Feasibility of Quantitative Sensory Testing in Juvenile Idiopathic Arthritis.

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Abstract

Background Juvenile Idiopathic Arthritis (JIA) is a childhood-rheumatic disease with pain as a major complaint. Very few data exist on sensory thresholds changes at the knee in JIA, a location in which inflammation often manifest. We determined whether JIA is associated with sensory threshold changes at the knee by using Quantitative Sensory Testing (QST) and established reference values at the knee of children.

Methods 16 JIA patients aged 9-18 years with one affected knee and a patient-reported pain (VAS)>10 on a 0-100 scale, and 16 healthy controls completed the study and were included for the analysis. QST was assessed in compliance with the DFNS standard. Disease severity was determined using JADAS. Perceived pain was assessed with a visual analogue scale(0-100). Feasibility of QST was tested in patients aged 5-9.

Results JIA patients reported an average VAS pain score of 54.3. QST identified a significant reduction in PPT and increase in CDT compared to healthy controls. Under the age of 9, QST testing showed not to be feasible.

Conclusion Sensory threshold changes at the knee are restricted to pressure pain and cold detection thresholds in JIA patients. This study shows that in a Dutch population, the extensive QST protocol is only feasible in the age group from 9 years and older, and a reduced set of QST tests containing at least pressure pain thresholds and cold detection thresholds could prove to be better suited to the pediatric setting with arthritis.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common childhood rheumatic disease[1]. JIA is characterized by chronic joint inflammation, stiffness, swelling and pain. JIA can result in long-term disability that persists into adulthood in more than one-third of the patients[2, 3]. Pain in JIA patients is common and often persists for months to years, despite the current advances in treatment of affected joints[3]. Chronic pain is one of the major complaints of JIA patients and severely affects quality of life[1, 4–6]. Moreover, JIA patients have reduced pain thresholds compared to healthy subjects that persist after the inflammation in the joints had subsided[7, 8]. Persistent pain is difficult to treat, has a high socioeconomic burden, can be very debilitating, and causes absenteeism from school, reduced physical activity, and social isolation[9].

Quantitative Sensory Testing (QST) is a reliable methodology to objectively and accurately assess changes in sensory functioning beyond that of self-reported pain assessments. This technique enables measurement of sensory sensitivities, including that for pain and different sensory modalities[10]. A validated QST protocol was originally developed for testing the somatosensory system in adults [10–13], and the QST protocol was validated in healthy children from 5 years and older[11]. A few studies using QST in children with JIA showed an increased sensitivity to painful mechanical and thermal stimuli at the

thenar eminence and knee; even in absence of markers of disease activity, and for a prolonged period of time[14, 15]. However, each joint is differently innervated and sensitivity levels differ depending on the tested location (e.g., the face yields different values from the hand)[10, 11]. In JIA, the knee is the most frequently affected joint. It is currently unknown whether and how different sensory thresholds at the knee are affected by JIA.

In this study, we tested an extensive set of sensory modalities in the knees of Dutch JIA patients and provide novel reference data of sensory thresholds for the knee of children aged between 9-18. To this end, a validated QST battery was used in children with JIA and healthy controls.

Materials & Methods

Study Design

Patients who visited the outpatient clinic of the pediatric rheumatology in the Wilhelmina children's hospital were screened for eligibility. Patients were included if the following criteria were met: age between 6 and 18 years, able to speak and understand the Dutch language, JIA according to the International League Against Rheumatism (ILAR) criteria, inflammation in the knee, and a general pain score of 10 or more on a 0-100mm patient Visual Analogue Scale (VAS). Exclusion criteria were: damaged skin on one or both knee(s), severe (psychiatric) co-morbidity, or active substance abuse. In total 21 patients were included and 21 healthy controls were matched by age and gender. The study was designed and conducted in accordance with the Declaration of Helsinki (7th amendment, October 2013), and approved by the ethics review board of the University Medical Center Utrecht (protocol number 13-577). Written informed consent was obtained from all participating patients and from their parents or custodial caregiver.

Clinical parameters

Patient characteristics were derived from the medical records. As part of standard of clinical care, a complete physical examination was performed by the rheumatologist, comprising the assessment of the number of active joints, Physician Global Assessment, and erythrocyte sediment rate (ESR). Patient or parent provided the Childhood Health Assessment Questionnaire (CHAQ) from which the disease severity score on a 0-100 scale was derived (with 0 being no disease activity and 100 being the most severe activity)[16]. From these measurements, the Juvenile Arthritis Disease Activity Score (JADAS) was calculated as described previously[17]. VAS scales are validated for children aged five years or older[18].

Quantitative sensory testing

QST was performed by trained personnel according to the QST protocol for children as described previously[11]. In all patients, the tests were carried out on the inflamed knee and the contralateral control knee. In healthy controls the right knee was tested. Before each actual test, a practice trial was performed, to ascertain that the subject understood the test. The QST protocol consisted of the following tests:

1. Thermal detection thresholds for cold (cold detection threshold; CDT) and warm (warm detection threshold; WDT) stimuli. Thermal stimuli were applied using a thermal stimulation device with a 3x3 cm² surface Peltier-type thermode (Pathway, Medoc®, Israel). Thermal detection thresholds were determined by the mean of three consecutive stimuli.
2. Thermal pain thresholds for cold (cold pain threshold; CPT) and hot stimuli (heat pain threshold; HPT). Stimuli were either continuously increasing or decreasing in temperature until the patient presses a button to indicating the detection of a change from a neutral sensation to a painful hot/cold sensation. Thermal pain thresholds were determined by the mean of three consecutive stimuli.
3. Thermal sensory limen (TSL) was determined using a ramped increase from 32 degrees Centigrade upwards. The subject was asked to press a button as soon as the subject experiences a change of temperature to a warm sensation. Thereafter the temperature would decrease, and the subject was asked to press as soon as a cold sensation was perceived. This scheme was repeated for a total of six times and the TSL was determined based on the difference between the means of the two extremes in temperature.
4. Mechanical detection threshold (MDT) is determined using a standardized set of modified von Frey hairs (Optihair2-Set, Marstock Nervtest, Germany) that exert forces between 0.25 and 512 mN. The MDT was determined as the geometric mean of five consecutive series of ascending and descending stimulus intensities.
5. Mechanical pain threshold (MPT) is determined using pinprick stimuli using a set of seven custom-made (DFNS, Germany) weighted pinprick stimulators (flat contact area of 0.2 mm diameter) that exert forces between 8 and 512 mN. The MPT is the geometric mean of five consecutive series of ascending and descending stimulus intensities.
6. Wind-up ratio (WUR) compares the numerical ratings of five series of a) a single pinprick stimulus (mostly 256 mN, depending on the pinprick threshold) with five series of b) 10 repetitive pinprick stimuli at a 1/s rate. Each series of stimuli is applied within an alternating surface area of 1 cm², immediately followed by an average numerical pain rating of the preceding series. The WUR is calculated as the averaged ratio: b/a.
7. Vibration detection threshold (VDT) is determined using a Rydel–Seiffer 64 Hz tuning fork placed over the head of the fibula. Vibration threshold is determined with three series of diminishing stimulus intensities. The average of the three detection thresholds is used as the VDT.
8. Pressure pain threshold (PPT) is determined with a pressure gauge device (FDN100, Wagner Instruments, USA) with a probe area of 1 cm² that exerts pressure up to 10 kg/cm². Three series of ascending stimulus intensities are applied as a slowly increasing ramp of 0,5kg/cm² per second and the mean is taken as the PPT.
9. Mechanical pain / dynamic mechanical allodynia (ALL) assesses pain in response to stroking light touch (cotton wisp; cotton wool tip; brush). The three tactile stimuli are applied five times each with a

single stroke of approximately 1–2 cm in length over the skin. This is pseudo-randomly alternated with pinprick stimuli of various forces as described above.

All tests were executed in accordance with the protocol (see complementary material).

Sample size calculation and feasibility criteria

Sample size was calculated based on published data on QST measurements in JIA patients[7, 14]. Data were assumed to be normally distributed. In order to detect a 38.5% difference in cold pain thresholds between the affected body regions in JIA patients and control body regions in healthy controls with and standard deviation of 42.3%, a total sample size of 21 per age group was needed. Two age groups were defined: age 6 to 9, and 9 to 18. Sample size calculations were performed using G*Power 3 for a 2-tailed independent T-test. We assumed a type-I-error of 0.05 and a type-II-error of maximal 0.20. Based on the initial results from Blankenberg et al.[7] QST testing was deemed feasible if less or equal than 10% of subjects per age group failed to complete the procedure.

Statistics

Data are represented as median and IQR, or (geographic) mean and SD where appropriate. For the QST tests, one-way ANOVA with Tukey's post hoc analysis was performed for parametric data, and Kruskal-Wallis test for non-parametric data. For the statistical analysis, R (v.3.3.2) was used. Data were log-transformed where appropriate and z-values were calculated[19].

Results

In the age group of 6 to 9 years, participants were not able to complete the tests because of lack of understanding or inadequate attention span. After four inclusions within this age range, three subjects had not been able to complete the QST protocol. In this age group, the endpoint of feasibility had been reached (3 incomplete tests out of 21 yields 14% failure). Therefore we decided to only include and analyze children at an age of 9-18 years from that point on.

The demographic and clinical data of JIA patients of the older age group (9-18 years) are shown in Table 1. The duration of the disease ranged from 3 to 196 months. The mean age was 14.8 $\pm$ 2 years, and the mean time between diagnosis and study inclusion was 74 months. The mean JADAS score of the patients was 10.2 $\pm$ 5.6 and the (CHAQ) pain score averaged 54.3 $\pm$ 29.5 (on a scale of 0-100). All patients had pain duration of more than 2 months.

Pain threshold

Pressure pain thresholds of the inflamed knee of JIA patients were significantly lower than that of the knee of healthy control subjects (df=2, F=5.176 Pr(>F)=0.00979 **, $p=0.015^*$). Moreover, even the unaffected contralateral control knee PPT thresholds of JIA patients were lower than at the knees from

healthy control subjects ($p=0.033^*$). Pressure pain thresholds did not differ significantly between the affected and the unaffected knee of the JIA patients ($p=0.93$). (see Fig. 1A)

Heat pain thresholds ($p=0.57$), cold pain thresholds ($p=0.46$), or mechanical pain thresholds ($p=0.67$) of the ipsilateral knee of JIA patients did not differ significantly from contralateral unaffected knees or knees of healthy control subjects (see Figure 1 of supplementary material).

Sensory detection thresholds

Cold detection thresholds were significantly higher in the unaffected knee of JIA patients compared to knees of healthy control subjects ($p<0.01$; Fig. 1B). In contrast, the inflamed knee of JIA patient did not differ from healthy control knees. Warm detection thresholds ($p=0.73$), temperature sensory limen ($p=0.1$), mechanical detection thresholds ($p=0.83$), allodynia ($p=0.46$), vibration detection thresholds ($p=0.3$) and windup ratio ($p=0.31$) did not significantly differ between the groups (see Figure 1 of supplementary material).

Associations between perceived pain and QST measures

Next we tested for correlations between reported pain and QST measures. Heat pain threshold (HPT) and patient VAS were correlated (Pearson's $r = 0.70$, $p<0.01$; Fig. 2). All other QST modalities did not correlate with the magnitude of reported pain (Table 2).

Discussion

JIA is a well-known childhood disease with chronic pain being one of the symptoms. Objective quantification of changes in somatosensory processing such as QST in children with JIA aids in better understanding of pain in this disease. We show here that the German Research Network on Neuropathic Pain validated QST protocol[10] is feasible in Dutch children aged 9 years and up, but not in children between 6-8 years of age.

Importantly, we identified that the pressure pain threshold is reduced at the inflamed and contralateral knee of JIA patients compared to healthy controls, whilst other pain thresholds did not differ from healthy control. Unexpectedly, the cold detection threshold was reduced only in the unaffected knee of JIA patients, while no significant differences were detected in the affected knee of JIA patients compared to controls. Possibly, the study population was too small to show significant CDT change in the ipsilateral knee. In conclusion, in our JIA patient population, Cold Detection Test and Pressure Pain Test were significantly different between JIA patients and healthy controls.

We detected a reduction in PPT at both the ipsi- and unaffected contralateral knee of JIA patients, indicating a generalized enhanced pain sensitivity (of hyperalgesic response) to pressure stimuli. Although others also have found that a unilateral inflammation induces a bilateral reduction in PPT in patients with JIA[8], we now confirm these findings with validated and standardized QST measures. The question rises why in both the affected and unaffected knee changes in PPT were observed. In adult

rheumatoid arthritis patients, pain symptoms often arise before clinical manifestation of the arthritis[20], thus by analogy the possibility exists that some of JIA patients had subclinical inflammation at the contralateral knee causing the reduction in PPT. Alternatively, in JIA patients systemic inflammatory responses may cause bilateral reduction in PPT. For example, experimental systemic inflammation induced with an i.v. bolus with lipopolysaccharide induced a generalized reduction in pressure pain threshold in healthy volunteers[21]. Similarly, in patients with a unilateral neuropathy, pain sensory abnormalities, in particular for pressure pain threshold, were also observed at the non-affected site[22]. It has been proposed that spreading of spinal glial activation and central sensitization induces bilateral alterations in sensory detection thresholds[23] in preclinical mouse studies and pilot data in JIA patients[24]. However, it remains to be determined whether such spinal changes occur in patients with JIA.

Importantly, the most frequent site of pain in JIA is the knee, and changes in sensory modalities specifically in the knee joint has not been studied in the context of JIA.

An earlier study has included QST measures of the knee of JIA patients, however, these knee QST datasets were combined with datasets of the ankle joint to compare active (n=17) and in-active joints (n=12). Whether the combined knee and ankle joint thresholds differed from that of healthy controls was not reported[14]. In this study, we assessed sensory changes specifically at the knee of 21 healthy controls and 21 JIA patients with an active and inactive inflamed knee. We observed that only two sensory modalities (CDT and PPT) at the knee were affected compared to healthy control knee. No significant differences were observed between the inflamed and unaffected contralateral knee, similar to what was previously observed when knee and ankle joints were combined[14]. An earlier study by Cornelissen *et al.*[14] showed significant differences for all QST modalities when the inflammation of the ankle, knee or face was compared to the thenar eminence of a healthy control. However, QST data obtained from different joints is difficult to compare, as sensory thresholds of each joint are different. For example, the density of nerve endings at the thenar eminence is higher than at the knee, reducing the discriminatory sensitivity at the knee compared to the hand[25].

One limitation of this study is that the average duration of JIA was 6.2 years at the time of study. Thus the data represent sensory changes associated with chronic inflammation. Future studies could focus on sensory changes at the onset of rheumatic disease and how these changes correlate to pain levels during later stages of the disease. Also, in this population, medication was used extensively and ranged from NSAIDs to DMARDs. These drugs are known to have a dampening effect on pain[26], and as such could have affected pain VAS score and possible even QST measures

In conclusion, this study provides information that in Dutch children, the complete QST protocol is only feasible in the age group from 9 years and older, because children younger than 9 years were not able to complete the more extended DFNS QST test battery. In future studies, a reduced set of QST tests containing at least pressure pain thresholds and cold detection thresholds could prove to be better suited

to the pediatric arthritis population, with the purpose of identifying patients with persistent changes in somatosensory processing.

Abbreviations

JIA	Juvenile Idiopathic Arthritis
QST	Quantitative Sensory Testing
ILAR	International League Against Rheumatism
VAS	Visual Analogue Scale
ESR	erythrocyte sediment rate
CHAQ	Childhood Health Assessment Questionnaire
JADAS	Juvenile Arthritis Disease Activity Score
DFNS	German Research Network on Neuropathic Pain
CDT	cold detection threshold
WDT	warm detection threshold
CPT	cold pain threshold
HPT	heat pain threshold
TSL	Thermal sensory limen
MDT	Mechanical detection threshold
MPT	Mechanical pain threshold

WUR	Wind-up ratio
VDT	Vibration detection threshold
PPT	Pressure pain threshold
ALL	allodynia
IQR	Interquartile range
SD	Standard deviation
ANOVA	Analysis of variance
NSAID	Non-steroidal anti-inflammatory drug
DMARD	Disease-modifying antirheumatic drugs

Declarations

Financial declaration:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
 - The study was designed and conducted in accordance with the Declaration of Helsinki (7th amendment, October 2013), and approved by the ethics review board of the University Medical

Center Utrecht (protocol number 13-577). Written informed consent was obtained from all participating patients and from their parents or custodial caregiver

- Consent for publication
 - Not applicable
- Availability of data and materials
 - The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request
- Competing interests
 - Not applicable
- Funding
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- Authors' contributions
 - All authors contributed equally to the study protocol and the manuscript
- Acknowledgements
 - Not applicable
- Authors' information (optional)

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Tables

Table 1: Patient characteristics

Overview of clinical data of patients included (N=21); SD = standard deviation; JIA=juvenile idiopathic arthritis; RF = Rheumatoid Factor; JADAS = Juvenile Arthritis Disease Activity Score; CHAQ = Childhood Health Assessment Questionnaires; ESR = erythrocyte sedimentation rate.

Mean age (years) (SD)	14.8 (2.1)
Type JIA	
- persistent oligoarthritis (%)	57.1
- extended oligoarthritis (%)	7.1
- RF negative polyarthritis (%)	28.6
- RF positive polyarthritis (%)	7.1
Duration since diagnosis (months) (SD)	74.0 (67.3)
JADAS score (SD)	10.2 (5.6)
CHAQ pain (SD)	54.3 (29.5)
Number of affected joints (SD)	2.7 (2.7)
ESR (SD)	24.4 (18.9)
medication used (in %)	
- Methotrexate	35.7
- NSAID	64.3
- Leflunomide	7.1
- Humira	14.3
- Triamcinolon	7.1

Table 2: Correlation between QST tests and reported clinical pain

From all tested QST measures HPT correlated with reported clinical pain in JIA patients. Depicted values are Pearson's R (*p*-level). CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; VDT, vibration detection threshold; PPT, pressure pain threshold; WUR, wind-up ratio; ALL, allodynia. * Significant at 0.01

Reported pain	
CDT	0.25 (0.38)
WDT	0.32 (0.25)
TSL	0.16 (0.57)
CPT	0.31 (0.26)
HPT	0.70 (<0.01*)
MDT	0.12 (0.67)
MPT	0.06 (0.84)
VDT	0.08 (0.78)
PPT	0.34 (0.24)
WUR	0.10 (0.73)
ALL	0.38 (0.20)

Figures

Figure 1

Sensory deficits were measured using the QST. (A) PPT were significantly lower at the control and inflamed knee of JIA patient in comparison with healthy controls (B) Sensory detection thresholds were significantly higher at the control knee of JIA patient compared to healthy control knee, as well as

inflamed knee. PPT: pressure pain threshold, CDT: cold detection threshold. Higher value means less sensitive to cold detection. * $p<0.05$.

Figure 2

Correlation between HTP and VAS pain. VAS: visual analog scale; HPT: heat pain threshold, n=14.
* $p<0.001$

Supplementary Files

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- [QSTsupplementaryfigure1.docx](#)