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Research Article

Pain Insensitivity in Cri du Chat Syndrome

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Abstract

Background: Cri-du-Chat Syndrome (CdCS) is a rare genetic disease, caused by a deletion of variable size on the short arm of chromosome 5, and characterized by a cat-like cry, intellectual disability and high frequency of self-injured behavior, such as Skin Picking. Parents often report an altered pain perception in these patients during their activities of daily life.

Aim: To evaluate the sensory peripheral pathways in CdCS patients.

Methods: We evaluated four patients with CdCS by Quantitative Sensory Study (QST), neurological exam and nerve conduction studies.

Results: All four CdCS patients showed a high threshold and an exaggerate tolerance to thermal (cold and warm) stimuli at QST, even if the clinical history, the neurological exam and the nerve conduction study were negative for a peripheral neuropathy.

Conclusions: Our study is the first description of an altered perception of pain in CdCS patients. Potential peripheral and central mechanisms are discussed.

Keywords: Insensitivity; Chat Syndrome; Pain; CdCS

Introduction

Cri-Du-Chat Syndrome (CdCS) is a hereditary congenital syndrome (OMIM #123450) with an incidence ranging from 1:15.000 to 1:50.000 live-born infants [19], associated with deletion of part of the short arm of chromosome 5. The deletions can vary in size from extremely small and involving only band 5p15.2 to the entire short arm. The syndrome is characterized by a high-pitched cat-like cry at birth, microcephaly, facial dysmorphisms, intellectual disability.

Although the main clinical features of CdCS are well known, the neurocognitive and behavioural characteristics of the phenotype are rarely described in detail. From a parental perspective, the main behavioural problems, in order of frequency, are the following: aggressive behaviour, stereotypies, anxiety, phobias, and genital manipulation/masturbation [13], as well as high frequency (61 - 85%) of pathological body-focused repetitive behaviors such as pathological skin picking (SP) [26].

Interestingly, CdCS patients show an altered pain perception in the daily life [10] with family members reporting patients having a prolonged shower with very hot water without any discomfort.

To our knowledge, no study has specifically investigated whether patients with CdCS experience pain differently from healthy subjects and if their peripheral nervous system is intact.

Aim of the present study is to explore if patients with CdCS present an alteration of sensory pathways.

Subjects and Methods

We recruited four patients (2 males and 2 females, aged 27-32 years) with genetically confirmed CdCS.

All patients presented pathological SP. All patients reported the absence of painful symptoms in any region of the body, scoring 0 for the Facial Pain Scale [31].

The Scientific Committee of Italian Association of cri du chat syndrome (A.B.C., Associazione Bambini Cri du chat) approved this study and parents of the patients provided written, informed consent after receiving a detailed description of the study's aims. The identities of the participants remained anonymous.

The scientific protocol included:

- A nerve conduction study (NCS) of peroneal and ulnar motor fibers as well as of sural and ulnar sensory fibers performed bilaterally.
- A neuropathy symptoms score (NSS), in order to evaluate neuropathic abnormalities through a standardized neurological examination by Dick's criteria [4].
- A quantitative sensory testing technique (QST, Medoc), in order to determine the sensation and pain threshold for cold and warm temperatures by stimulating the skin and comparing the results to normative values by the literature [30]. Each test was performed on the hand palmar index, little finger, bilaterally. Thermal sensation and pain were tested by means of a thermode, aluminium coated, capable of heating or cooling, attached to the patient's skin sites. The stimulus progressively increased in intensity and was halted by the subject with a simple push-button response, as soon as sensation was first perceived [5]. The analysis of heat and cold-induced pain was not a pain tolerance test; the patients were instructed to press the button when thermal sensation became unpleasant.

All four CDC patients performed the QST composed of cold sensation (normal range: 3,7 - 28 °C), warm sensation (normal range: 37,9 - 48,3°C), cold-induced pain (normal range: 9,9 - 26,6°C), heat-induced pain (normal range: 39,1 - 46,7°C). Thermal thresholds were averaged from the responses of three successive stimuli applied to each test site. Pain thresholds were averaged from the responses of three successive stimuli for each site. Degree of difference of values between CdC data (P2) and intermedium value of normal QST interval (P1) were calculated according to the formula Δ= (P2 - P1)/(P1) Δ% 100.§Δ All patients were able to understand simple instructions and to express pain or discomfort, however we exclude the face as investigated area, because of reduced compliance of patients.

Results

The demographic and genetic characteristics of the four CdCS patients and QST results are illustrated in the table 1.

In all patients, neurological exam showed normal tendon reflexes at the upper and lower limbs, clinical examination for discriminative sensation was normal for tactile, pallesthesic, thermal and pain modalities (NSS = 0) and NCS demonstrated a normal nerve conduction.

The QST study showed a dramatic alteration of thermal pain, both for cold and warm sensation, associated with a slightly altered or normal threshold of sensation. Differences were particularly significant for cold tolerance pain test (see table 1).

PTS	Sex	Age	Genetic	Cold threshold (C°)	Warm threshold (C°)	Cold pain (C°)	Warm pain (C°)
1	Female	32	46, XX, del(5)(p14.1)	24	39	4 **(-73.3%)	49*(+14.2.%)
2	Male	22	46, XY, del(5)(p14.3)	25	44	0**(-100%)	50* (16.5%)
3	Male	25	46, XY, del(5)(p14.3)	4.6	49.9* (+15.7 %)	0**(-100%)	50*(16.5%)
4	Female	27	46, XX, del (5) (p15.2p14.3)	22.2	49.3* (+13.3 %)	0**(-100%)	50*(16.5 %)

Table 1: Quantitative Sensory Test data in four CdCS patients (mean data between right and left upper limb).

* Slight alteration; ** marked alteration

(P1) Degree of difference between CdCS data (P2) and intermedium value of normal QST interval (P1) according to the formula Δ= (P2-P1)/(P1) Δ% 100. §Δ

Normative Value: cold sensation (normal range: 3,7- 28 °C), warm sensation (normal range: 37,9- 48,3°C), cold-induced pain (normal range: 9,9-26,6°C), heat-induced pain (normal range: 39,1- 46,7°C).

The difference between right and left hand's QST values was not significant, so a medium value of right and left upper limb is reported. In figure 1, detailed results of a representative case (n. 4) are reported.

Figure 1: Clinical Case n. 4: Here are reported the responses to cold and heat with a mean value (white) of the three stimulus administration. On the left side, the threshold of cold (blue) sensation is normal, while the heat (red) is higher (13.35%) than the intermedium value of normal QST interval (37.9-48.3); on the right side, the cold-induced pain is tremendously far (100%) from range of intermedium value of range of normality, and even the heat-induced pain is altered (16.5% different from the normal range.

Discussion and Conclusion

There is increasing attention to somatic substrates of behavior in genetic syndromes, and growing evidence of the association between discomfort or pain and self-injured behaviors in people with intellectual disability and genetic syndromes.

Generally, painful syndromes and altered perception of pain are frequent manifestations of peripheral neuropathy detected by NCS.

Peripheral neuropathies are mostly described in single case reports of patients affected by genetic conditions and intellectual disability [15,33,22], however a possible association with an alteration of pain sensation has not been discussed, and the literature is lacking larger samples. Brandt., *et al.* [2] reported impaired peripheral somatosensory function in children with Prader-Willy Sindrome.

Insensitivity to pain has been associated to a genetic mutation in a large number of genes, in syndromes with hereditary sensory and autonomic neuropathy (HSAN).

Among them, the gene RETREG1 (OMIM 613115), causing an HSAN2 type B, an autosomal recessive form of the disease, is localized on 5p15.1. Heterozygotes for mutations in this gene are expected to be unaffected but no definitive detailed studies on their sensitivity to pain have been performed. Conversely, individuals affected by mutation of WNK1 gene, located on 12p13.33 (OMIM 201300) pathogenic variants, causing HSAN2 type A, show an increased sensitivity to thermal stimuli [17]; of course, deletion of an allele may result in phenotypic different from effects of various types of mutations.

Furthermore, perception thresholds of touch/pressure, vibration, and two-point discrimination are significantly higher, and proprioception sensitivity is significantly lower [14] in patients with congenital insensitivity to pain with anhidrosis, which is a rare autosomal recessive disorder caused by homozygous or compound heterozygous mutation in the NTRK1 gene on 1q23 (OMIM 256800) and characterized by lack of pain and thermal sensation, anhidrosis, thermodysregulation, and mental retardation.

Lack of pain and thermal sensation, anhidrosis, thermodysregulation, and mental retardation have been described as congenital features within HSAN, but cases presented in the literature may differ concerning presence or not of anhidrosis and/or peripheral neuropathy.

All CdCs cases of the present study present altered pain and thermal sensations and mental retardation but not anhidrosis and neuropathy.

In a Moroccan family, authors described HSAN without anhidrosis but with axonal sensory polyneuropathy [16]; Sagafos., *et al*. described a family with all alterations, of different degree, according to presence of homozygote or heterozygote mutation [24]. Shatzky., *et al*. reported full alterations even in an Israeli- Bedouin family [25].

Single-fibers studies on mices with NAV1.7 mutations [12] and HSAN patients caused by a mutation of the NGFβ gene, located on 1p13.2 (OMIM *162030) [24] confirm an impaired heat and mechanical nociception in behavioural tests.

The sodium channel NaV1.7 contributes to action potential generation and propagation and these loss-of-function mutations lead to congenital indifference to pain, though it remains unclear where, on the way between sensory terminals and central nervous system, the signaling is disrupted. The clear deficits in somatic primary afferent functions shown in our study may be complemented by previously reported synaptic dysfunction and opioidergic inhibition, together accounting for the complete insensitivity to pain in the human mutants lacking NaV1.7.

To our knowledge, this is the first study evaluating nerve conduction along with pain threshold and reporting pain insensivity in CdCS patients. There are not previous NCS studies or even clinical reports of peripheral neuropathy on CdCS. An auditory neuropathy has been reported in a single case [27], based on abnormal auditory evoked potentials.

Clinically, insensitivity to pain in a syndrome characterized by a catlike-cry - which looks like a flat, monotonous melody type in spectography sound analysis [20], suggesting a pain decoding inability - is curious [23].

Our CdCs cases are characterized by normal NCS and insensitivity to hot and warm pain, and moderate alteration of thermal thresholds for warmth and cold detection testing. These data support a substantial integrity of type II Aβ fibers and a possible alteration of type III Aδ and type IV C fibers of the spinothalamic tract.

These findings may have a practical impact on the local anesthesia planning both for the management of dental problems, very frequent in CdCS patients [9], and for general anesthesia planning, the latter reported in the 73.5 % in Italian cases by a previous study of our group [8].

Our data open a window into further studies, both by carrying on the investigation on sensory processing focusing on central pathways (for instance by neuroimaging), and to search for therapies focusing on a central control of sensory disturbances.

In support of therapeutical strategies with the aim to modify central mechanisms of sensory control, a previous study reported a reduction of SP by using high dosage of N-acetylcysteine [21], which stimulates inhibitory metabotropic glutamate receptors and, thereby, reduces synaptic release of glutamate [18]. Glutamate is the predominant excitatory neurotransmitter used by primary afferent synapses and neurons in the spinal cord dorsal horn; glutamate receptors are also located in areas of the brain, spinal cord and periphery involved in pain sensation and transmission [32].

A final consideration concerns our hypothetical correlation between thermal pain insensitivity and SP. Of course further studies are needed but it is interesting that SP, a frequent manifestation in CdCs, is associated with neuroanatomic alterations of sensorimotor control. Self-injury may be related to alterations in somatosensory cortical and subcortical regions and their white-matter pathways, thus reflecting an alteration of brain development. Indeed, both neuroimaging and neurocognitive studies suggest that people affected by pathological SP find it difficult to inhibit dominant motor responses due to a failure of "top-down" control mechanisms. An incomplete development of the sensorimotor organization may be highlighted from our recent PET studies on CdCS patients presenting SP [3] that revealed an hypometabolism in the right caudate body, in the left temporal lobe, the right frontal subcallosal gyrus, the caudate body, and in the cerebellar tonsils.

Our PET findings are in agreement with previous neuroimaging studies [1] on patients with SP that showed the presence of structural abnormalities in the insular cortex and parietal and occipital regions (regions involved in the integration of sensory motor informations) and a reduced gray-matter volume in the left cerebellar lobules [29]. Furthermore, in individuals with SP, impulsiveness correlated positively with increased cortical thickness in the left insula, and SP severity correlated negatively with cortical thickness in the left supramarginal gyrus and in the region encompassing the right inferior parietal, right temporal and right supramarginal gyrus, suggesting that similarities and differences exist in symptomatology between SP and the other obsessive-compulsive and related disorders [11]. Furthermore, Wabnegger., *et al*. [29] demonstrated that during picking, SP patients exhibit an increased activation of the left ventrolateral prefrontal cortex, as if the action of picking was a compensatory strategy in order to activate hypofunctional circuits.

Finally, various neuroimaging studies support a correlation between behavior disorders and anatomic alterations of sensory function networks in patients with intellectual disability or genetic disorders: children who engaged in self-injury had significantly lower fractional anisotropy and higher mean diffusivity values in the left posterior limb of the internal capsule [6]; patients affected by autism spectrum disorder show self-injury scores negatively correlated with thickness in the right superior parietal lobule, in the bilateral primary somatosensory cortex and in the left ventral-posterior nucleus of the thalamus [28].

A limitation of the present study is related to the lack of a control group of CdCS patients without SP or a group if individuals with intellectual disability without SP, or even healthy controls with and without SP.

In addition, a bias of our investigation, is the small number of the enrolled patients. Nevertheless, it should be kept in mind that CdCS is a rare condition and recruitment of these individuals is difficult.

Another limitation is that the threshold of pain has been evaluated by QST and not by laser-evoked potentials, the latter considered a gold standard assessment for small sensory fibers study. However, the clinical utility of QST has been well documented in a variety of pain disorders and it has been used to characterize pain and predict prognosis and response to therapy [7].

Bibliography

1. Blum AW., *et al.* "Neuroanatomical correlates of impulsive action in excoriation (skin-picking) disorder". *The Journal of Neuropsychiatry and Clinical Neurosciences* 30.3 (2018): 236-241.

2. Brandt BR and I Rosén. "Impaired Peripheral Somatosensory Function in Children with Prader-Willi Syndrome". *Neuropediatrics* 29.3 (1998): 124-126.

3. Cistaro A., *et al.* "18F-FDG PET Identifies Altered Brain Metabolism in Patients with Cri du Chat Syndrome". *The Journal of Nuclear Medicine* 61.8 (2020): 1195-1199.

4. Dick PJ., *et al.* "Human diabetic endoneurial sorbitol, fructose and myo-inositol related to sural nerve morphometry". *Annals of Neurology* 8.6 (1980): 590-596.

5. Dick PJ., *et al.* "A 4, 2, and 1 stepping algorithm for quick and accurate estimation of cutaneous sensation threshold". *Neurology* 43.8 (1993): 1508-1512.

6. Duerden EG., *et al.* "Self-injurious behaviours are associated with alterations in the somatosensory system in children with autism spectrum disorder". *Brain Structure and Function* 219.4 (2014): 1251-126.

7. Dworkin RH., *et al.* "Interventional management of neuropathic pain: NeuPSIG recommendations.; International Association for the Study of Pain Neuropathic Pain Special Interest Group". *Pain* 154.11 (2013): 2249-2261.

8. Guala A., *et al.* "Anesthesia in Cri du Chat syndrome: Information on 51 Italian patients". *American Journal of Medical Genetics A* 167A.5 (2015): 1168-1170.

9. Hall C., *et al.* "The association between Cri du chat syndrome and dental anomalies". *Journal of Dentistry for Children* 81.3 (2014): 171-177.

10. Han I., *et al.* "Anesthetic experience of a patient with cri du chat syndrome". *Korean Journal of Anesthesiology* 65.5 (2013): 482-483.

11. Harries MD., *et al.* "A structural MRI study of excoriation (skin-picking) disorder and its relationship to clinical severity". *Psychiatry Research: Neuroimaging* 269 (2017): 26-30.

12. Hoffmann T., *et al.* "NaV1.7 and pain: contribution of peripheral nerves". *Pain* 159.3 (2018): 496-506.

13. Honjo RS., *et al.* "Cri du Chat syndrome: Characteristics of 73 Brazilian patients". *The Journal of Intellectual Disability Research* 62.6 (2018): 467-473.

14. Iijima M and Haga N. "Evaluation of nonnociceptive sensation in patients with congenital insensitivity to pain with anhidrosis". *Child's Nervous System* 26.8 (2010): 1085-1089.

15. Kabzińska D., *et al.* "Warburg microsyndrome type 1 associated with peripheral neuropathy and cardiomyopathy". *Folia Neuropathologica* 54.3 (2016): 273-281.

16. Kissani N., *et al.* "Congenital insensitivity to pain: clinical and neurophysiological study in three sisters of a Moroccan family". *Archives de Pédiatrie* 20.11 (2013): 1219-1224.

17. Kurth I. "Hereditary Sensory and Autonomic Neuropathy Type II". In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. Seattle (WA): Universityof Washington, Seattle (2010).

18. Lafleur DL., *et al.* "N-acetylcysteine augmentation in serotonin reuptake inhibitor refractory obsessive-compulsive disorder". *Psychopharmacology (Berl)* 184.2 (2006): 254-256.

19. Mainardi PC. "Cri Du Chat Syndrome". *Orphanet Journal of Rare Diseases* 1 (2006): 33.

20. Michelsson K., *et al.* "Cry analysis of infants with karyotype abnormality". *Neuropediatrics* 11.4 (1980): 365-376.

21. Miller JL and Angulo M. "An open-label pilot study of N-acetylcysteine for skin-picking in Prader-Willi syndrome". *American Journal of Medical Genetics A* 164A.2 (2014): 421-424.

22. Ram S., *et al.* "Axonal neuropathy in female carriers of the fragile X premutation with fragile x-associated tremor ataxia syndrome". *Muscle Nerve* 52.2 (2015): 234-239.

23. Reid D., *et al.* "Executive functioning in Cornelia de Lange syndrome: Domain asynchrony and age-related performance". *Journal of Neurodevelopmental Disorders* 9.1 (2017): 29.

24. Sagafos D., *et al.* "Single-Fiber Recordings of Nociceptive Fibers in Patients with HSAN Type V With Congenital Insensitivity to Pain". *The Clinical Journal of Pain* 32.7 (2016): 636-642.

25. Shatzky S., *et al.* "Congenital insensitivity to pain with anhidrosis (CIPA) in Israeli-Bedouins: genetic heterogeneity, novel mutations in the TRKA/NGF receptor gene, clinical findings, and results of nerve conduction studies". *American Journal of Medical Genetics* 92.5 (2000): 353-360.

26. Spunton M., *et al.* "Skin picking disorder in 97 Italian and Spanish Cri du chat patients". *American Journal of Medical Genetics A* 179.8 (2019): 1525-1530.

27. Swanepoel D. "Auditory Pathology in Cri-Du-Chat (5p-) Syndrome: Phenotypic Evidence for Auditory Neuropathy". *Clinical Genetics* 72.4 (2007): 369-373.

28. Tordjman S., *et al.* "Relationships Between Self-Injurious Behaviors, Pain Reactivity, and β-Endorphin in Children and Adolescents with Autism". *The Journal of Clinical Psychiatry* 79.2 (2018).

29. Wabnegger A and Schienle A. "The Role of the Cerebellum in Skin-Picking Disorder". *Cerebellum* 18.1 (2019): 91-98.

30. Wasner GL and Brock JA. "Determinants of thermal pain thresholds in normal subjects". *Clinical Neurophysiology* 119 (2008): 2389-2395.

31. Wong D and Baker C. "Pain in children: comparison of assessment scales". *Pediatric Nursing* 14.1 (1988): 9-17.

32. Wozniak KM Rojas C., *et al.* "The role of glutamate signaling in pain processes and its regulation by GCP II inhibition". *Current Medicinal Chemistry* 19.9 (2012): 1323-1334.

33. Yuan B., *et al.* "Nonrecurrent PMP22-RAI1 contiguous gene deletions arise from replication-based mechanisms and result in Smith-Magenis syndrome with evident peripheral neuropathy". *Human Genetics* 135.10 (2016): 1161-1174.