

Commentary: Congenital corneal anesthesia: A rare form of type-4 familial dysautonomia

“So many of the males have killed themselves by their late 20s by doing ridiculously dangerous things, not restrained by pain” – Geoff Woods

While pain is considered an unpleasant experience, intact normal physiological pain is a fundamental prerequisite for human existence. We shall discuss rare medical conditions in affected people who never feel pain. Congenital corneal anesthesia (CCA) is a rare, complex neurological condition frequently overlooked or under-diagnosed, and often delayed, leading to irreversible damage to the optical quality of the cornea. CCA is characterized by neurosensory deficits that encompass the ocular surface innervated by the first branch of the trigeminal nerve, but other divisions of the trigeminal nerve may be involved. This corneal sensory deficit may be an isolated finding as part of a complex neurological syndrome or associated with multiple somatic abnormalities and congenital insensitivity to pain with anhidrosis (CIPA). CIPA has two pathognomonic features: the inability to feel pain and temperature, and decreased or absent sweating (anhidrosis). This condition is hereditary sensory and autonomic neuropathy (HSAN) type IV. The signs and symptoms of CIPA appear early, usually at birth or during early infancy; but with careful medical attention, affected individuals can live into adulthood.^[1-7]

Mutations in the nerve growth factor (NGF) gene cause CIPA.^[5,6] NGF as a pain mediator: by binding to TrkA and NTRK1 receptors, it regulates the survival and differentiation of sensory neurons during development and mediates pain transmission and perception during adulthood by acting at different levels of the nervous system.^[6] Loss of sensory neurons leads to the inability to feel pain and losing the nerves leading to their sweat glands, which causes the anhidrosis seen in affected individuals. An inability to feel pain and temperature often leads to repeated severe injuries. Pain insensitivity predisposes these children to unintentional self-mutilating behavior, and anhidrosis may lead to poor body heat dissipation, resulting in recurrent episodes of unexplained hyperpyrexia that could be life-threatening due to febrile seizures.^[2-5] Typically, the ocular manifestation is bilateral in early childhood, presenting with a lusterless ocular surface, poor tearing, painless sterile erosions, and, without intervention, may result in the deterioration of the optical quality of the cornea and decrease in vision.^[1-3]

Also, corneal hypoesthesia results in poor corneal epithelial turnover and a defective epithelial repair mechanism due to depleted cAMP levels and acetylcholine and acetylcholine transferases at nerve terminals. Besides, there is a decrease in reflex tearing, reduced blink rates, and increased tear mucus secretion, aggravated by progressive abnormalities of corneal epithelial microvilli, making the cornea increasingly vulnerable to self-inflicted injury and infection and poor self-repair.^[1-4] Children with this disorder are prone to recurrent epithelial erosions, which, unless recognized and managed promptly, can progress rapidly, leading to corneal ulceration and perforation or opacities, described as neurotrophic keratitis.^[1] Ramappa *et al.*^[2] have previously hypothesized that the onset of corneal

damage occurs between 6 and 12 months after birth; this could be attributed to developmental milestones such as altered sleep patterns, and better hand–eye coordination can trigger corneal insult due to eye rubbing. In their series, 2/3rd of the patients were males, 2/3rd had bilateral disease, 1/3rd had generalized pain insensitivity with anhidrosis, and nearly half had a history of parental consanguinity.

Because of the challenges involved in evaluating these children, the diagnosis of CCA is often missed or delayed, leading to permanent visual disability. Patients with obscure neurological manifestations like generalized pain insensitivity, anhidrosis, poor heat dissipation, or self-mutilating behavior associated with an impaired corneal sensation should be suspected of having congenital corneal anesthesia or other sensory deprivation-associated neuropathies. A detailed history and meticulous clinical examination help make an accurate early diagnosis. A lusterless ocular surface is observed with interpalpebral corneal involvement in the form of erosions, ulcers, or opacities. Neurotrophic keratopathy exhibits a spectrum of disease severity and may manifest as dry geographic spots on the cornea, recurrent epithelial detachments, or frank stromal lysis with perforation and secondary infections. Slit-lamp examination demonstrates a sparse distribution or complete absence of corneal nerves, though a normal neural pattern has also been observed. Corneal sensations are severely reduced or absent, with altered ocular surface stability and decreased tear secretion, as evidenced by a reduced Schirmer’s test, decreased tear meniscus height, and tear break-up time.^[1-3]

Perhaps the only effective treatment strategy is performing a 2/3rd-width tarsorrhaphy. Therefore, timely recognition is the key to minimizing morbidity. If unrecognized, the condition may lead to dense amblyopia due to obscuration of the visual axis due to recurrent epithelial defects, ulceration, and stromal lysis ensuing perforation. This entity can be accurately assessed by testing corneal sensation and performing Schirmer’s test in cooperative patients very early in the natural course of the disease. In addition, careful observation of clinical parameters, such as reduced reflex tearing and blink rates, impassive response to eyedrop installation, or increased mucus secretions should arouse suspicion. There is no confirmatory diagnostic test, though various ancillary investigations may be performed, including neuroimaging, nerve conduction studies, and *in vivo* confocal microscopy (IVCM). Gopal *et al.*^[3] describe the use of IVCM to objectively demonstrate a decreased density of sub-basal corneal nerve fibers in cases of CCA, which correlates with the subjective decrease in corneal sensation. One must rule out other masqueraders in children, such as post-herpes simplex keratitis, dry eye disorder, keratomalacia, and Hansen’s disease, particularly in the developing world. Rarely, Cerebello-pontine-angle (CPA) tumours such as acoustic neuromas, sinuous venous abnormalities, or any space-occupying lesions that involve the trigeminal nerve can have similar presentations.^[2]

The management of CCA is targeted toward preventing inadvertent corneal damage resulting from corneal hypoesthesia and self-inflicted corneal trauma. This condition must be diagnosed through comprehensive examination by a pediatric neurologist and ophthalmological evaluation early, before the child presents with sterile corneal ulcerations

or dense corneal scarring. Parents should be thoroughly educated about the importance of preventing self-inflicted corneal damage by applying arm splints, protective goggles, and other protective gear in cases of generalized anesthesia. Genetic diagnosis frequently empowers families with the knowledge to care for and advocate for their children and make decisions regarding family planning. Several children with CIPA have lesser-known or unidentifiable mutations, not captured by conventional genetic panels. Whole-exome sequencing should be clinically considered to expedite diagnosis, reduce laboratory investigations, and guide informed decisions.

Cases with generalized anesthesia in other body regions might develop recalcitrant neurotropic ulcers over bony prominences. Self-mutilation tendencies that correspond to an eruption of primary dentition around 6–12 months provide the first interface between hard tissues and soft tissues in the mouth. This period marks the initiation of oral self-mutilation (biting of tongue, lips, and buccal mucosa) and biting of fingertips, leading to spontaneous amputation of the affected area. Often these children with a congenital insensitivity to pain and anhidrosis (CIPA) presents with generalized bruising, scarring, and skin infection, multiple bone fractures or malunion of fractures, and recurrent joint dislocations resulting in joint deformity. In addition, people with CIPA heal slowly from skin and bone injuries. Repeated trauma can lead to chronic bone infections (osteomyelitis) or a condition called Charcot joints in which the bones and tissue surrounding the joints are destroyed. Many affected children may have thick, leathery skin on the palms of their hands or mutilation of fingernails or toenails. They can also have patches on their scalp where hair does not grow. About half of the people with CIPA show signs of hyperactivity or emotional instability, and many affected individuals have an intellectual disability. Some people with CIPA have weak muscle tone when they are young, but muscle strength and tone become more normal as they get older.

Prompt and timely attention should be given to limit self-mutilation by extracting appropriate teeth. Also, children with generalized insensitivity have a relatively higher risk of developing corneal damage due to combined impaired vision and mental impairment. For a child with a CCA, the symptoms and signs in most cases are successfully reversed with copious tear substitutes, arm splints, and tarsorrhaphy. This is further supported by the fact that most unilateral patients do not experience repeated corneal damage. The consensus is that these children may need topical, preservative-free lubricants for the rest of their lives to support normal corneal homeostasis. A permanent 2/3rd-width tarsorrhaphy is the most effective strategy for maintaining the integrity of the corneal epithelium and should be performed as soon as a diagnosis has been made. If bilateral involvement is likely, prophylactic tarsorrhaphy should be expedited in the unaffected eye.^[2] Anecdotally, for recalcitrant neurotrophic keratitis, NGFs have been used with limited success, and NGF is prohibitively expensive. Newer modalities like corneal neurotization may not work in these cases, considering the generalized condition, and might have abnormality at the level of the receptor.^[8] Gene therapy is

not yet at a stage where we could contemplate rescuing the mutated NGF gene and perhaps giving back pain to someone who never had it.

Although in most cases, tarsorrhaphy restored the surface integrity of the cornea, advanced cases may have suffered irreversible stromal scarring and vascularization. Efficient ocular surface protection is crucial in eyes with CCA to retain long-term functional vision. Successful management of CCA mandates lifelong monitoring with an emphasis on protecting the ocular surface from inadvertent trauma in the absence of normal protective mechanisms of the eye. Dysautonomia cases should be managed in collaboration with various inter- and intra-specialties involving pediatric neurologists, pediatric dentists, pediatric orthopedician, medical geneticists, and genetic counselors within ophthalmic and pediatric clinics are likely to improve the delivery of clinical care in these settings.

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