Benign Joint Hypermobility Minimally Impacts Autonomic Abnormalities in Pediatric Subjects with Chronic Functional Pain Disorders

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Objective To determine if children with benign joint hypermobility (BJH) syndrome and chronic functional pain disorders have more autonomic dysfunction.

Study design Retrospective chart review study of pediatric patients seen in the pediatric neurogastroenterology and autonomic clinic who underwent autonomic testing and had either a Beighton score of ≥6 and met Brighton criteria for BJH (with BJH) or a score of ≤2 (no BJH).

Results Twenty-one female subjects (10 without BJH) met inclusion criteria; 64% of BJH had diagnosis confirmed by genetics consultation. We evaluated for postural tachycardia syndrome, syncope, orthostatic intolerance, and orthostatic hypotension. None of these diagnoses, as well as baseline heart rate, peak heart rate in first 10 minutes of head up tilt ($P = .35$ and $P = .61$, respectively), and sudomotor index (suggestive of autonomic neuropathy) ($P = .58$), showed differences between the groups. Age of onset of symptoms was also similar ($P = .61$) (BJH vs without BJH: median [range]:15.6 years [12.9-17.5] vs 15.4 years [11.1-18.2]). There was no difference between groups in complaints of migraine, chronic nausea, chronic fatigue, lightheadedness, dizziness, fainting >3 times/lifetime, delayed onset of sleep, irritable bowel syndrome, dyspepsia, abdominal migraine, functional abdominal pain, constipation, or fibromyalgia.

Conclusions Children with chronic functional pain disorders and BJH have autonomic testing findings and comorbid features compared with a similar cohort of subjects without BJH, suggesting that BJH is not the driver of the autonomic and comorbid disorders. *(J Pediatr 2016;177:49-52).*

Benign joint hypermobility (BJH) syndrome involves musculoskeletal symptoms in the presence of excessive joint laxity.[1] BJH is associated with dysfunction of multiple body systems, including the autonomic nervous system[2] and the gastrointestinal (GI) tract, along with a wide range of neuropsychiatric disturbances.[3,4] Because BJH develops quite early in life, it may predispose to these other syndromes or it may simply represent another comorbid symptom in individuals prone to functional pain syndromes. Studies of the pediatric population may help clarify this question because joint hypermobility begins in childhood.

We previously reported a high prevalence of joint hypermobility in adolescents with functional GI disorders.[5] This was confirmed by Pacey et al.[6] Essentially no studies address the relationship between autonomic abnormalities and pediatric joint hypermobility. However, we have reported that adolescents with chronic functional pain disorders and postural tachycardia syndrome (POTS) do not have a higher prevalence of BJH compared with similar patients without POTS.[7] The majority of subjects with BJH had a borderline Beighton score of 4 or 5 out of 9, suggesting mild to moderate BJH. We hypothesize that POTS is associated with more severe BJH. Further, most studies of adult patients compare those with BJH with otherwise healthy individuals, instead of comparing subjects with similar, chronic pain syndromes who do not have BJH. This comparison confounds the actual contribution of BJH to the presence of autonomic abnormalities because subjects with BJH are phenotypically very different from healthy subjects.

To determine if subjects with BJH have more autonomic dysfunction, instead of comparing healthy controls with subjects with BJH, we need to compare subjects with and without BJH who are otherwise presenting with similar complaints, such as chronic aches and pains, migraine, fatigue, and GI issues. The aim of the current study was to determine whether pediatric patients with and without moderate to severe BJH who suffer from at least 1 chronic functional pain

BJH	Benign joint hypermobility
BP	Blood pressure
GI	Gastrointestinal
OH	Orthostatic hypotension
POTS	Postural tachycardia syndrome

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disorder and have undergone autonomic testing differ in their level of autonomic abnormalities.

Methods

This retrospective, institutional review board-approved chart review was conducted on about 300 pediatric visits of patients in our autonomic disorders registry, seen between August 2015 and February 2016 in the pediatric neurogastroenterology and autonomic disorders clinic. Patients referred to this clinic usually have a myriad autonomic complaints, migraines, nausea, fatigue, and/or functional GI disorders. All subjects had at least 1 chronic functional disorder. To avoid overlap of mild or borderline joint hypermobility, inclusion required a Beighton score of ≥6 (group with BJH) and the Brighton criteria for BJH.[8] The comparison group included otherwise similar subjects with a Beighton score ≤2 (no BJH) and who did not meet Brighton criteria for BJH. To find the subjects who met the inclusion criteria, we reviewed all the epic encounters seen in the clinic and included only those that met criteria. The other ones who had Beighton scores of 3, 4, or 5, or those who may have met Beighton criteria but did not meet the Brighton criteria for BJH, were not included. The Brighton criteria are based on major and minor criteria, which include the Beighton score, arthralgia, dislocation, subluxation, skin and eye findings, and soft tissue lesions such as bursitis.[8] Standard examination in our clinic includes detailed review of systems, a general and neurologic examination, fibromyalgia tender point examination,[9] and joint hypermobility evaluation through a Beighton score.[10] The evaluation is done by 2 well-trained physicians. We collected the following data from systematic chart review as was previously described[5,7]: (1) demographics and medical history; (2) comorbid symptoms including symptoms of chronic fatigue (>6 months), sleep disturbances, dizziness, syncope, chronic nausea, GI symptoms with functional GI diagnoses based on fulfillment of Rome III criteria, migraine headaches as per the 2013 International Classification of Headaches Disorders,[11] and fibromyalgia assessed by tender point[9]; (3) Beighton scores and information about Brighton criteria as well as review of genetic notes when available; and (4) autonomic testing results.

All subjects completed autonomic testing at our institution or at an outside institution with a similar protocol. Clinical autonomic testing includes a motorized tilt table test with the patient supine for 10 minutes followed by 70° upright for 30 minutes (40 minutes with a history of syncope) and continuous beat-to-beat blood pressure (BP)[12] and heart rate measurements.[13] The deep breathing response assesses cardiac parasympathetic function, the Valsalva maneuver (using 15 seconds and 40 mm Hg) assesses cardiac sympathetic and parasympathetic functions, and quantitative sudomotor axon reflex test evaluates for autonomic neuropathy. Norms were used as described by Low and Sletten.[14] All autonomically active medications were stopped at least 5 half-lives prior to testing, except 1 subject who did not stop fludrocortisone (this subject had BJH, and the test showed orthostatic intolerance and syncope despite the presence of fludrocortisone, suggesting that the medication did not influence classification).

Autonomic Measures

Autonomic testing results were quantified using a modified composite autonomic severity score[14] and, as we have previously described,[15] with sudomotor and cardiovascular heart rate indices. The tilt table test baseline heart rate was taken as the average of the last 4 minutes of the 10-minute supine recording prior to tilt-up. The peak heart rate in the first 10 minutes of upright tilt table test was taken as the mean of the 3 minutes of highest heart rate not including the first minute upright (all subjects have a transient heart rate increase). Reflex syncope was defined as an abrupt drop in BP[12] and sometimes heart rate upon head-up tilt. Orthostatic hypotension (OH) required a drop in systolic BP of >20 mm Hg or diastolic BP of >10 mm Hg in the first 3 minutes upright. Delayed OH was defined as OH after the first 3 minutes upright.[16] POTS required an increase in heart rate >40 bpm[17] during the first 10 minutes of the head-up tilt test, without sustained BP drop (systolic BP >20 mm Hg or diastolic BP >10 mm Hg), and accompanied by symptoms of orthostatic intolerance while upright, such as dizziness, lightheadedness, tunnel vision, and nausea.[13] Orthostatic intolerance was defined as the presence of orthostatic symptoms such as nausea, dizziness, and lightheadedness, while upright without meeting criteria for POTS, OH, or syncope. Clearcut autonomic neuropathy was defined as a sudomotor score of 3 in the modified composite autonomic severity score.

Statistical Analyses

SPSS v 22 (IBM Software; SPSS Inc, Chicago, Illinois) was used to analyze the data. Nonparametric tests were used for the analyses of continuous or ordinal variables. Fisher exact test was performed for categorical variables. A P value of <.05 was considered significant.

Results

Of 21 female subjects, 11 (52%) had BJH, which was confirmed in 7 of the 11 (64%) patients with genetics consultation, and meeting classic Brighton criteria in 3 of 4 remaining subjects.[8] The last subject had a Beighton score of 8/9, high arched palate, and affected first-degree relatives along with complaints of easy bruising, lightheadedness, and dyspepsia symptoms. Geneticists recommended a reassessment in 2 years before committing to a final diagnosis of BJH. Given that this subject met the Brighton criteria, the subject was included. **Table I** details the major and minor criteria for each subject based on the Villefranche 1997 criteria.[18] The Villefranche criteria include 2 major diagnostic criteria and 3 minor criteria (**Table I**). Based on this classification, subjects need to have 1 or more major criteria and have 1 or more minor criteria in the diagnosis.[18]

The tilt table diagnoses of POTS, syncope, orthostatic intolerance (symptoms while upright during head-up tilt but not meeting criteria for POTS), and OH did not differ between the 2 groups (**Table II**), nor did baseline heart rate and peak