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Clinical Study

Evidence of impaired pain modulation in adolescents with idiopathic scoliosis and chronic back pain

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Abstract

BACKGROUND CONTEXT: Although 40% of adolescent idiopathic scoliosis (AIS) patients present with chronic back pain, the pathophysiology and underlying pain mechanisms remain poorly understood. We hypothesized that development of chronic pain syndrome in AIS is associated with alterations in pain modulatory mechanisms.
PURPOSE: To identify the presence of sensitization in nociceptive pathways and to assess the efficacy of the diffuse noxious inhibitory control in patients with AIS presenting with chronic back pain.
STUDY DESIGN: Cross-sectional study.
PATIENT SAMPLE: Ninety-four patients diagnosed with AIS and chronic back pain.
OUTCOME MEASURES: Quantitative sensory testing (QST) assessed pain modulation and self-reported questionnaires were used to assess pain burden and health-related quality of life.
METHODS: Patients underwent a detailed pain assessment using a standard and validated quantitative sensory testing (QST) protocol. The measurements included mechanical detection thresholds (MDT), pain pressure threshold (PPT), heat pain threshold (HPT), heat tolerance threshold (HTT), and a conditioned pain modulation (CPM) paradigm. Altogether, these tests measured changes in regulation of the neurophysiology underlying the nociceptive processes based on the patient's pain perception. Funding was provided by The Louise and Alan Edwards Foundation and The Shriners Hospitals for Children.
RESULTS: Efficient pain inhibitory response was observed in 51.1% of patients, while 21.3% and 27.7% had sub-optimal and inefficient CPM, respectively. Temporal summation of pain was observed in 11.7% of patients. Significant correlations were observed between deformity severity and pain pressure thresholds ($p = .023$) and CPM ($p = .017$), neuropathic pain scores and pain pressure thresholds ($p = .015$) and temporal summation of pain ($p = .047$), and heat temperature threshold and pain intensity ($p = .048$).
CONCLUSIONS: Chronic back pain has an impact in the quality of life of adolescents with idiopathic scoliosis. We demonstrated a high prevalence of impaired pain modulation in this group. The association between deformity severity and somatosensory dysfunction may suggest that spinal deformity can be a trigger for abnormal neuroplastic changes in this population contributing to chronic pain syndrome.

Keywords: Chronic pain; Diffuse noxious inhibitory control; Pain; Psychological tests; Scoliosis.

FDA device/drug status: Not applicable.

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Introduction

Adolescent idiopathic scoliosis (AIS) is a common spinal disorder with a reported prevalence from 0.47% to 5.2% [1]. Approximately 40% of patients with AIS present with back pain [2], a proportion greater than that of age and sex-matched controls [3]. The pathophysiology and underlying pain mechanisms of AIS remain poorly understood [4]. Several attempts to explain this association provided conflicting results on the relationship between the deformity and self-reported pain [5–7,4]. Interestingly, patients' self-perception of their image often correlates with pain [8].

The past few decades have witnessed improvement in the understanding of mechanisms involved in persistent pain. Musculoskeletal (MSK) injury typically results in nociceptive pain due to activation of nociceptors in joint tissues or muscles. Following this initial injury, peripheral sensitization of primary afferent neurons at the site of injury results in increased pain sensitivity of the affected area, a phenomenon known as primary hyperalgesia [9]. Persistent nociceptive stimulus can lead to other neuroplastic changes in the central nervous system resulting in increased pain sensitivity also in areas other than the original injury [9]. Clinically, peripheral and central sensitization can be indirectly identified as hyperalgesia and allodynia [9,10].

Pain sensitization has been associated with chronic pain development in several MSK disorders [11–14]. In addition to these facilitatory mechanisms of pain modulation, strong evidence shows that deficient endogenous pain inhibitory control plays a role in the development of chronic pain in patients with MSK disorders [15–17]. The endogenous pain modulatory systems can be assessed in the clinical setting with quantitative sensory testing (QST) [18]. QST incorporates cutaneous mechanical and thermal procedures that provide reproducible quantitative evidence of pain transduction and modulation and the patient's perception and expectation of pain [19].

We hypothesized that development of chronic pain syndrome in AIS is associated with alterations in pain modulatory mechanisms. In this study, we performed a detailed pain assessment in patients with AIS and chronic back pain in order to identify the presence of sensitization of nociceptive pathways as well as to assess the efficacy of the diffuse noxious inhibitory control in this population. This mechanism-based approach may provide new insight for the explanation of chronic pain in this group of patients.

Methods

This study was designed specifically to assess chronic back pain in patients with AIS. Ethics approval was obtained before the beginning of the recruitment from the Research Ethics Board of our Institution (A00-M17-17B).

Participants

Patients aged between 10 and 21 years old were approached from the outpatient spine clinics at the Shriners Hospital for Children-Canada and prospectively enrolled in the study after signing an informed consent. Inclusion criteria consisted of any patient with a diagnosis of AIS confirmed by an orthopedic surgeon, experiencing back pain lasting 3 months or longer, and no previous spine surgery. Patients who did not speak English or French, had a diagnosis of developmental delay that would interfere with completing measures (eg, autism or mental limitation), or had major chronic medical conditions (American Society of Anesthesiology status III or higher) were excluded.

Procedure

A research assistant collected information on demographics, medical history, and self-reported questionnaires on strategies to manage pain for each enrolled patient.

Pain and health-related quality of life assessment

Pain intensity during the prior month was assessed with the Faces Pain Scale-revised [20] and reported by the patient with a numerical rating score on 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable. The duration and frequency of pain, and aggravating factors were assessed in the form of an interview. The location of pain was reported in a body outline diagram of the back divided into several segments completed by the patient (Fig. 1). The neuropathic component of pain was assessed with the Douleur Neuropathique 4 (DN4) questionnaire in which a total score ≥4 indicates that the pain experienced by the patient is likely neuropathic [21].

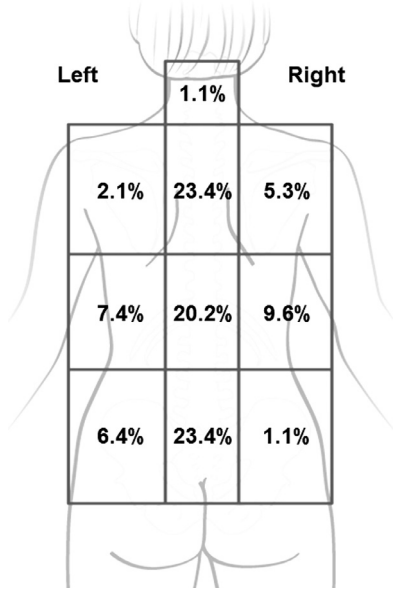

Fig. 1. Location of pain in patients with adolescent idiopathic scoliosis (N = 94).

Disability was assessed with the Functional Disability Inventory (FDI) [22]. FDI is a well-established and commonly used measure of physical functioning and disability in youth with chronic pain. The inventory is based on four-level classifications system: scores from 0 to 12 indicate no/minimal disability, 13 to 20 mild, 21 to 29 moderate, and ≥30 severe disability.

The Revised Child Anxiety and Depression Scale (RCADS) assessed self-reports on depression and anxiety symptoms corresponding to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [23]. Based on the patient's age and grade in school, their scores are converted into a T-score. A T-score of 65 or higher indicates borderline clinical threshold, and a T-score of 70 or high indicates above clinical threshold for anxiety and depression.

Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) in which a global score of 5 or higher indicated poorer sleep quality [24].

Radiological assessment

Each participant underwent full length, standing, biplanar scoliosis radiographs to assess the coronal and sagittal planes. Measurements were made of coronal Cobb angle, thoracic kyphosis, lumbar lordosis, pelvic incidence, and sagittal vertical axis (SVA). We also reported on the presence or absence of cervical kyphosis. Classification of each curve was carried out using a modified Lenke classification [25]. Curves present on standing X-rays were considered structural, in the absence of bending films, as these are not obtained on nonsurgical patients.

Pain modulation assessment: the quantitative sensory testing

Training of experiments, including standardization of all verbal instructions, occurred before the beginning of the study. QST was assessed using a protocol adapted from previous studies by Marchand et al. [26,27] and Rolke et al. [28]. The protocol consisted of four tests examining altogether six parameters and allowed for a comprehensive profile of somatosensory functions assessed with thermal and mechanical procedures.

For all participants, the left volar forearm, 2 inches from the left elbow crease served as the control area. Participants were instructed to locate with one finger the most painful location in the back, which was marked by an "X" with a washable marker. This served as the affected area (ie most painful back area). Each test always started on the control area, followed by testing on the affected area. For all parameters, the mean of 3 consecutive measurements on each area was calculated.

Mechanical quantitative sensory testing assessment

Mechanical testing started with the mechanical detection threshold (MDT) to detect tactile sensitivity. MDT was evaluated with standardized von Frey filaments (Touch-Test Sensory Evaluators) and data were reported in grams. Pressure pain threshold (PPT) was assessed using an algometer (JTech Medical, USA) to detect the presence of hypersensitivity of deep tissue to pressure. Thresholds were reported in Newtons (N). Data from German Research Network on Neuropathic Pain shows that healthy individuals are generally more sensitive at the hand than the back [29]. In this study, we compared the back-PPT with the control area-PPT in order to assess regional pain sensitivity (pain facilitation), the results are presented in ratio.

Thermal quantitative sensory testing assessment

Thermal thresholds were measured using a 3×3 cm warm calibrated thermode connected to the Q-Sense apparatus (Medoc, Israel) and reported in degree Celsius (°C). The initial temperature (t^o) was set to 32°C and programed to gradually increase at a rate of 0.3°C/sec. Thermal testing started with the heat pain threshold (HPT), followed by the heat tolerance threshold (HTT), which was self-reported as a 10/10 pain intensity and t^o recorded.

After determining the patient's HTT, a conditioned pain modulation paradigm was performed using the tonic heat as the test stimulus and the cold-water immersion as the conditioned stimulus [27,26]. The paradigm started with the warm thermode being applied on the forearm to reach the pre-determined target temperature (temperature necessary to induce a 5/10 pain intensity). Once the target temperature was reached, it remained constant for 120 seconds. To avoid expectation effects, patients were not told that the temperature of the test stimulus would remain constant over time. Patients were asked to continuously rate their pain using a computerized visual analogue scale (CoVAS). This test allows to identify if there is a temporal summation of pain (TSP) if the patient reports an increase in pain intensity over time during the application of constant noxious. Once the tonic heat test was completed, patients immersed their opposite forearm to approximately 2 inches above the elbow in a bath filled with cold water (12°C) for 2 minutes as the conditioning stimulus that triggers a descending inhibitory pain response. Immediately after, the tonic heat test was performed once again. The conditioned pain modulation (CPM) efficacy was calculated as the percentage of the difference between the mean pain intensity over the 2 minutes during the test stimulus before and after the conditioning stimulus over the mean pain intensity during the test stimulus before the conditioning stimulus. Efficient CPM was defined as the ability of the patient to inhibit at least 30% of pain. Inefficient CPM was defined as the ability of the patient to inhibit at least 10% of pain after the conditioning stimulus. Temporal summation of pain was defined as an increase in 20% of pain intensity at the end of test in relationship with pain intensity 60 seconds after the beginning of the test (stable heating).

Statistical analysis

Statistical analyses were conducted with Statistical Package for the Social Sciences (SPSS v24.0, SPSS Inc., Chicago,

Table 1
Characteristic of AIS patients with chronic back pain (N = 94)

Age, mean (SD)	15.1 (2.1)
Female, n (%)	81 (86.17)
Ethnicity, n (%)	
Caucasian	81 (86.17)
Black or African American	7 (7.45)
Asian	1 (1.06)
Middle Eastern	1 (1.06)
Interracial	4 (4.26)
Radiological assessment	
Lenke classification, n (%)	
1	26 (27.66)
2	6 (6.38)
3	13 (13.83)
4	10 (10.64)
5	23 (24.47)
6	16 (17.02)
Mean magnitude of the largest Cobb angle, mean±SD	28.8±11.9
Cervical kyphosis (%)	47 (50.0)
Thoracic kyphosis	
Mean magnitude of thoracic kyphosis, mean±SD	35.7±12.2
Thoracic hypokyphosis (%)	2 (2.13)
Thoracic hyperkyphosis (%)	30 (31.91)
Lumbopelvic mismatch	
Mean magnitude of lumbar lordosis, mean±SD	56.3±12.9
Mean magnitude of pelvic incidence, mean±SD	49.8±10.1
Mean magnitude of lumbopelvic mismatch, mean±SD	16.4±11.8
Presence of a lumbopelvic mismatch of ±10° (%)	76 (80.85)
Sagittal plane assessment	
Mean sagittal vertical axis (cm), ±SD	−0.50±2.9
Sagittal vertical axis >3cm (%)	17 (18.09)
Pain assessment	
Average pain intensity (NRS0-10), mean±SD	5.1±2.1
Duration of pain, n (%)	
3–6 months	6 (6.38)
6–12 months	16 (17.02)
>12 months	72 (76.60)
Frequency of pain, n (%)	
Daily	52 (55.32)
Every 2nd day	25 (26.60)
Once a week	16 (17.02)
Once a month	1 (1.06)
Duration of painful episodes, n (%)	
Few seconds	3 (3.19)
Few minutes	21 (22.34)
One hour	25 (26.60)
Constant	45 (47.878)
Painful Factors, n (%)	
Sitting	40 (42.55)
Standing	53 (56.38)
Lying down	6 (6.38)
Strategies to alleviate pain, n (%)	
Lying down	44 (46.81)
Bending	13 (13.83)
Cold	4 (4.26)
Warmth	12 (12.77)
Other (stretching, standing, sitting, changing position, medication)	47 (50.0)
Nothing	6 (6.38)
Medication taken in the last 24 hours, n (%)	
Over the counter pain medication	17 (18.08)
Narcotics	0
Antidepressants	1 (1.06)
Neuroleptics	0
Neuropathic component	
DN4 score, mean±SD	2.1±2.1
Neuropathic pain (DN4≥4), (%)	20 (21.23)

AIS, adolescent idiopathic scoliosis; SD, standard deviation; DN4, Douleur Neuropathique 4.

IL). Continuous variables were submitted to Kolmogorov-Smirnov test to assess normality. Categorical variables were presented as number and proportion. Continuous variables were presented as mean and standard deviation. Spearman correlation test was used to assess the association between continuous variables. Chi square tests were conducted to verify association between categorical variables. Given the high variability in pain processing and expression among people, we calculated our sample size based on a weak correlation between radiographic parameters and pain sensitivity values. To detect a correlation of 0.3 between any QST measurement and curve severity, a minimum of 85 patients was necessary to provide 5% level of significance and 80% power.

Results

Demographics, radiological, and pain assessment

Table 1 presents the general features, radiological data and pain assessment of 94 AIS patients with chronic back pain enrolled in the study (Table 1). The mean self-reported pain intensity was 5.1 (±2.1). The location of pain was referred as the upper back in 31.9% of patients (N = 30), middle back in 37.2% (N = 35), and lower back in 30.9% (N = 29; Fig. 1).

Functional disability, sleep quality, and mood disorders

The FDI questionnaire demonstrated that 21.3% of AIS patients with chronic back pain presented moderate to severe functional disability (Table 2). Item-to-item assessment of FDI revealed that over 10% were having a lot of trouble or it was impossible to be at school due to their pain, and over 20% reported having a lot of trouble or impossibility to participate in gym class (Table 2). The RCADS questionnaire revealed that 5.4% of patients were borderline (N = 4) or above (N = 1) the clinical threshold for depression and anxiety. Sleep quality was considered poor in 75.5% of patients, according to the PSQI questionnaire (Table 3).

Table 2
Functional disability index of AIS patients with chronic back pain (N = 94)

Functional disability index questions, n (%)	No trouble	A little trouble	Some trouble	A lot of trouble	Impossible
Walking to the bathroom	87 (92.55)	2 (2.13)	5 (5.32)	0	0
Walking up stairs	48 (51.06)	25 (26.60)	17 (18.09)	3 (3.19)	0
Doing something with a friend (for example playing a game)	56 (59.57)	19 (20.21)	14 (14.89)	4 (4.26)	1 (1.06)
Doing chores at home	32 (34.04)	26 (27.66)	28 (29.79)	7 (7.45)	1 (1.06)
Eating regular meals	82 (87.23)	5 (5.32)	7 (7.45)	0	0
Being up all day without a nap or rest	37 (39.36)	16 (17.02)	19 (20.21)	16 (17.02)	6 (6.38)
Riding the school bus or traveling in the car	39 (41.49)	28 (29.79)	19 (20.21)	7 (7.45)	1 (1.06)
Being at school all day	28 (29.79)	27 (28.72)	28 (29.79)	8 (8.51)	3 (3.19)
Doing the activities in gym class (or playing sports)	18 (19.15)	23 (24.47)	33 (35.11)	16 (17.02)	4 (4.26)
Reading or doing homework	50 (53.19)	26 (27.66)	12 (12.77)	5 (5.32)	1 (1.06)
Watching TV	63 (67.02)	16 (17.02)	13 (13.83)	2 (2.13)	0
Walking the length of a football field	53 (56.38)	31 (32.98)	7 (7.45)	2 (2.13)	1 (1.06)
Running the length of a football field	35 (37.23)	18 (19.15)	24 (25.53)	10 (10.64)	7 (7.45)
Going shopping	39 (41.49)	26 (27.66)	22 (23.40)	6 (6.38)	1 (1.06)
Getting to sleep at night and staying asleep	50 (53.19)	20 (21.28)	15 (15.96)	8 (8.51)	1 (1.06)

AIS, adolescent idiopathic scoliosis.

Quantitative sensory testing

Table 4 presents the overall results of QST in this cohort of AIS patients with chronic back pain. Fig. 2 presents the results on the relationship of pain pressure thresholds at the back and the forearm (control site). These results demonstrate that 74.5% of AIS patients had lower PPT at the back than on their forearm, with 36.3% of them having at least 50% lower pain thresholds at the back in comparison with their forearm. These results suggest higher pain sensitivity at the back (lower back-PPT) in this group of patients.

High variability in CPM results was observed in the sample (Fig. 3). Efficient pain inhibitory response was observed in 51.1% of patients, while 21.3% and 27.7% had sub-optimal and inefficient CPM, respectively. Fig. 4 presents the patterns of the CPM paradigm of the three groups. Temporal summation of pain, a clinical demonstration of central sensitization, was observed in 11.7% of patients. Duration of back pain was not associated with any QST parameter ($p > .05$).

Table 3
Psychological characteristics of AIS patients with chronic back pain (N = 94)

Anxiety and depression symptoms	
RCADS T-Score, Mean±SD	45.04±10.48
Below clinical threshold, n (%)	89 (94.68)
Borderline, n (%)	4 (4.26)
Above clinical threshold, n (%)	1 (1.06)
Sleep Quality	
PSQI Global Score, Mean±SD	6.71±2.94
Good sleep quality, n (%)	23 (24.47)
Poor sleep quality, n (%)	71 (75.53)

AIS, adolescent idiopathic scoliosis; RCADS, The Revised Child Anxiety and Depression Scale; PSQI, the Pittsburgh Sleep Quality Index; SD, standard deviation.

Table 4
Neurophysiological characteristics of AIS patients with chronic back pain (N = 94)

Quantitative sensory testing measures	Mean±SD
Mechanical detection threshold (g)	
Control site	0.712±2.35
Affected site (back)	0.620±1.22
Pressure pain threshold (N)	
Control site	27.47±12.68
Affected site (back)	25.58±16.85
Heat pain threshold (°C)	39.24±3.32
Heat tolerance threshold (°C)	45.04±2.38

AIS, adolescent idiopathic scoliosis.

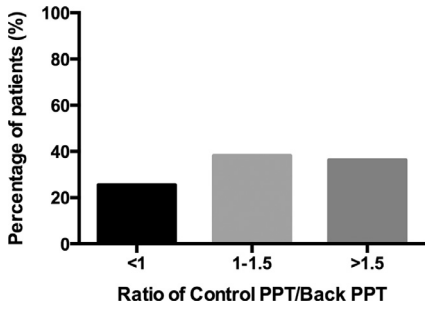

Fig. 2. Pain pressure threshold ratio between nonpainful area (control) and painful area (back).
Note: Control PPT (pain pressure threshold at the forearm), back PPT (pain pressure threshold at the painful area in the back).

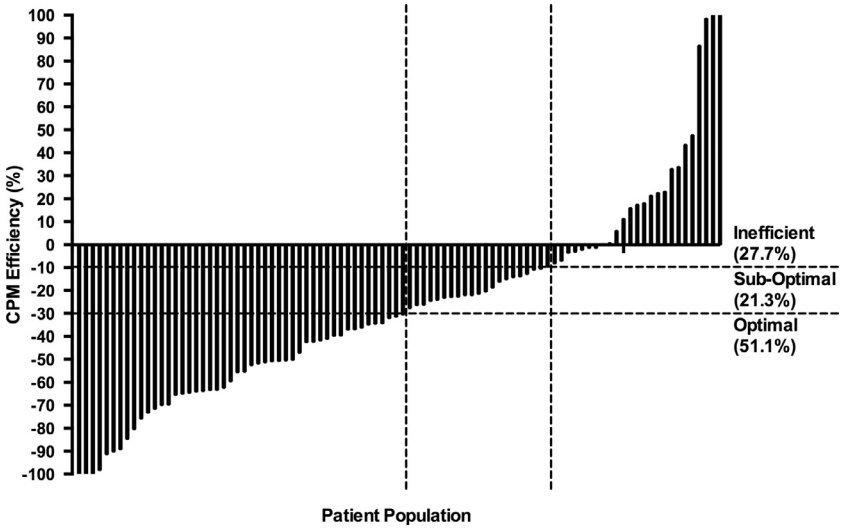

Fig. 3. Distribution of conditioned pain modulation in 94 patients with adolescent idiopathic scoliosis and chronic back pain.

Association between pain, quantitative sensory testing, and radiological parameters

There was a significant association between curve type and location of pain (Fig. 5, p = .05). Nearly 70 (60.9) percent of patients with thoracolumbar/lumbar curves reported pain at the lower back, while only 15.6% of patients with main thoracic or double thoracic curve types reported pain in their lower back. No associations were found between pain location and cervical kyphosis (p = .906), thoracic hypokyphosis (p = 0.545), thoracic hyperkyphosis (p = .149), presence of lumbopelvic mismatch greater than 10 (p = .779), or SVA greater than 3 cm (p = .770). Curve severity, curve type, cervical kyphosis, thoracic hypokyphosis or hyperkyphosis, lumbopelvic mismatch, or SVA greater than 3 cm were not associated with self-reported pain intensity (p > .05).

A statistically significant but weak negative correlation was observed between deformity severity and back-PPT (Fig. 6A; r = −0.234, p = .023). In other words, the larger the Cobb angle, the more sensitive for pain was the back region (lower PPT). In addition, a significant weak correlation between endogenous pain inhibitory capacity and deformity severity was observed (Fig. 6B; r = 0.245, p = .017). The larger the Cobb angle, the less efficient was the CPM. There was an association between neuropathic pain scores in DN4 and back-PPT (r = −0.250, p = .015). The more sensitive is the back, the higher is the neuropathic pain score. Finally, a negative association between pain intensity scores and HTT was observed (r = −0.205, p = .048). Higher pain scores correlate to lower heat tolerance. Neuropathic pain score was also correlated with temporal summation of pain (r = 0.206; p = .047), demonstrating the relationship between objective assessment of sensitization and neuropathic pain characteristics (DN4) in this cohort.

There was a correlation between pain intensity and disability (r = 0.209, P = .043), and sensory (r = 0.270, P = .009) and affective (r = 0.214, p = .038) pain descriptors. DN4 scores presented a positive correlation with disability (r = 0.321, p = .002), anxiety and depression scores (r = 0.250, p = .015), and sensory (r = 0.332, p = .001) and affective (r = 0.246, p = .017) pain descriptors. Disability was also correlated higher anxiety and depression scores (r = 0.339, p = .001), and sensory (r = 0.337, p = .001), affective (r = 0.449, p<.0001), and evaluative (r = 0.336, p<.0001) pain descriptors. When comparing patients with efficient versus suboptimal and inefficient CPM, no difference was observed in FDI (p = .704), RCADS (p = .739), pain descriptors (sensory: p = .317; affective: p = .348; evaluative: p = .589; temporal: p = .604), and pain intensity (p = .187).

Discussion

In this study, we performed a detailed pain assessment in patients diagnosed with AIS and chronic back pain. Using age-specific validated instruments, we demonstrated a high prevalence of disability (52.1%), and poor sleep quality (75.5%) in this population. These results provide evidence on the negative impact of chronic pain syndrome on health-related quality of life of these patients. Surprisingly, a large proportion of this cohort presented with back pain for more than 1 year (76.6%) and most of them reported daily pain (55.3%), corroborating other studies that showed lack of adequate pain management in these patients [5]. Growing preclinical and clinical evidence demonstrate that stress in the first decades of life results in abnormalities that may account for maladaptive development and/or functionality within pain circuits, enhancing susceptibility to the development of chronic pain in adulthood [30]. These results

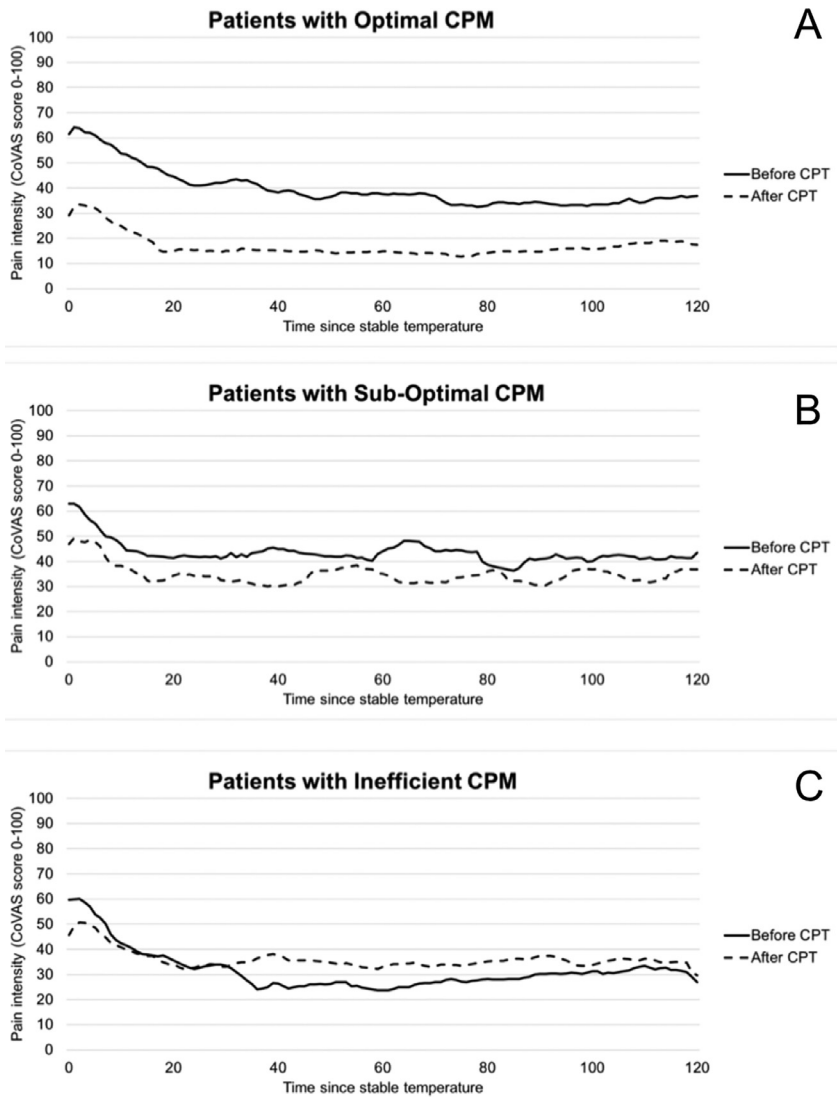

Fig. 4. Conditioned pain modulation paradigm demonstrating different patterns of endogenous pain inhibitory capacity: (A) optimal, (B) suboptimal, and (C) inefficient.

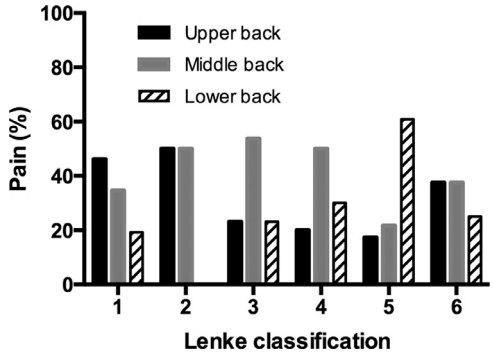

Fig. 5. Location of pain according to the type of spinal deformity (Lenke classification).
Note: 1 (main thoracic), 2 (double thoracic), 3 (double major), 4 (triple major), 5 (thoracolumbar/lumbar), 6 (thoracolumbar/lumbar − main thoracic).

highlight the need for better pain characterization and management strategies in this group of patients.

Pain is a dynamic phenomenon under the influence of several excitatory and inhibitory endogenous pain control mechanisms [26]. In the clinical setting, QST is a well-established tool to assess endogenous pain modulation. The tool presents good reliability in healthy individuals and chronic pain sufferers, and it can be used in all age-groups [31–36]. This assessment is very useful for pain phenotyping and identification of pain sensitization, also in patients with presumed nociceptive pain [37–39]. To the best of our knowledge, this was the first study that used QST to assess chronic back pain in AIS. We observed that 36.3% of patients present at least 50% lower pain pressure thresholds on their backs in relation to their control (unpainful) site, evidence of regional sensitization [29]. In addition,

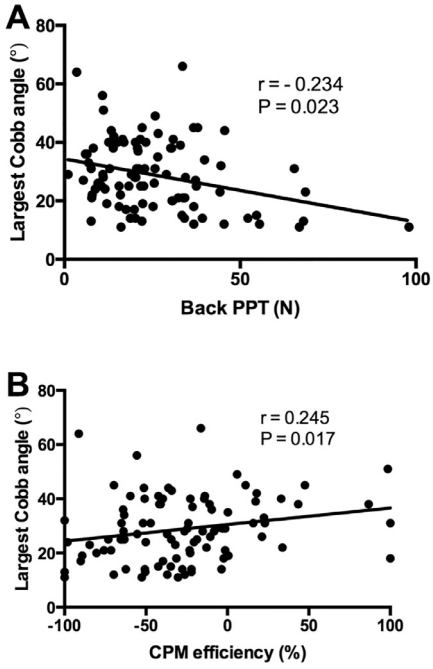

Fig. 6. Scatter-plots showing the correlations between (A) severity of deformity and pain pressure thresholds at the painful area, (B) severity of deformity and conditioned pain modulation efficacy.

central sensitization was clearly evident in 11.7% of patients and reflected by the central pain process of temporal summation of pain in the CPM paradigm test [26]. In fact, despite not being previously demonstrated in AIS, somatosensory disturbances are frequent features of other chronic pain conditions [40].

Conditioned pain modulation paradigm is a quantitative measurement of each individual's ability to inhibit pain [41,42], reflecting the efficacy of the diffuse noxious inhibitory control [43,44]. The CPM is part of the QST protocol. In short, a painful test stimulus is evaluated before and after the application of a second painful (conditioning) stimulus applied to another region of the body. In a normally functioning nociceptive system, the amount of pain experienced after the application of the conditioning stimulus will be reduced in comparison with the amount of pain experienced before the application of the conditioning stimulus (Fig. 4A). Our results demonstrated sub-optimal or inefficient endogenous pain inhibitory response in 48.9% of patients with AIS and chronic back pain (Fig. 4B-C). Deficient CPM has been associated with several chronic pain conditions [45], and it may be responsible for pain chronification in children and adolescents [46]. Pain phenotyping with the identification of an increased in activity of facilitatory pain mechanisms or a deficiency of pain inhibitory control (mechanism-based approach) has been shown to be extremely important for the management of patients with chronic pain [47].

Our results identified a statistically significant weak association ($r \approx 0.3$) between spinal deformity and somatosensory dysfunction in idiopathic scoliosis (Fig. 6). Curve severity was associated with lower pressure pain thresholds and reduced endogenous pain inhibitory capacity. Despite identifying weak associations, we believe our observations are clinically relevant. For example, Bisson et al. [48] recently demonstrated that AIS facet joints present advanced cartilage deterioration as seen in osteoarthritis, providing compelling evidence for the genesis of nociceptive pain in this population. It is well-established that persistent nociceptive stimulus can cause abnormal central nervous system pain processing via pain facilitation or reduction of pain inhibition [49]. Recently, in a population-based study with 3,184 participants, Clark et al. [50] demonstrated that scoliosis at the age of 15 was an independent risk factor for self-reported back pain, days off school and avoidance of activities at the age of 18. Although not providing an absolute causal relationship, our observation of an association between scoliosis severity and pain processes abnormalities suggests that the nociceptive stimulus from the spinal deformity (ie, osteoarthritis) may contribute to the development of chronic pain syndrome in these patients. Moreover, we observed that the more sensitive the patient (HTT), the greater the self-reported pain intensity.

Identification of different pain mechanisms has been suggested to provide basis for a targeted and rational precision medicine approach for pain management, ultimately improving clinical outcomes in chronic pain patients [47]. For example, we found a relatively high prevalence of neuropathic pain (21.3%) in this population. Neuropathic pain was associated with lower pressure pain thresholds and higher temporal summation, both representing dysfunction of the pain processing system. Moreover, neuropathic pain was associated with higher disability and greater scores in anxiety and depression scale. Future studies are needed to evaluate different treatment strategies for pain management according to this mechanism-based approach in AIS with chronic pain.

The main limitation of this study is the lack of normative values for QST in pediatrics for the sites tested in this cohort of AIS (back and forearm). As for comparison, we used data from the German Research Network for Neuropathic Pain [29] that suggested that upper extremity is generally more sensitive to pressure pain than the back. Their study evaluated adults from 18 to 79 years old. For our analyses, we used the patient as his own control and observed that a significant proportion of the sample (36.3%) had at least 50% lower PPT on their back than on the upper extremity tested site. In order to fill the current gap regarding to assessment of pain processing and modulation in children, our group is currently conducting a large epidemiological study using the same technique of QST assessment in healthy children and adolescents. Another limitation is the cross-sectional design of this study which precludes definite conclusion whether these findings of abnormal pain modulation being caused by deformity or patients' own inability to inhibit pain, or enhanced pain facilitation. Despite recent advances in pain research, there is a lack of

longitudinal data in this field. Future studies following patients after diagnosis and evaluating the somatosensory system using standard techniques could detect the nociplastic changes in relationship with deformity progression. This would certainly provide a definitive conclusion for this issue and could potentially define the moment of intervention for prevention of chronic back pain in this population.

Conclusions

Chronic back pain has an important impact in quality of life of adolescents with idiopathic scoliosis. Using a detailed pain assessment, we were able to demonstrate a high prevalence of impaired pain modulation in this group. The association between deformity severity and somatosensory dysfunction corroborates with previous studies which demonstrated abnormal neuroplastic changes in central and peripheral nervous systems caused by structural pathology and continuous nociceptive stimulus. More importantly, our results suggest that different pain processing mechanisms may be involved in this group of patients, such as peripheral and central sensitization as well as a deficient pain inhibitory control. A mechanism-based approach to back pain might help clinicians to better manage these patients.

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