Office-Based Anesthetic and Oral Surgical Management of a Child With Hereditary Sensory Autonomic Neuropathy Type IV: A Case Report

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Hereditary sensory and autonomic neuropathy type IV (HSAN IV), or congenital insensitivity to pain with anhidrosis, is an exceptionally rare genetic disorder that results in the complete loss of pain and temperature sensation as well as anhidrosis. Anesthetic management of these patients can be difficult because of significantly increased risks during general anesthesia. Literature on perioperative anesthetic management is typically written in the context of a hospital setting. As such, our case presents a unique report on the anesthetic management of a HSAN IV patient who presented for extraction of 2 teeth in an office-based setting. In determining how to safely manage the procedure, we decided against general anesthesia as we lacked the facilities and equipment to safely handle previously reported complications. We were successful in providing sedation with nitrous oxide in oxygen and applying 20% benzocaine topical ointment on the surgical site in lieu of administering general anesthesia. We had an anesthesiologist present and obtained intravenous access prior to the surgery to help manage any complications. This report provides support that simple dental extractions can be accomplished safely in the HSAN IV patient in the office-based setting, thereby avoiding unnecessary risk.

Key Words: Hereditary sensory and autonomic neuropathy type IV; Congenital insensitivity to pain with anhidrosis; Anesthetic management.

Hereditary sensory and autonomic neuropathies (HSAN) are a clinically and genetically distinct group of rare inherited disorders that result in the dysfunction of the sensory and autonomic nervous systems.¹ Dyck² originally characterized 5 types of HSAN by age of onset, disease progression, clinical features, and inheritance.² Since then, there have been additions of new types and subtypes (the Table).^{3,25,29} These disorders occur because of neuronal atrophy and degeneration of the small myelinated and unmyelinated nerve fibers.³⁰ Each type of HSAN differs in its clinical presentation, age of onset, and associated genetic profile. The predominant clinical feature among all of the HSANs involves the dysfunction of the autonomic

nervous system and, importantly, an individual's lack of pain sensation.

HSAN type IV, also known as congenital insensitivity to pain with anhidrosis or familial dysautonomia type II, is a rare autosomal recessive disorder with an incidence of approximately 1 in 25,000 births.^{1,31} The pathogenesis for HSAN type IV is a loss-of-function mutation in the nerve growth factor receptor tyrosine kinase 1 (NTRK1) gene that is coded on chromosome 1q21-q22 and encodes tropomyosin-related kinase A (TrkA).³² The mutation results in a loss of nerve growth factor-dependent small myelinated A δ and unmyelinated C-fibers and postganglionic autonomics, which clinically manifests as a loss of sensation to painful stimuli and autonomic dysfunction.³² The mutation to *NTRK1* prevents nerve cell formation, which normally signals pain and temperature to the brain, and prevents appropriate binding by nerve growth factor.³³ Nerve growth factor plays a prominent factor in regulating immune cell function by helping with formation of

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HSAN Classifications*

Type	Gene/Locus	Inheritance	Disease Onset	Clinical Features	OMIM
HSAN IA ^{3–5}	<i>SPTLC1/9q22.31</i>	AD	Adolescence	Paresthesias; numbness; reduced temperature sensation; ulcerative mutilations	162400
HSAN IB ^{3,6–8}	Unknown/3p24-p22	AD	Adulthood	Digital sensory loss; characteristic cough and gastroesophageal reflux; normal distal muscle strength	608088
HSAN IC ^{3,9}	<i>SPTLC2/14q24.3</i>	AD	Adulthood	Loss of touch and vibration in feet; dysesthesia; severe sensory loss in upper and lower limbs; ulcerative mutilations	613640
HSAN ID ^{3,10}	<i>ATL1/14q22.1</i>	AD	Adulthood	Lack of sensation in hands and feet leading to mutilations and amyotrophy; variable motor function	613708
HSAN IE ^{11,12}	<i>DNMT1/19p13.2</i>	AD	Adulthood	Loss of hearing; complete loss of somatosensory modalities; lancinating pain; dementia; gradual loss of sensation in the feet and legs	614116
HSAN IF ¹³	<i>ATL3/11q13.1</i>	AD	Adulthood	Distal sensory loss in lower extremities; ulcerations on feet without pain; normal autonomic function	615632
HSAN IIA ^{3,4,14}	<i>WNK1/12p13.33</i>	AR	Infancy to adolescence	Numbness in hands and feet; loss of pain and temperature sensation; variable issues with autonomic nervous system; diminished motor system	201300
HSAN IIB ^{3,15,16}	<i>FAM134B/5p15.1</i>	AR	Early childhood	Distal sensory impairment; impaired nociception; progressive mutilation ulceration of hands and feet with osteomyelitis and acro-osteolysis	613115
HSAN IIC ^{3,17}	<i>KIF1A/2937.3</i>	AR	Childhood	Progressive distal sensory loss; ulceration and amputation of fingers and toes; distal muscle weakness of lower limbs	614213
HSAN IID ^{18,19}	<i>SCN9A/2q24.3</i>	AR	Birth to adolescence	Loss of nociception and temperature sensation; autonomic nervous dysfunctions; hearing loss; hyposmia	243000
HSAN III ^{3,4}	<i>IKBKAP/9q31.3</i>	AR	Birth	Predominant sensory and autonomic disturbances; hypotonia and hypothermia; stunted physical growth; poor motor coordination; scoliosis; normal intelligence	223900
HSAN IV ^{3,4,20,21}	<i>NTRK1/1q23.1</i>	AR	Birth	Loss of pain and temperature sensation; anhidrosis; intellectual disability; impaired physical growth; self-mutilation; normal sense of pressure, vibration, and position	256800
HSAN V ^{3,4}	<i>NGFβ/1p13.2</i>	AR	Birth	Loss of pain and temperature sensation; no mental retardation; mild anhidrosis; characteristic loss of deep pain sensation; prone to development of Charcot joints	608654
HSAN VI ²²	<i>DST/6p12.1</i>	AR	Birth	Neonatal hypotonia; respiratory and feeding difficulties; lack of psychomotor development; autonomic abnormalities	614653
HSAN VII ^{23,24}	<i>SCN11A/3p22.2</i>	AD	Birth	Lack of pain and temperature sensation; mild muscle weakness; delayed motor development; painless fractures	615548
HSAN VIII ^{25,26}	<i>PRDM12/9q34.12</i>	AR	Birth to early childhood	Reduced pain and temperature sensation; lack of corneal reflex; reduced sweating and tear production; abnormal sensory nerve conduction	616488
HSAN with spastic paraplegia ^{3,27,28}	<i>CCT5/5p15.2</i>	AR	Early childhood	Loss of all somatosensory modalities; mutilating acropathy; spastic paraplegia	256840

* AD, autosomal dominant; AR: autosomal recessive; HSAN, hereditary and sensory autonomic neuropathy.

wounds and the development of scars.³⁴ The lack of pain sensation is compounded by delayed wound healing, potentially leading to infections.³⁵

Clinically, patients lose all sensation to pain and temperature, and they have an absent or reduced level of perspiration, despite the presence of normal sweat glands.³¹ The lack of sympathetic postganglionic neurons results in the inability to have normal sweat production.³⁶ The ability to feel position, touch, pressure, and vibration are unaffected. Many patients will exhibit varying degrees of intellectual disability and physical growth. The lack of pain sensation frequently results in lacerations, fractures, joint dislocations, infections, and self-mutilation of the eyes, mouth, hands, and feet. Oral injuries commonly occur with mutilation and ulceration of the tongue, lips, and oral mucosa. Patients can develop corneal abrasions from constant rubbing and scratching of their eyes.

In patients with HSAN type IV, conventional motor and orthodromic sensory nerve conduction studies are normal.³⁷ A morphometric study of the sural nerve demonstrated a marked reduction in the total number of small myelinated fibers and unmyelinated fibers.³⁷ Patients typically have limited mental capabilities but maintain other sensory modalities, muscle strength, and deep tendon reflexes.³⁸

After an extensive literature search, we were unable to find any information detailing the anesthetic management of patients with HSAN IV in an outpatient setting. In this report, we discuss the perioperative anesthetic management involving a 7-year-old male patient diagnosed with HSAN IV in an office-based setting.

CASE PRESENTATION

Our patient was a 7-year-old boy of Chinese descent. The child presented for extraction of the maxillary deciduous canines. The child had significant maxillary and mandibular crowding in addition to prior instances of autoextraction of teeth because of his absence of pain. Because of our patient's intellectual disabilities, he was unable to remain motionless during the panoramic x-ray (the Figure). During the extraoral examination, it was noted there was no evidence of soft-tissue swelling of the mid or lower face. The patient's neck was supple, and he had a maximal incisal opening no greater than 30 mm without deviation.

The deciduous maxillary canines were retained with occlusal wear on the right side. The patient previously had general anesthesia for placement of 3 stainless steel crowns. Per outside hospital notes, the patient had 5 instances of hypotensive events that were corrected with phenylephrine, but his course was otherwise uneventful.

Panoramic x-ray.

Hospital notes also stated that the patient has gastroesophageal reflux disease. After consultation with our office-based anesthesiologist, we determined general anesthesia would be unsafe because of the patient's anhidrosis and increased risk of aspiration. Our plan was revised to proceed with nitrous oxide and oxygen via face mask to obtain intravenous access and avoid local anesthetic infiltration secondary to the patient's self-mutilation tendencies.

Prior to the operation, monitors were placed on the patient. Nitrous oxide and oxygen were administered via face mask, then intravenous access was obtained in the dorsum of the left hand in case of emergency. The anesthesiologist remained in the room throughout the entire operation to monitor vital signs and the patient's airway. Benzocaine 20% topical ointment was placed circumferentially around teeth C and H. Both sites were easily extracted using a No. 150 upper universal forcep, and there were no additional surgical complications. Follow-up on postoperative day 1 indicated no complications. After 10 days, the patient returned for his postoperative checkup with well-healing surgical sites and no signs or symptoms of infections, mutilation, or other complications.

DISCUSSION

Since patients with HSAN type IV have anhidrosis, they have difficulty regulating their body temperature. As a result, these patients are prone to several complications during the perioperative period, including difficulties with thermal irregularities and cardiac complications such as bradycardia and hypotension.³⁹ In a study conducted by Rozentsveig et al⁴⁰ on anesthetic complications of 20 patients with HSAN type IV, 15 patients developed cardiac complications, including 1 case of cardiac arrest and 1 case of mild hypothermia. The exact mechanism of the cardiac irregularities is unknown; however, it is likely that autonomic dysfunction may adversely affect cardiac stability.⁴¹ In a study of 358 procedures performed under

general anesthesia on patients with HSAN IV, it was discovered that tachycardia was present in 3% of the patients.⁴¹ However, 73% of these tachycardia cases occurred immediately after induction, indicating that increased sympathetic activity after airway manipulation could have been a contributing factor.⁴¹ Many clinicians believe sedation in these patients is unnecessary because of anhidrosis and their inability to experience pain. However, the literature has suggested that sedation can, in fact, be beneficial.^{39,40,42} Tomioka et al⁴² suggested 3 important considerations for anesthetic management when treating patients with HSAN type IV: (1) necessity of sedation to reduce anxiety, (2) body temperature management, and (3) maintenance of adequate perioperative sedation to avoid potential self-harm during the operation. As such, it is important to continuously monitor body temperature and the ambient operating room temperature. It is also imperative to ensure heating and cooling blankets are available. Although patients are unable to feel pain, they have reported feeling noxious surgical stimuli.⁴³ Providing sufficient sedation based on a patient's needs and behavior can mitigate these issues.

Other case studies have reported similar characteristics to our patient, including autoextraction of teeth, small maximal incisal opening, and trauma to the tongue, lip, and buccal mucosa.^{31,33,44–46} While a prior case report suggested performing the extraction under local anesthesia to promote hemostasis,⁴⁶ there were no complications for our patient with the sole use of 20% benzocaine topical ointment. Infiltration of local anesthetic could have provoked further self-mutilation tendencies in our patient. Loss of teeth, in addition to injuries to the tongue and buccal mucosa, should be monitored by dentists as it could be indicative of a genetic disorder.⁴⁷ While there is no standard protocol for treating or preventing orofacial self-inflicted injuries, removal of all remaining teeth to prevent further damage to the oral cavity has been practiced in the past.⁴⁸ Additional preventive methods include the removal of sharp edges of teeth and wearing a mouth-guard.⁴⁹ It should be noted that instances of oral self-mutilations decrease with age and with intellectual, social, and/or emotional development.⁴⁹ As the child develops and becomes trained to avoid self-mutilation, dental implants can be used to correct for the dental damage that occurs in early childhood.

When presented with a patient diagnosed with HSAN IV in an outpatient setting, the use of office-based general anesthesia can be hazardous without thermoregulatory equipment, such as warming and cooling blankets, advanced monitoring systems, and a pediatric intensive care unit should it be needed. The autonomic irregularities can present challenges for anesthesiologists since there is an increased risk of irregularities in blood

pressure and heart rate, including the possibility of cardiac arrest, in addition to thermoregulation issues.⁴¹ In particular, HSAN IV patients have absent or diminished autonomous protective airway reflexes that can increase the risk of regurgitation of gastric contents, leading to aspiration.⁴² The current literature advocates for most surgical procedures to be performed in a hospital setting to most effectively manage these potential complications. As such, complex procedures should be conducted within a hospital. However, in our case, treatment in a hospital setting was challenging because of financial limitations. Further, we deemed the procedure minor and quick enough to be done without general anesthesia, especially considering the patient's insensitivity to pain. However, we chose to err on the side of caution by placing an IV in addition to having an anesthesiologist present in the room to immediately treat any unforeseen complications. To the best of our knowledge, this is the first report demonstrating the effective perioperative anesthetic management of a HSAN IV patient in an office-based setting. As such, this case can be considered unique and presents novel information on providing anesthesia for HSAN IV patients.

CONCLUSION

Treating patients diagnosed with HSAN IV presents a number of unique challenges in terms of anesthetic management. Regardless of the procedure, it is ideal to treat these patients in a hospital setting. However, in a dental or oral surgery setting, if the procedure is not complex, then our case presents an example of successfully performing a minor surgery with only nitrous oxide–oxygen sedation while still yielding positive results.

REFERENCES

1. Davidson GL, Murphy SM, Polke JM, et al. Frequency of mutations in the genes associated with hereditary sensory and autonomic neuropathy in a UK cohort. *J Neurol*. 2012; 259:1673–1685.
2. Dyck PJ. Neuronal atrophy and degeneration predominantly affecting peripheral sensory and autonomic neurons. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. *Peripheral Neuropathy*. Vol 2. 2nd ed. Philadelphia, Pa: WB Saunders; 1984:1557–1559.
3. Rotthier A, Baets J, Timmerman V, Janssens K. Mechanisms of disease in hereditary sensory and autonomic neuropathies. *Nat Rev Neurol*. 2012;8:73–85.
4. Butler J, Fleming P, Webb D. Congenital insensitivity to pain—review and report of a case with dental implications.

- Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2006;101:58–62.
5. Rotthier A, Baets J, De Vriendt E, et al. Genes for hereditary sensory and autonomic neuropathies: a genotype-phenotype correlation. *Brain.* 2009;132:2699–2711.
 6. Spring PJ, Ing AJ, Nicholson GA, et al. Autosomal dominant hereditary sensory neuropathy with gastro-oesophageal reflux and cough: clinical features of a family. *J Neurol Sci.* 2002;suppl:199–S64.
 7. Spring PJ, Kok C, Nicholson GA, et al. Autosomal dominant hereditary sensory neuropathy with chronic cough and gastro-oesophageal reflux: clinical features in two families linked to chromosome 3p22-p24. *Brain.* 2005;128:2797–2810.
 8. Kok C, Kennerson ML, Spring PJ, Ing AJ, Pollard JD, Nicholson GA. A locus for hereditary sensory neuropathy with cough and gastroesophageal reflux on chromosome 3p22-p24. *Am J Hum Genet.* 2003;73:632–637.
 9. Rotthier A, Auer-Grumbach M, Janssens K, et al. Mutations in the SPTLC2 subunit of serine palmitoyltransferase cause hereditary sensory and autonomic neuropathy type I. *Am J Hum Genet.* 2010;87:513–522.
 10. Guelly C, Zhu PP, Leonardis L, et al. Targeted high-throughput sequencing identifies mutations in atlastin-1 as a cause of hereditary sensory neuropathy type I. *Am J Hum Genet.* 2011;88:99–105.
 11. Klein CJ, Botuyan MV, Wu Y, et al. Mutations in DNMT1 cause hereditary sensory neuropathy with dementia and hearing loss. *Nat Genet.* 2011;43:595–600.
 12. Klein CJ, Bird T, Ertekin-Taner N, et al. DNMT1 mutation hot spot causes varied phenotypes of HSAN1 with dementia and hearing loss. *Neurology.* 2013;80:824–828.
 13. Kornak U, Mademan I, Schinke M, et al. Sensory neuropathy with bone destruction due to a mutation in the membrane-shaping atlastin GTPase 3. *Brain.* 2014;137:683–692.
 14. Lafreniere RG, MacDonald ML, Dube MP, et al. Identification of a novel gene (HSN2) causing hereditary sensory and autonomic neuropathy type II through the Study of Canadian Genetic Isolates. *Am J Hum Genet.* 2004;74:1064–1073.
 15. Ilgaz Aydinlar E, Rolfs A, Serteser M, Parman Y. Mutation in FAM134B causing hereditary sensory neuropathy with spasticity in a Turkish family. *Muscle Nerve.* 2014;49:774–775.
 16. Kurth I, Pamminger T, Hennings JC, et al. Mutations in FAM134B, encoding a newly identified Golgi protein, cause severe sensory and autonomic neuropathy. *Nat Genet.* 2009;41:1179–1181.
 17. Rivière JB, Ramalingam S, Lavastre V, et al. KIF1A, an axonal transporter of synaptic vesicles, is mutated in hereditary sensory and autonomic neuropathy type 2. *Am J Hum Genet.* 2011;89:219–230.
 18. Cox JJ, Reimann F, Nicholas AK, et al. An SCN9A channelopathy causes congenital inability to experience pain. *Nature.* 2006;444:894–898.
 19. Yuan J, Matsuura E, Higuchi Y, et al. Hereditary sensory and autonomic neuropathy type IID caused by an SCN9A mutation. *Neurology.* 2013;80:1641–1649.
 20. Yagev R, Levy J, Shorer Z, Lifshitz T. Congenital insensitivity to pain with anhidrosis: ocular and systemic manifestations. *Am J Ophthalmol.* 1999;127:322–326.
 21. Hepburn L, Prajsnar TK, Klapholz C, et al. A Spaetzle-like role for nerve growth factor-beta in vertebrate immunity to *Staphylococcus aureus*. *Science.* 2014;346:641–646.
 22. Edvardson S, Cinnamon Y, Jalas C, et al. Hereditary sensory autonomic neuropathy caused by a mutation in dystonin. *Ann Neurol.* 2012;71:569–572.
 23. Leipold E, Liebmann L, Korenke GC, et al. A de novo gain-of-function mutation in SCN11A causes loss of pain perception. *Nat Genet.* 2013;45:1399–1404.
 24. Woods CG, Babiker MO, Horrocks I, Tolmie J, Kurth I. The phenotype of congenital insensitivity to pain due to the Nav1.9 variant p.L811P. *Eur J Hum Genet.* 2015;23:1434.
 25. Chen Y-C, Auer-Grumbach M, Matsukawa S, et al. Transcriptional regulator PRDM12 is essential for human pain perception. *Nat Genet.* 2015;47:803–808.
 26. Zhang S, Malik Sharif S, Chen YC, et al. Clinical features for diagnosis and management of patients with PRMD12 congenital insensitivity to pain. *J Med Genet.* 2016;53:533–535.
 27. Thomas PK, Misra VP, King RH, et al. Autosomal recessive hereditary sensory neuropathy with spastic paraplegia. *Brain.* 1993;117:651–659.
 28. Bouhouche A, Benomar A, Bouslam N, Ouazzani R, Chkili T, Yahyaoui M. Autosomal recessive mutilating sensory neuropathy with spastic paraplegia maps to chromosome 5p15.31-14.1. *Eur J Hum Genet.* 2006;14:249–252.
 29. Yuan J, Matsuura E, Higuchi Y. Hereditary sensory and autonomic neuropathy type IID caused by an SCN9A mutation. *Neurology.* 2013;80:1641–1649.
 30. Auer-Grumbach M, Mauko B, Auer-Grumbach P, Pieber TR. Molecular genetics of hereditary sensory neuropathies. *Neuromol Med.* 2006;8:147–158.
 31. Ashwin DP, Chandan GD, Jasleen HK, Rajkumar GC, Rudresh KB, Prashanth R. Hereditary sensory and autonomic peripheral neuropathy-type IV: case series and review of literature. *Oral Maxillofac Surg.* 2015;19:117–123.
 32. Indo Y. Neurobiology of pain, interoception and emotional response: lessons from nerve growth factor-dependent neurons. *Eur J Neurosci.* 2014;39:375–391.
 33. Othman SA, Malik AA. Congenital insensitivity to pain with anhidrosis in Sudanese children. *Sudan J Paediatr.* 2016;16:80–85.
 34. Bonini S, Rasi G, Bracci-Laudiero ML, Procoli A, Aloe L. Nerve growth factor: neurotrophin or cytokine? *Int Arch Allergy Immunol.* 2003;131:80–84.
 35. Varma AV, McBride L, Marble M, Tilton A. Congenital insensitivity to pain and anhidrosis: case report and review of findings along neuro-immune axis in the disorder. *J Neurol Sci.* 2016;370:201–210.
 36. Sarasola E, Rodríguez JA, Garrote E, Aristegui J, García-Barcina MJ. A short in-frame deletion in NTRK1 tyrosine kinase domain caused by a novel splice site mutation in a patient with congenital insensitivity to pain with anhidrosis. *BMC Med Genet.* 2011;12:86.
 37. Nolano M, Crisci C, Santoro L, et al. Absent innervation of skin and sweat glands in congenital insensitivity

to pain with anhidrosis. *Clin Neurophysiol.* 2000;111:1596–1601.

38. Kayani B, Sewell MD, Platinum J, Olivier A, Briggs TWR, Eastwood DM. Orthopaedic manifestations of congenital indifference to pain with anhidrosis (hereditary sensory and autonomic neuropathy type IV). *Eur J Paediatr Neurol.* 2017;21:318–326.

39. Ergül Y, Ekici B, Keskin S. Cardiac arrest after anesthetic management in a patient with hereditary sensory autonomic neuropathy type IV. *Saudi J Anaesth.* 2011;5:93–95.

40. Rozentsveig V, Katz A, Weksler N, et al. The anaesthetic management of patients with congenital insensitivity to pain with anhidrosis. *Paediatr Anaesth.* 2004;14:344–348.

41. Zlotnik A, Natanel D, Kutz R, et al. Anesthetic management of patients with congenital insensitivity to pain with anhidrosis: a retrospective analysis of 358 procedures performed under general anesthesia. *Anesth Analg.* 2015;121:1316–1320.

42. Tomioka T, Awaya Y, Nihei K, Sekiyama H, Sawamura S, Hanaoka K. Anesthesia for patients with congenital insensitivity to pain and anhidrosis: a questionnaire study in Japan. *Anesth Analg.* 2002;94:271–274.

43. Okuda K, Arai T, Miwa T, Hiroki K. Anaesthetic management of children with congenital insensitivity to pain with anhidrosis. *Paediatr Anaesth.* 2000;10:545–548.

44. Haga N, Kubota M, Miwa Z. Hereditary sensory and autonomic neuropathy types IV and V in Japan. *Pediatr Int.* 2015;57:30–36.

45. Alexander C, Dasarathy J, Chaudhry L, Tandra S. Case report. *J Fam Pract.* 2016;65:620.

46. Ravichandra KS, Kandregula CR, Koya S, Lakhota D. Congenital insensitivity to pain and anhidrosis: diagnostic and therapeutic dilemmas revisited. *Int J Clin Pediatr Dent.* 2015;8:75–81.

47. Paduano S, Iodice G, Farella M, Silva R, Michelotti A. Orthodontic treatment and management of limited mouth opening and oral lesions in a patient with congenital insensitivity to pain: case report. *J Oral Rehabil.* 2009;36:71–78.

48. Neves BG, Roza RT, Castro GF. Traumatic lesions from congenital insensitivity to pain with anhidrosis in a pediatric patient: dental management. *Dent Traumatol.* 2009;25:545–549.

49. Amano A, Akiyama S, Ikeda M, Morisaki I. Oral manifestations of hereditary sensory and autonomic neuropathy type IV: congenital insensitivity to pain with anhidrosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998;86:425–431.