protocol was devised by a consensus panel including a pediatric neurophysiologist and two pediatric rheumatologists, based on a combined score obtained as the sum of: 1) presence of denervation signs (fibrillation potentials) and 2) motor unit remodeling (mixed pattern of short and long duration motor unit action potentials). The EMG-scoring protocol was then validated following the Outcome Measures in Rheumatoid Arthritis Clinical Trials filter for outcome measures in rheumatology and the consensus-based standards for the selection of health measurement instruments methodology.

Results: Thirteen children (77% females) were included in the study, with a median age of 10 years (IQR 7-17 years) and median disease duration of 11.8 months (IQR 2.1-44.5). A total of 39 EMG examinations were evaluated. A strong positive association between a standardized tool for muscle strength assessment and the combined score was observed. No significant associations were found with both creatine kinase and erythrocyte sedimentation rate levels.

Discussion: Our EMG-scoring protocol is the first standardized and reproducible tool for the neurophysiologic evaluation and grading of muscle involvement in patients with JIIM and could provide relevant additional information in the assessment and follow-up of these rare conditions.

Key words: Myopathies, electromyography, juvenile dermatomyositis, juvenile polymyositis

INTRODUCTION

Idiopathic Inflammatory Myopathies (IIM) consist of a group of rare and highly heterogeneous diseases characterized by a systemic inflammatory process. Juvenile Dermatomyositis (JDM) is the commonest childhood IIM, seen in 85% of pediatric IIM cases, while Juvenile Polymyositis (JPM) consists of less than 5% of cases.[1] One of the major challenges in the clinical management of the patients is to accurately assess disease activity to optimize therapeutic strategies.

Pediatric electromyography (EMG) is an invaluable diagnostic test for the investigation of neuromuscular diseases. [2] According to the Bohan and Peter criteria for JDM and JPM, EMG has a prominent role in supporting diagnosis in juvenile IIM (JIIM).[3,4] EMG may also provide relevant information for the assessment of progression of the disease and response to treatment in patients with myopathies.[5]

Recently, there has been a great deal of effort to devise quantitative measures for the assessment of disease activity and health status of children with rheumatologic disorders.[6] However, no validated scoring protocol for the evaluation and grading of EMG in patients with IIM has been provided so far. Pediatric EMG is a valuable investigative tool for the specialists in neuromuscular disorders, but it remains a daunting technical challenge to some practitioners[7], and minimize both invasiveness and duration of the procedure is critical in pediatric setting.

In the present study, we developed and investigated the contribution of a new EMG-score in the assessment of the inflammatory burden, and provide a preliminary evidence of its validity on a subset of JIIM patients followed in a tertiary level care center.

METHODS

Study sample

All patients with diagnosis of JDM or JPM according to the Bohan and Peter criteria[3,4] consecutively seen in our Centre during the period January 2015 to December 2019 were included in the study. Consecutive visits, in which an EMG assessment was performed, were considered for each patient.

Simultaneous clinical assessment in all patients included standardized muscle strength score (MSS) measurement by the Manual Muscle Testing 8 (MMT8) (score range 0 = worst to 80 = best) [8] or the hybrid MMT8/ Childhood Myositis Assessment Scale CMAS (hMC) (score range 0 = worst to 100 = best)[9]. In order to uniform the MMT8 score to the hMC score, MMT8 was converted to percentile to obtain a score range for both measures from 0 = worst to 100 = best.[10]

Laboratory measurements, including creatine kinase enzyme (CK) and erythrocyte sedimentation rate (ESR) determination, were collected if performed within 15 days before clinical assessment. Standardized assessment of dermatologic involvement was not considered in this study because cutaneous extension is not directly related to muscular disease activity. [9,10]

This study was approved by Ethics Committee of our Institute.

EMG Procedure

EMG studies were performed in the Department of Neurology, by a single neurophysiologist with long-term experience in evaluation of JIIM (AMC), in order to avoid the possible heterogeneity in exam execution and results interpretation. Studies were conducted in the conscious, non-sedated state. All studies followed the departmental protocol for investigation of myopathies, including nerve conduction studies (one sensory and motor nerve), and needle EMG assessment (one proximal and distal muscle of the upper and lower limbs) on the dominant side. The neurophysiologist was blinded to the results of muscle strength testing and laboratory results.

Development of the EMG-score

The EMG-score was devised by a consensus panel consisting of a pediatric clinical neurophysiologist (AMC) and two pediatric rheumatologists (GF, FM), with high expertise in clinical management of JIIM, after a review of the most relevant literature.

EMG in IIM is characterized by muscle membrane irritability signs (fibrillation potentials), especially in proximal muscles.[11,12] The degree of abnormal muscle membrane irritability reflects the ongoing disease activity.[13] Therefore, the panel considered the quantity of fibrillation potentials as a surrogate of the inflammatory burden. Although short duration motor unit action potentials (MUAPs) are commonly seen in inflammatory and necrotizing myopathies, some reinnervation and motor unit remodeling may also occur overtime and a mixed pattern of short and long duration MUAPs may be seen in chronic myopathies.[13] A mixed pattern was also reported in the (sub)acute stages of IIM, and treatment with corticosteroids resulted in less EMG abnormalities.[14] Therefore, the panel considered the presence of a mixed pattern as a surrogate of motor unit remodeling.

The pattern of muscle weakness in IIM is nonselective, and the weakness is diffuse although it is usually more severe in the shoulder and pelvic girdle muscles.[15] Evaluation of a patient with myopathy should include selected proximal muscles as well as distal muscles.[16] Sampling four different regions of the muscle through a single skin insertion has been suggested, as consistently as the child's cooperation allowed.[17] The panel identified four muscles (*deltoid* and *extensor digitorum communis* for the upper limb, and *vastus medialis* and *tibialis anterior* for the lower limb) on the dominant side for needle EMG examination to be scored. Four different regions of each muscle were sampled, whenever possible. Although paraspinal muscles show the most prominent features on EMG examination,[18] their investigation should be considered in patients with suspected IMM in which abnormalities are not found in limb muscles.[5] Therefore, the panel decided not to include their evaluation, in order to minimize the time required for the EMG assessment and improve its feasibility in young patients.

A score for both muscle inflammatory burden and motor unit remodeling was attributed by the neurophysiologist who performed the EMG. The inflammatory burden for each muscle were scored using a 0-2 point scale (0= fibrillation potentials in > 50% of the sites analyzed 1= fibrillation potentials in ≤ 50% of the sites analyzed; 2=no fibrillation potentials). The degree of motor unit remodeling in every muscle was also scored using a 0-2 point scale (0= short duration MUAPs; 1= mixed pattern in ≤ 50% of the sites analyzed; 2= mixed pattern in > 50% of the sites analyzed). The total score for muscle inflammatory burden was obtained as an arithmetical sum of all muscle scores, ranging from 0 (elevated muscle inflammation) to 8 (no muscle inflammation). The total score for motor unit remodeling was obtained as an arithmetical sum of all muscle scores, ranging from 0 (no reinnervation) to 8 (maximal reinnervation). Finally, we summed the two scores to obtain the combined score (range: 0-16)

Validation procedures

The EMG-score validation was performed following the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) filter for outcome measures in rheumatology[19,20] and the COSMIN methodology.[21]

Feasibility or practicality was determined by addressing the issues of brevity, simplicity and easy scoring.[22] Timing of the examination was evaluated for each examination. The score was developed considering the basic electrophysiological features commonly used in the clinical practice. Face and content validity were established by determining that:1) the items refer to relevant aspects of the construct to be measured (i.e., disease activity), 2) the items are relevant to a pediatric population with JIIM, 3) the items shave good discriminative and evaluative properties, and 4) the items comprehensively reflect, altogether, the construct to be measured. In addition, the limitations of designs and methods of the study were acknowledged. Content validity was assessed by the members of the panel.

Construct validity was assessed by calculating the correlations between the EMG-score, the abovementioned clinical outcome measures (MSS) and muscle-related laboratory findings.

Criterion validity is a benchmark to evaluate how the study results fit with the gold standard. However, so far there is no universally validated gold standard measure by which the validity of the EMG-score can be tested. Therefore, a convergent construct validity was investigated. Construct validity is a validation method to evaluate if the EMG-score (construct) is convincing related to priori prediction measurements. Since the EMG-score was devised to measure the burden of disease activity, we predicted that:1) correlation with the measures of muscle strength was expected to be moderate as they depend not only on the disease activity, but also on patient compliance during execution of the tasks; 2) correlations with CK and acute phase reactants (i.e. ESR) were predicted to be low since these values do not always correlate with muscle inflammation activity.[8]

Discriminative ability by comparing EMG-scores between patients with JIIM and healthy controls was not assessed for ethical reasons.

Responsiveness to change could be evaluated only in a small subgroup of patients for which multiple EMG examinations over time were available.

Statistical analysis

Quantitative data are presented as medians and interquartile ranges and categorical data as absolute numbers and percentages.

To take into account intra-subject correlation we fitted univariate random intercept linear regression models to analyze the relationship between MSS (dependent variable) and EMG, CK, ESR, and disease duration (independent variables) at each visit [23] In case of fibrillation potentials and mixed pattern, a better fit to the observed data was obtained by adding a quadratic term to the linear component. Results of quadratic regression models were visualized in graphs showing the fitted

lines and their 95% confidence bands. Statistical analyses were adjusted for patients with repeated assessments.

The responsiveness to change of the EMG-score between the diagnostic examination and the latest examination was assessed by computing the standardized response mean (SRM), calculated as the mean change in score divided by the SD of an individual's change in score. According to Cohen,[24] the threshold levels for the SRM were defined as follows: ≥0.2–0.4 = small, ≥0.5–0.7 = moderate, and ≥0.80 = good.

Interrater reliability and internal consistency were not evaluated in this preliminary validation phase because all examinations and scores were assessed by a single operator and they will be considered for a future prospective multicentric study. Test-retest reliability was not evaluated because of the invasiveness of the EMG examination.

Statistical analyses were performed with Stata 16 (StataCorp. 2019).

RESULTS

Study sample

We included in the analysis 13 children (77% females) with a median age of 10 years (IQR 7-17 years) and median disease duration of 11.8 months (IQR 2.1-44.5). Demographic and clinical features of the population analysed are summarized in Table 1.

A total of 39 EMG examinations were performed over a 4 years period; 8 patients had one single assessment, while 5 patients had repeated examinations (range 2-7).

In 8 patients the first visit was performed at disease onset, out of therapy or within 5 days from the beginning of medical treatment (glucocorticoids associated with methotrexate and/or cyclosporine with or without intravenous immunoglobulins, as per standard of care). In the rest of patients, the

first visit and EMG were performed once the patient was referred to our center from other hospitals, on systemic glucocorticoid treatment.

At first examination, median MSS score was 81 (IQR 41-90), median fibrillation potential score was 5 (IQR 4-8), median neurogenic MUAPs score was 0 (IQR 0-2), and the combined score had a median of 6 (IQR 4-8).

Feasibility

The EMG-score resulted easy to compute. The time to complete the score ranged from 10 to 20 minutes depending on age and compliance of the single child.

Face and content validity

As stated above, content validity was established by the members of the panel who devised the score and assessed face validity.

Construct validity

In crude analyses, we found a strong positive association between MSS and both fibrillation potential scores (+7.7 MSS points per each fibrillation potential score point), and mixed pattern score (+5.7 MSS points per each neurogenic MUAPs score point). The combined score was also strongly associated with MSS (+4.1 MSS points per each combined score point) (Table 2). A better fit was obtained by fitting a quadratic regression line, as shown in Figure 1. No significant associations were found between MSS and both CK and ESR, while disease duration showed a strong positive association. These findings were confirmed by a multivariable analyses adjusted for sex and age (Table 2).

Responsiveness to change

Five patients had multiple EMG examinations over time and the responsiveness to change was assessed as the Standardized Response Mean (SRM) between the examination, when the patients were out of treatment or within 5 days from the treatment beginning, and the latest electrophysiological assessment available, performed during ongoing treatment. The SRM for the EMG-score was 0.59, showing a moderate responsiveness to change.

DISCUSSION

Our study represents the first application of an EMG-scoring protocol to a population of JIIM patients to better assess global inflammatory burden and integrate clinical examination and laboratory findings.

The role of EMG in JIIM has diminished considerably in the last years, due to its invasiveness and difficult cooperation of very young children, as well as marked increase in the use of muscle magnetic resonance imaging (MRI).[25] However, adverse perceptions of the level of discomfort with EMG, which pain is not different from venipuncture, as well as heterogeneity in expertise of neurophysiologists in performing and interpreting the EMG, have probably further limited its widespread use in pediatric practice.[17] Furthermore, MRI is expensive, not widespread available and requires sedation in younger children.[25]

Pediatric EMG is very sensitive (91%) in detecting myopathic disorders in children, with a specificity of 67%.[26] The presence of spontaneous activity on needle EMG is helpful in narrowing the differential diagnosis.[13] Abnormal spontaneous activity in myopathy may be caused by damage to the distal part of the motor nerve fiber,[16] and its presence is expected in active myositis.[13] Fibrillation potentials are often referred to as denervating potentials, and they indicate the presence of muscle inflammation or necrosis.[13] Our study confirmed that fibrillation potentials can be

considered a marker of active myositis, and should be included in the assessment of disease activity in patients with JIIM.

Some reinnervation may occur overtime, and a mixed population of short and long duration MUAPs may be seen in sub(acute) and chronic IIM. [13,14] In contrast with spontaneous activity, the possible role of mixed pattern during voluntary muscle activity the course of IIM has not been emphasized in the literature. Our study suggested that evaluation of MUAPs changes over time is another factor to consider in the management of patients with JIIM.

In clinical practice, in our cohort of patients, EMG contributed to optimize treatment strategy when combined with standardized clinical examination, muscles enzymes, and muscle MRI

Our study should be viewed in the light of certain limitations. First of all, the validation procedure was performed on a small population. However, the small number is consistent with the rarity of JIIM. Moreover, our sample represent the entire population of JIIM patients in follow-up at our center, and are likely representative of the patients seen in most tertiary pediatric rheumatology centers. Another limitation is the lack of a second-operator assessment, that limited our possibility to evaluate the interrater reliability and the internal consistency of the tool.

In conclusion, we have devised the first scoring EMG protocol for the evaluation and grading of muscle involvement in patients with JIIM, and we have provided a preliminary evidence of its validity. To note, evaluation of the ability of the EMG-score in discrimination between inflammatory myopathies and other conditions was beyond the scope of this paper, thus its role in the diagnostic work-up could not be assessed. To foster regular quantitative assessment in daily practice, there is a need for tools that are simple, easy to administer and quick to score. This objective should be achieved without compromising their integrity and capacity to capture the entire range of the construct assessed. In validation analysis, the EMG-score was found to be feasible and to possess face and content validity, good construct validity and moderate responsiveness to change.

Application of our scoring EMG protocol in larger patient cohorts is deserved to further assess its performance.

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Disclosure of conflict of interest

The authors declare non conflict of interest related to this study.

Patient and public involvement

All information from patients is sufficiently anonymized. Patients cannot be traced.

Data availability statement

All data related to the manuscript are available at authors' center by request from any qualified investigator.

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Table 1. Baseline demographic and clinical characteristics of patients

	Patients with juvenile idiopathic inflammatory myopathy N 13
JIIM clinical classification	
Juvenile Dermatomyositis, n (%)	11 (85%)
Juvenile Polimyositis, n (%)	2 (15%)
Female, n (%)	10 (77%)
Age at baseline, years	10 (7-17)
Age at disease onset, years	6.5 (3.7-9.1)
Disease duration, months	11.8 (2.1-44.5)
MSS value[#]	81 (41-90)
CK, U/l[#]	112 (71.5-520)
ESR, mm/h[#]	24 (13-30)
Fibrillation potentials score[#]	5 (4-8)
Mixed pattern score[#]	0 (0-2)
Combined score[#]	6 (4-8)

Except where indicated otherwise, data are median (IQR). [#] Data refer to the total of episodes

evaluated (N=39)

MSS = Muscle streght score, evaluated by Manual Muscle Testing 8 (MMT8) (score range 0 = worst to 80 = best) or hybrid MMT8/ Childhood Myositis Assessment Scale CMAS (hMC) (score range 0 = worst to 100 = best). In order to uniform the MMT8 score to the hMC score, MMT8 was converted to percentile in order to obtain a score range for both measures from 0 = worst to 100 = best; CK = Creatinine Kinase; ESR = Erythrocyte Sedimentation Rate

Table 2. Results of random intercept linear regression analyses on the relationship between muscle streght score (dependent variable), and electromyography, creatinine kinase, erythrocyte sedimentation rate, and disease length (independent variables) at each visit.

Variable	Slope	95% confidence interval	P-value
Crude analysis			
Fibrillation potentials score	+7.7	+5.4, +9.9	<0.001
Mixed pattern score	+5.7	+3.1, +8.4	<0.001
Combined score	+4.1	+2.9; +5.4	<0.001
Log10 CK, U/l	-9.6	-24.4, +5.3	0.21
ESR, mm/h	+0.04	-0.4, +0.5	0.87
Disease duration, years	+5.8	+1.8, +9.8	0.005
Multivariable analysis, adjusted for sex and age			
Fibrillation potentials score	+7.7	+5.4, +9.9	<0.001
Mixed pattern score	+5.8	+3.0, +8.7	<0.001
Combined score	+4.2	+2.9, +5.6	<0.001
Log10 CK, U/l	-5.7	-20.1, +8.8	0.44

ESR, mm/h	-0.2	-0.8, +0.3	0.41
Disease duration, years	+10.4	+5.3, +15.6	<0.001

CK = Creatinine Kinase; ESR = Erythrocyte Sedimentation Rate

Figure legend

Figure 1. Relationship of the combined electromyography (EMG) score with muscle strength score (MSS).

MSS was evaluated by Manual Muscle Testing 8 (MMT8) (score range 0 = worst to 80 = best) or hybrid MMT8/ Childhood Myositis Assessment Scale CMAS (hMC) (score range 0 = worst to 100 = best). In order to uniform the MMT8 score to the hMC score, MMT8 was converted to percentile in order to obtain a score range for both measures from 0 = worst to 100 = best.

Solid line: fitted linear random-intercept regression line; dashed lines: 95% confidence bands.