**Ocular Manifestations of Congenital Insensitivity to Pain: A Long-Term Follow-Up**

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Congenital insensitivity to pain with anhidrosis (CIPA) and congenital insensitivity to pain (CIP) are rare autosomal recessive neuropathies characterized by the inability to sense noxious stimuli as pain and heat. Both belong to the group of hereditary sensory and autonomic neuropathies.1 The exact prevalence of these disorders remains poorly known, although CIPA is relatively common among Israeli Bedouins and in the Japanese population.2 Haga et al estimated the prevalence of CIPA as 1 in 600,000–950,000, and CIP as 1 in 2,200,000–4,200,000, respectively.2 Patients with CIPA and CIP are predisposed to self-inflicted injuries such as bitten lips and fingers, especially with the eruption of their first teeth; therefore, surgical extraction of incisors is routine. Sometimes there is spontaneous loss or self-extraction of teeth. Patients also have bone fractures and burns, and often develop poorly healing injuries and abscesses that may cause permanent devastating disabilities.3,4

CIPA is characterized by reduced sensitivity to pain, with anhidrosis and some degree of mental retardation. Mardy et al found that mutations in the neurotrophic receptor tyrosine kinase1 (*NTRK1*) gene, which cause failure to support survival of nerve growth factor (NGF)-dependent sympathetic ganglion neurons and nociceptive sensory neurons derived from the neural crest, are responsible for CIPA.5

CIP patients have normal intellect and sweat function.6 Mutations in several genes can lead to different types of CIP. Among them are missense mutations in the voltage-gated sodium channel type IX α subunit (SCN9A) that cause loss of function of voltage-gated sodium channels in sensory neurons,7 and mutations in the epigenetic regulator PR domain zinc finger protein 12 (*PRDM12*) that lead to CIP through a defect in the normal development of nociceptive sensory neurons.8 Another, less frequent, form of CIP results from mutations in the nerve growth factor B (*NGFB*) gene that lead to loss of small myelinated fibers.9

The ocular manifestations of CIPA and CIP are related to impaired corneal innervation due to loss of NGF-dependent neurons responsible for corneal innervation and may include dry eye syndrome, superficial punctate keratopathies (SPKs), corneal opacities, neurotrophic keratopathy, and corneal ulcers.10 However, few data exist on long-term ocular sequelae of CIPA and there are very few studies mentioning ocular findings in patients with CIP.

Yagev et al studied 15 Bedouin children with CIPA and found corneal opacities in 10 and corneal ulcers in 7;11 Amano et al examined 18 Japanese patients with CIPA in whom the most frequent abnormality was SPKs with no corneal ulcerations.12 Ocular findings in patients with CIP are reported as reduced lacrimation, corneal abrasions, and possibly absent corneal reflex leading to keratitis and corneal scarring.8,13 To the best of our knowledge no study to date has compared the ocular manifestations of CIPA and CIP patients. The aim of this study is to describe ocular findings in a large group of patients with CIPA and CIP followed in our institution since 2008 (up to 11 years) and to compare the natural histories of the diseases.

# Methods

This study was conducted at the Soroka University Medical Center (SUMC), a tertiary medical center located in Southern Israel, and included a total of 39 patients: 32 diagnosed with CIPA and 7 with CIP. The research was approved by SUMC Institutional Review Board and Ethics Committee and adhered to the tenets of the Declaration of Helsinki.

All patients were followed by an ophthalmologist and a pediatrician at the CIPA outpatient unit at SUMC during the period 2008–2019. Pediatric evaluation included sensitivity to painful stimuli, thermal sensation, sweat production, and intelligence level. Demographic data as well as medical history were obtained from patients’ medical records. The collected ophthalmic data included visual acuity (VA), cycloplegic refraction, presence of corneal opacities, SPKs, corneal sensitivity, tear breakup time (TBUT), Schirmer test results, and posterior segment findings. Results of ancillary exams, such as corneal tomography and anterior segment photos, were included if performed.

VA was evaluated by Snellen chart. For non-verbal children and those with cooperation difficulties or developmental delay, fixation was evaluated by the central, steady, maintained method. SPKs were measured according to the SPK grading method,14 whereby the area and density of the lesions were used as parameters to quantify SPKs. A represents the area of the lesion, ranging from A0 (no staining) to A3 (area occupies more than two-thirds of the cornea), and D represents the density, ranging from D0 (no punctate staining) to D3 (high density; lesions overlap). Corneal sensitivity was assessed using a cotton thread. The Schirmer test was performed by Tear Flow test strip (TearFlo®), which was inserted in the lower fornix after local anesthesia with oxybuprocaine hydrochloride 0.4% drops. The length of the wet strip was measured after 5 minutes. Corneal opacity was assessed by 3 parameters: location (central, eccentric, or peripheral), diameter (less than 2 mm, 2–4 mm, or more than 4 mm), and depth (subepithelial, superficial stromal, or deep stromal). Active corneal ulcer was defined as a corneal infiltrate with epithelial defect and was described by location, diameter, and depth.

All patients were diagnosed with CIPA or CIP based on clinical characteristics; a few had a genetic analysis. Clinical criteria for diagnosis of CIPA included insensitivity to painful stimuli and impaired temperature perception manifested as self-mutilation and repeated traumatic injuries, anhidrosis that manifested as recurrent episodes of unexplained fever, and mental retardation of some degree. CIP patients were diagnosed by the same criteria, except anhidrosis and reduced intelligence.

Some patients had their blood sampled for genetic analysis, which was performed at the Institute of Human Genetics at SUMC by a real-time polymerase chain reaction technique.

# Results

The study included 39 patients, 32 with CIPA from 26 unrelated families and 7 with CIP from 4 unrelated families. Demographic data are shown in Table 1.

VA findings at the end of follow-up are presented in Table 2. VA could not be determined in 1 patient (2 eyes) in the CIPA group. In the CIP group, 1 patient had VA of light perception in 1 eye and it could not be determined in the other eye (Table 2).

Ocular surface findings revealed no active corneal ulceration in the most recent exam in both groups, although 8 CIPA patients and 5 CIP patients had 1 episode of corneal ulcer during the follow-up period. One CIPA patient had 2 episodes of corneal ulceration in both eyes. Corneal ulcers were more frequent during early childhood (age ≤10 years) in both groups. Surgical interventions such as tarsorrhaphy and amniotic membrane transplantation were required due to poor healing of corneal ulcers in 3 and 8 eyes of CIPA and CIP patients, respectively. One CIP patient had 8 surgeries of amniotic membrane transplantation combined with tarsorrhaphy, 2 corneal-covering grafts, and permanent punctual occlusion due to exposure keratopathy and poor healing of recurrent corneal erosions (Appendix Table 1).

Ocular findings are detailed in Table 3. In both groups, corneal opacities were mainly in the deep stroma and measured more than 4 mm in width. In the CIPA group the lesions were located mostly in the periphery (53.0%), whereas in the CIP group the opacities were mainly central (75.0%). Corneal reflex was evaluated in 26 of 32 patients with CIPA and in 6 of 7 patients with CIP, being present in 52.0% of eyes in the CIPA group and 33.3% of eyes in the CIP group. Schirmer test was performed in 18 of 32 patients with CIPA and in 4 of 7 patients with CIP. It was above the lower limit (10 mm) of the normal range in 83.3% of eyes in the CIPA group, whereas in the CIP group it was below the lower normal limit in 75% of eyes.

TBUT was measured in 24 of 32 patients in the CIPA group and in 4 of 7 patients in the CIP group. It was above the lower limit of normal (5 seconds) in 73% and 63% of eyes in the CIPA and CIP groups, respectively. The majority of the CIPA group showed no SPK findings (A0D0) with some having mild SPK (A1D1). In the CIP group SPKs were confined to less than one-third of the cornea (A1) in 41%, were diffuse (A3) in 33% of the eyes, and were extremely dense (D3) in 66% of the eyes. Strabismus was found in 4 patients in the CIPA group (3 with monocular esotropia and 1 with monocular exotropia) and in 1 patient in the CIP group, who had monocular esotropia. High astigmatism was found in 1 patient in the CIPA group who had keratoconus with corneal hydrops in 1 of his eyes and in 2 patients in the CIP groups (1 eye each). Posterior segment was normal in all patients.

# Discussion

Our study included patients with CIPA syndrome, 11 of whom had a confirmed mutation in the *NTRK1* gene (1926 T insertion), and patients with CIP syndrome who had mutations in *SCN9A* or *PRDM12*. To the best of our knowledge, the ocular manifestations in CIP patients have not previously been specifically addressed in the literature. The 2 groups presented with unique but similar ocular manifestations that are mainly restricted to the ocular surface. In the CIP group, corneal involvement showed a propensity toward severity as shown by SPK density and the presence of corneal opacities. Among CIPA patients, almost half of the examined eyes had intact corneal reflex, and corneal opacities were present in only 10 of 32 patients. This differs from the findings in a previous series of 15 Bedouin CIPA patients, where corneal reflex was absent from all eyes and corneal opacities were present in 10 out of 15 patients.11 In a study of 18 Japanese CIPA patients, corneal reflex was positive in both eyes of 1 patient, extremely diminished in both eyes of 7 patients, and absent in both eyes of 3 patients.12 According to Jarade et al, only 14 patients out of 52 worldwide showed corneal involvement, including lack of corneal sensitivity and absent corneal reflex, or neurotrophic corneal ulcers with poor healing, which predispose to repeated corneal infections and subsequent scarring. Normal corneal reflex was reported in 2 patients.15

Shatzky et al reported that some CIPA patients have conserved sensitivity, as a pain-sensation response to pinpricks was elicited in patchy areas over the bridge of the nose, behind the ears at the external auditory meatus, over the posterior cervical skin area, and on the palms.16 Hence, preserved corneal reflex may be found in CIPA patients that do not present the full spectrum of the syndrome and have some residual corneal sensation.

Tear production was normal in the majority of CIPA patients. Similar results were published previously by Amano et al.12 However, the corneal reflex was absent and tear production was decreased in the majority of CIP patients, consistent with findings in previous studies by Chen et al and Zhang et al.8,13 In our study, TBUT measurements were similar in the CIPA and CIP groups and were above the lower limit in most eyes. Yagev et al also reported that TBUT was normal in all patients,11 although Amano et al found that TBUT was decreased in all eyes of CIPA patients, leading to dry eye likely due to increased evaporative loss.12 However, in that study TBUT was measured only in 7 patients out of 18.

The pathogenic variant affecting the *NTRK1* gene leading to CIPA in our Bedouin population is different from that of the Japanese CIPA patients.16,17 Hence, the differences could be explained by different phenotypic expression. Our study includes the largest number of CIPA and CIP patients ever reported, with a long follow-up period. Patients of both groups developed corneal ulcers at least once during their lifetime, especially during childhood; CIP patients were more prone to develop corneal ulcers, which are difficult to treat and commonly required surgical interventions.

It has been shown that mutations in *PRDM12* and *NTRK1* cause PRDM12-CIP and CIPA, respectively, through absence of nociceptive sensory neurons, and in CIPA also through the lack of sympathetic innervation of sweat glands.4,8 Recently, *PRDM12* was found to be responsible for the expression and maintenance of NTRK1 during the development process of nociceptive sensory neurons in dorsal root ganglia and trigeminal ganglia.18 Thus both PRDM12-CIP and CIPA syndromes have the same common final pathway of abnormal development of nociceptive sensory neurons. As mentioned earlier, one study used confocal microscopy to demonstrate the lack of central corneal innervation, which is consistent with the loss of Aδ and C nerve terminals in corneas of CIPA patients.10 Given the same pathophysiological mechanism, ocular manifestations in both diseases are expected to be similar and to be a result of a lack of corneal sensation. It is unclear, therefore, why in our study *PRDM12*-dependent CIP tended to have poorer outcome than CIPA caused by *NTRK1* mutation, and it is possible that the bias was caused by there being a small number of CIP patients.

Corneal nerves also play a role in the homeostasis and the normal regeneration of corneal epithelium by secreting various neuropeptides, among them NGF and substance P. Moreover, corneal nerve impairment is responsible for epithelial defects, ulcerations, corneal perforations, and reduced function of corneolimbal stem cells as part of neurotrophic keratopathy.19 This factor may have impaired the healing of corneal ulcers in our patients.

Congenital insensitivity to pain is a group of rare disorders. Long-term prognosis of CIPA patients has not been established, and little data exist in ophthalmic literature regarding ocular manifestations of CIP. Owing to the paucity of the data it is hard to draw valid conclusions regarding the natural history of these disorders.

Our study is unique in its sample size and length of follow-up, which allows us to expand our understanding of the prognosis and suggest methods to manage these diseases. According to the results of our study, patients with CIPA and CIP may present with or without ocular involvement. Significant corneal opacities were noticed mostly in patients who lack corneal reflex and corneal sensitivity. In most eyes with intact corneal reflex, good vision was preserved.Yet there is wide phenotypic variability between disorders causing congenital insensitivity to pain and even among individuals with the same pathogenic variants, suggesting that interaction with other genetic and environmental factors may contribute to the phenotype. We found that CIPA patients had less frequent ocular involvement and relative vision conservation compared with CIP patients. Patients in both groups may have normal vision, especially if corneal sensitivity is not severely affected; however, children with these conditions should be closely followed by an ophthalmologist to identify and treat ocular surface disease early in order to prevent vision loss due to corneal ulceration and scarring. This is especially true for those who lack corneal reflex. Because of the impaired pain sensation, the symptoms of corneal ulceration or infection can be easily missed, and the parents should be advised to seek an urgent consultation with an ophthalmologist in any case of red eye, secretions, or blurred vision.

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# Figure captions

FIGURE 1. Pedigree of family 2 with congenital insensitivity to pain with anhidrosis (left) and family 7 with congenital insensitivity to pain without anhidrosis (right). Filled symbols indicate affected individuals. Small round filled symbols indicate abortions. Squares indicate males; circles indicate females. A diagonal line across a symbol indicates the individual is deceased.











FIGURE 2. Left eye of patient CIPA 1, showing permanent lateral tarsorrhaphy and central corneal opacity due to resolved corneal ulcer.

FIGURE 3: Eyes of patient CIPA 2 (brother of patient CIPA 1). Right eye has 2/3 permanent lateral tarsorrhaphy and minimal central corneal opacity. Left eye appears normal.

FIGURE 4: Eyes of patient CIPA 5. Left eye has permanent lateral tarsorrhaphy and central corneal opacity. Right eye has a clear cornea and appears normal.

FIGURE 5: Right eye of patient CIP 5, with central corneal opacity. Note the notch in upper and lower eyelids where tarsorrhaphy was made.

FIGURE 6: PENTACAM® tomography of the right eye of patients CIP 4 and CIP 5, respectively, showing high with-the-rule astigmatism.