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Parental-reported pain insensitivity in Dup15q

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ABSTRACT

Parents of children with chromosome 15q duplication syndrome (Dup15q) have anecdotally reported high pain threshold as a feature of the disorder. The purpose of this study was to document parental-reported estimates of the frequency of high pain tolerance and the stimuli that fail to evoke a normal pain response. We sent an online survey to 840 families with children with Dup15q to explore the frequency and clinical manifestations of high pain threshold. There were 216 respondents (25.7%). A high pain threshold was reported in 87% of children at some time. There was a trend ($p = 0.06$) for high pain threshold to be more commonly observed among children with the isodicentric (85.6%) and other genetic variants (95%) than interstitial (69.6%) duplications. There was no association between reports of high pain threshold and reports of an intellectual disability (91% of cases), autism spectrum disorder (83% of cases), or self-injurious behavior (40% of cases). Reports included many dramatic cases such as severe burns, broken bones, and electrical traumas, which were associated with little or no evidence of a painful stimulus. A high pain threshold is reported in other disorders associated with intellectual disability and autism; the underlying mechanism in Dup15q and other disorders remains undefined.

1. Introduction

The perception of pain and behavioral responses to pain are complex physiological processes involving diverse genes and neuroanatomical networks. Patients with autism spectrum disorder (ASD) and intellectual disability as well as catatonia and schizophrenia exhibit diminished responses to painful stimuli [1,2]. Historically, these patients were initially considered to suffer from 'indifference' or 'asymbolia' to pain. However, these individuals detect pain as "pain", although they may be insensitive to pain (i.e., unable to detect different levels of pain) or have altered pain reactivity [1,2]. The latter may result from an inability to assign emotional valence to pain, an impaired or atypical behavioral expression in response to pain, or both. For example, in individuals with ASD, absent or reduced behavioral pain reactivity was reported in 69% at home and observed during venipuncture in 56% [2]. Paradoxically, heart rate increase during venipuncture was significantly greater among individuals with ASD than controls [2], supporting aberrant emotional recognition or expression of pain but preserved or enhanced pain sensation. Further, some patients with ASD show increased sensitivity to pain [3,4], possibly reflecting sensory hypersensitivity in ASD [5]. The same child may experience apparent hyposensitivity to pain but hypersensitivity to light, sound, smell, and/or touch. In contrast, individuals with congenital insensitivity to pain can feel stimuli but do not perceive them as painful [6].

Chromosome 15q duplication syndrome (Dup15q) results from duplications in the long arm of chromosome 15 that causes high rates of ASD and intellectual disability [7]. Copy number variants in this region increase susceptibility to duplications. Maternally inherited mutations are more likely to lead to symptomatic phenotypes [8]. Clinical features include hypotonia, ASD, delays in motor and language development, cognitive and learning disabilities, treatment-resistant epilepsy, and facial dysmorphism. More severe impairments occur in patients with isodicentric chromosome 15 (idic15) [9,10], resulting from three copies of maternal 15q11–q13, while those with interstitial duplications have only two copies. Chromosome 15q duplication syndrome occurs in 0.5 to 3% of all ASD cases [11].

High pain tolerance in individuals with Dup15q remains poorly characterized [12]. There is limited evidence of high pain tolerance within specific genetic populations. The purpose of this preliminary study was to document parental-reported estimates of the frequency of high pain tolerance and the stimuli that fail to evoke an age or stimulus-appropriate response to pain.

2. Methods

Two surveys were emailed to registered members of the Dup15q Alliance — a volunteer-led nonprofit organization whose members include 840 families of children with Dup15q. There were 13 questions in total (Supplement 1). The first survey asked five questions that related to: whether or not the child had a high pain tolerance, the child's genetic diagnosis, a photograph of an injury, a descriptive example of an instance where the child reported minimal or no pain responses in

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response to a serious injury, and permission to share this information. The second survey asked eight questions: age, sex, if any of the child's injuries associated with high pain threshold required medical attention, if the child had self-injurious behaviors, if the child is on the autism spectrum, if the child has intellectual or cognitive impairment/delays, if the child showed decreased sweating unrelated to medications, and if the child had increased sensitivity to sensory stimuli. These 13 questions included multiple-choice, yes/no responses, or specific data (e.g., age) questions, and 2 questions that allowed for open-ended responses (e.g., please describe an incident where your child has exhibited a high pain tolerance). The questions were based on a review of the literature on high pain tolerance and informal parental interviews. They were administered via the Internet and were answered by the patients' parents. Parents reported examples of minimal or no pain responses over the course of the child's life. Responses consisting of quantitative data were analyzed for group averages and ranges while subjective/qualitative responses (e.g., examples of high pain tolerance) were reviewed and grouped by response type. Relationships between history of ASD by parental report and reported high pain tolerance were examined using Fisher's exact test. For instances of missing fields, the survey was readministered until the data for each patient were as complete as possible.

This study was deemed exempt from review by the NYU Langone Medical Center IRB since the surveys were initiated by the Dup15q Alliance, and clinical data including photographs have been de-identified.

3. Results

We received responses from 216 families (25.7%). Table 1 summarizes the clinical and genetic features in this sample. Of the 160 respondents on this question, 137 (85.6%) reported a high pain tolerance at some time in the patient's life, 10 (6.3%) reported that their child did not have a high pain tolerance, and 13 (8.1%) were unsure. All respondents were parents or caregivers. There was no association between the frequency of high pain tolerance and the presence of intellectual disability (>90%) or ASD (84.5%) and those without ASD or unsure of ASD status (81.6%). There was a trend ($p = 0.06$) for an increased frequency of high pain tolerance among those with idic15 (86%) and other genetic variants (95%) as compared with those with interstitial 15q (70%). Examples of pain responses are provided in Table 2 below. Figs. 1–3 illustrate examples of injuries in this population that were not associated with any painful responses. Hypersensitivity to stimuli other than pain (i.e., light, sound, smell, and/or touch) was reported in 78% of children. A lack or impairment in sweating that was not related to medication was reported in 13% of children. Self-injurious behavior was reported in 41% (50/123) of subjects. We followed up with six patients (ages 19, 21, 22, 23, 27, and 38 years old) whose parents consented to be contacted to investigate whether their tolerance for pain changed over time. Four of the six patients' tolerance remained the same throughout their lives, while one varied, and the other developed a higher tolerance for pain over time.

Table 1
Clinical features of respondents.

	# of respondents		
Age	135	Average	9.48 years
		Range	10 month–37 years
Sex	153	Female	68 (44%)
		Male	85 (56%)
Genetic diagnosis	215	idic15	137 (64%)
		Interstitial 15q	38 (18%)
		15q11.2	15 (7%)
		15q13.3	6 (3%)
		Other	12 (6%)
		Unsure	7 (3%)
Autism spectrum disorder	122	Yes	80 (66%)
		No	15 (12%)
		Unsure	27 (22%)
Intellectual or cognitive impairments	121	Yes	110 (91%)
		No	4 (3%)
		Unsure	7 (6%)

Note. Not all survey respondents answered all questions.

Table 2
Examples of aberrant pain threshold.

	# of respondents: N = 137
Fall leading to intense bleeding, bruising, or requiring stitches	34
Broken or fractured bone	18
Received a burn/blister from touching a hot object	16
Head bump on floor or other object	11
Surgery or procedure without anesthesia or post-pain medications	10
Self-injurious behaviors	7
Fingers or toes jammed in door/drawer	6
Blood draws	6
Injuries due to epileptic seizures	4
Multiple ant bites	3
Heat intolerance	2
Kidney stone	2
Injuries to feet but still walking on them	2
Chronic ear infections	1
Tore toenail off	1
Ripped mouth open	1
Grabbed an electric fence	1
Bitten by another child	1
Severed tongue	1
Cold tolerance	1
Unable to categorize (unknown injuries)	9

Note. For each patient, only the most severe instance of lowered pain threshold is reported.

4. Discussion

The results from this preliminary study suggest that high pain tolerance is a significant issue for 86% of individuals with Dup15q. In this study and previously reported cohorts, impaired pain responsiveness ranges from mild to profound. In some patients, emotional displays in response to moderate injuries are mildly attenuated while in others there is no evidence of pain perception or response despite injuries that normally evoke severe and prolonged pain. Commonly reported features include lack of withdrawal responses to intense or sustained heat stimuli; minimal or absent grimacing or crying after serious falls, cuts, or bruises;

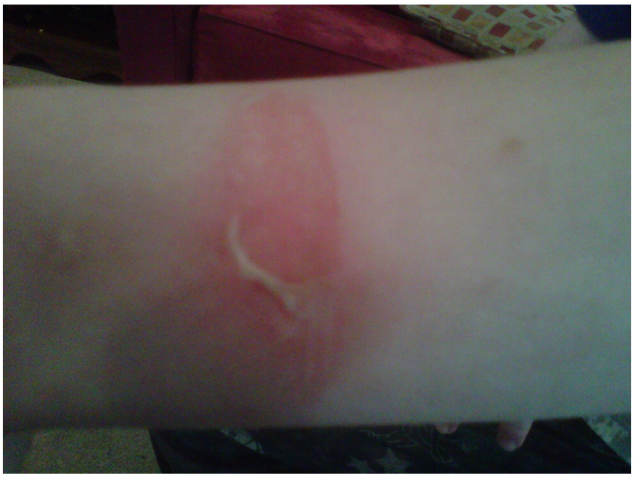

Fig. 1. Burn on arm from iron. This child awoke from sleep, found the iron, plugged it in and turned it on. When his mother found him, he was sitting on the floor looking at the iron calmly with no reaction. He was taken back upstairs and put back to bed and fell asleep. In the morning, his mother noticed burn marks all over his arms. He never said a word nor cried.