Congenital Pain Insensitivity in an Infant due to SCN9A Mutation

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INTRODUCTION

The sensation of pain serves as an important protective mechanism. The loss or insensitivity to pain sensation, as well as exaggerated pain, has severe health consequences. Congenital insensitivity to pain (CIP) is a condition where patients can feel stimuli but do not perceive them as painful or noxious. CIP differs from congenital "indifference" to pain, which refers to a lack of concern for a painful stimulus received through normal sensory pathways.[1]

Congenital insensitivity to pain (CIP) is an autosomal recessive trait caused by a mutation in the SCN9A gene, which is located on chromosome 2q24.3.[2] The SCN9A gene is important for the activation of sodium channels, which aid in the transmission of action potentials across excitable cells. The voltage-gated sodium-channel type IX subunit (SCN9A, also known as Nav1.7) has been identified as a key factor in disorders where recurring pain or the inability to detect pain is a prominent symptom.[3-4] Disorders such as primary erythermalgia, paroxysmal extreme pain disorder, and channelopathy-associated insensitivity to pain are identified by very different pain phenotypes.[5]

Patients with CIP present with a lack of pain awareness throughout the first decade of life. However, all other sensory modalities, such as normal touch perception, proprioception, itch, warm and cold temperature differentiation, and vibration, are preserved.[6] Self-mutilation is an almost invariable feature of this disorder, most often involving the teeth, lips, tongue, ears, eyes, nose, and fingers.[6]

This case report presents a 24-month old Hispanic male with SCN9A gene mutation, which has caused him to purposefully extract his primary teeth, and chew on his tongue and fingers to the point of causing bleeding and visible scarring.

ETIOLOGY AND EPIDEMIOLOGY

Congenital insensitivity to pain is a rare condition and very few cases have been reported in literature. Voltage-gated sodium channels are responsible for converting mechanical or chemical stimuli into electrical signals within excited cells. Thus far, nine distinct sodium channels encoded by nine distinct genes known as SCN(1–9A) have been identified. [7] Inactivating mutation of SCN9A causes indifference to pain, while activating mutations causes hyperalgesia.[8] Other SCN gene inactivation has been linked to epilepsy, myotonia disorders, cardiac arrhythmias in children, and cerebellar atrophy and ataxia.[9-1]

The SCN9A gene encodes Nav1.7, a tetrodotoxin-sensitive sodium channel that is expressed in the peripheral nervous system and primarily in the dorsal root ganglia.[12] Nav 1.7 channel is linked to inflammatory and mechanical pain but not neuropathic pain.[12] Mutations in the Nav1.7 channel have been associated with three pain disorders in humans. Primary erythromelalgia (PE) and paroxysmal extreme pain disorder (PEPD) are autosomal-dominant pain disorders.[13] The pain in both disorders is inflammatory and is caused by activating mutation in the SCN9A gene.[14] Congenital insensitivity to pain (CIP), on the other hand, is an autosomal-recessive disease caused by inactivating mutation in the Nav1.7 channel.[5]

DIAGNOSIS AND MANAGEMENT

Congenital Pain Insensitivity due to SCN9A mutation is diagnosed using a combination of patient and parental history, clinical examination, lab data, and genetic testing. Parents and/or caregivers are frequently the first to recognize signs of CIP, especially when their child does not show signs of pain following physical injuries. The symptoms of the disorder typically worsens as the primary dentition erupts. The tongue and lips are frequently affected, resulting in scarring and deformation.[15] Often injuries are self-inflicted and teeth extraction by oneself has also been reported.[16]

There is currently no treatment for congenital insensitivity to pain. Parental and caregiver education is required to understand the behaviors and injuries associated with CIP. Even if self-mutilation produces little pain, children may require physical and occupational therapy to learn certain motor skills to avoid self-mutilation. These individuals require multidisciplinary approach to improve their quality of life.

CASE REPORT

A 24-month-old Hispanic male was referred by his neurologist to the dental department at Children's Hospital of Los Angeles (CHLA) with a history of self-mutilation from 4 months of age. Since eruption of the teeth, patient has been chewing on his tongue, causing bleeding, and biting of his fingers (Figure 1A and 1C). Patient has touched burning mosquito coil incense and burned his finger without any apparent response (Figure 1B). Patient originally presented to the neurologist with missing upper incisor, multiple scars on both hands, up to wrists, open sore on his right forefinger; and sores and scars on his tongue. He has exhibited an absence of normal reaction to painful stimuli such as falls, cuts, and receiving vaccinations. Social history includes parental consanguinity and family history significant for the miscarriage of an older brother due to a brain tumor.

Per neurology patient was diagnosed with congenital sensory neuropathy with absence pain, and genetic testing revealed homozygous SCN9A mutation, validating the diagnosis of Congenital Insensitivity to Pain (CIP). Lesch-Nyhan syndrome was excluded since the patients' uric acid levels were normal.

At the oral examination during first dental visit, #F was avulsed and #E exhibited incisal fracture limited to enamel (Figure 1D). A healing traumatic ulcers was noted on right dorsal of the tongue. Patient returned one month later to the dental clinic with a 5x2mm ulceration on lower left labial mucosa (lip bite) and #M was avulsed (Figure 1E). Per mother, the child started heavily grinding on Saturday and self extracted the tooth on Sunday. Upon clinical exam, tissues appeared healthy, no erythema, swelling, or signs of infection noted at the site of #M.

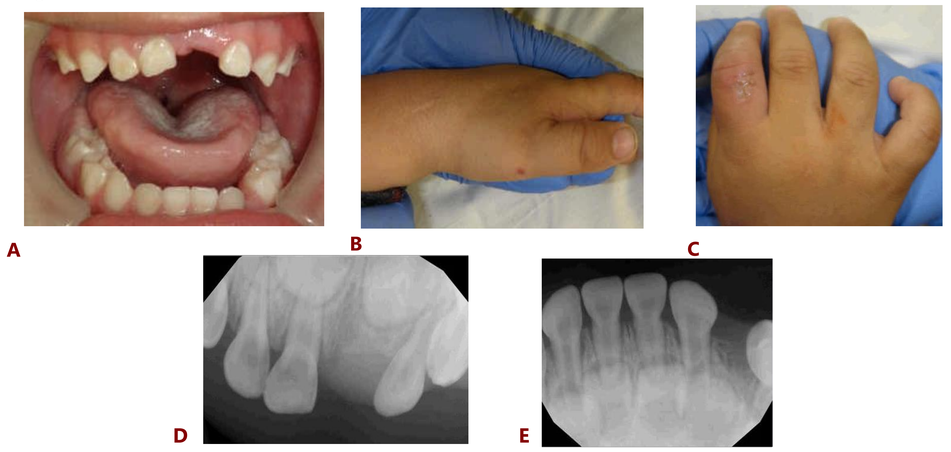

Figure 1A: Clinically missing #F and M and fibrous tissue on lateral border of the tongue due to morsicatio linguarum. **B:** Visible scarring on wrist and burn from mosquito coil incense on thumb. **C:** Self-inflicted bite marks on the fingers. **D:** #F avulsed due to self extraction by the patient during first dental visit. **E:** One month later, patient presents to clinic with self avulsion of #M.

DENTAL IMPLICATIONS

Patients with CIP have oral manifestations such as intraoral chronic non-healing ulcers, restricted mouth opening due to thick fibrous scars from cheek biting, increased incidence of jaw fractures and osteomyelitis, severe tooth attrition, and cervical abrasions.[19] As the primary dentition erupts, the disorder's symptoms usually worsen. Scarring and deformation of the tongue and lips are the most common manifestations. Self-inflicted injuries are common, and self-extraction of teeth has also been documented.

To prevent such injuries, a dentist can smooth down the sharp surfaces of the teeth in a form of a enameloplasty, add composite to sharp teeth, create a mouthguard/intraoral appliance, or extract teeth. Because mutilation may begin as early as childhood, implementing intraoral appliances is often difficult. The degree of self-injury must also be evaluated when deciding on appropriate treatments; extractions may be required if the mutilation is exceedingly severe or conservative treatment options have been unsuccessful.

In these patients, dental disease prevention is critical, as caries can progress to the pulp without causing pain. As soon as the diagnosis is made, the dental team should be involved and patients should be monitored throughout their lives. If primary dentition extractions are performed, the effects of space loss and subsequent crowding or impaction of the teeth must be evaluated and addressed as needed.

CONCLUSION

Congenital insensitivity to pain is a rare disorder in which oral manifestations is often the chief complaint of the parents. CIP provides a challenge to the dentist since the child frequently exhibits oral ulcerations, premature tooth loss, and self-mutilation. To avoid such catastrophic harm to the mouth and other regions of the body, providers should identify early indications of this rare disorder and proceed with an appropriate dental treatment.

REFERENCES

1. Dyck, Peter James, et al. "Not 'indifference to pain' but varieties of hereditary sensory and autonomic neuropathy." *Brain* 106.2 (1983): 373-390.
2. Cox, James J., et al. "An SCN9A channelopathy causes congenital inability to experience pain." *Nature* 444.7121 (2006): 894-898.
3. Yang, Y., et al. "Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia." *Journal of medical genetics* 41.3 (2004): 171-174.
4. Drenth, Joost PH, et al. "SCN9A mutations define primary erythermalgia as a neuropathic disorder of voltage gated sodium channels." *Journal of Investigative Dermatology* 124.6 (2005): 1333-1338.
5. Cox, James J., et al. "An SCN9A channelopathy causes congenital inability to experience pain." *Nature* 444.7121 (2006): 894-898.
6. Nilsen, K. B., et al. "Two novel SCN9A mutations causing insensitivity to pain." *Pain* 143.1-2 (2009): 155-158.
7. Suls, Arvid, et al. "Microdeletions involving the SCN1A gene may be common in SCN1A-mutation-negative SMEI patients." *Human mutation* 27.9 (2006): 914-920.
8. Fertleman CR, Baker MD, Parker KA, et al. SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. *Neuron*. 2006;52:767–774.
9. Sugiura Y, Makita N, Li L, et al. Cold induces shifts of voltage dependence in mutant SCN4A, causing hypokalemic periodic paralysis. *Neurology*. 2003;61:914–918.
10. Keller DI, Huang H, Zhao J, et al. A novel SCN5A mutation, F1344S, identified in a patient with Brugada syndrome and fever-induced ventricular fibrillation. *CardiovascRes*. 2006;70:521–529.
11. Trudeau MM, Dalton JC, Day JW, et al. Heterozygosity for a protein truncation mutation of sodium channel SCN8A in a patient with cerebellar atrophy, ataxia, and mental retardation. *J Med Genet*. 2006;43:527–530.
12. Akopian, Armen N., et al. "The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways." *Nature neuroscience* 2.6 (1999): 541-548.
13. Yang, Y., et al. "Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia." *Journal of medical genetics* 41.3 (2004): 171-174.
14. Drenth, Joost PH, et al. "The primary erythermalgia–susceptibility gene is located on chromosome 2q31-32." *The American Journal of Human Genetics* 68.5 (2001): 1277-1282
15. Axelrod, Felicia B., and John Pearson. "Congenital sensory neuropathies: diagnostic distinction from familial dysautonomia." *American Journal of Diseases of Children*138.10 (1984): 947-954.
16. Thompson, Charles C., Richard I. Park, and Gerald H. Prescott. "Oral manifestations of the congenital insensitivity-to-pain syndrome." *Oral Surgery, Oral Medicine, Oral Pathology*50.3 (1980): 220-225.
17. Amano, Atsuo, et al. "Oral manifestations of hereditary sensory and autonomic neuropathy type IV: Congenital insensitivity to pain with anhidrosis." *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*86.4 (1998): 425-431.
18. Gorlin, Robert J., M. Michael Cohen Jr, and Raoul CM Hennekam. *Syndromes of the head and neck*. Oxford university press, 2001.
19. Kumar, A. Vijay, H. P. Jaishankar, and Purnachandrarao Naik. "Congenital insensitivity to pain: Review with dental implications." *Indian Journal of Pain* 28.1 (2014): 13.