**This retrospective observational case series of six children with congenital insensitivity to pain analyzes the ocular manifestations of their condition. Patients were diagnosed by clinical criteria and genetic analysis: three had mutations in the *PRDM12* gene and three in the *SCN9A* gene. Mean follow-up times were 56 months and 130 months, respectively. The former group had a poorer prognosis, more severe corneal involvement, and lower visual acuity than the second group.**

**Abstract**

**Purpose:** To describe ocular manifestations among children with Congenital insensitivity to pain and to analyze the natural history of their ocular disease.

**Design:** Retrospective observational case series.

**Methods**: Records of all patients who visited the outpatient clinic at Soroka medical center with confirmed diagnosis of congenital insensitivity to pain syndrome were reviewed. Diagnosis was established by clinical criteria and by genetic analysis. Collected data included demographic information, medical history, ocular surgeries, genetic analysis, and ophthalmic examination. Retrieved data included visual acuity, cycloplegic refraction, ocular surface findings, corneal sensitivity, tear film production and fundoscopy.

**Results**: A total of 6 patients, equally divided into two groups. 3 had mutations at the PRDM12 gene and 3 had mutations at the SCN9Agene. Mean follow-up time was 56 months and 130 months, respectively. Corneal opacities were found in 5/6 eyes and in 2/6 eyes of 2 different patients, respectively. Most patients in the first group had diffuse and dense superficial punctate keratopathies (SPK), while among patients in the second group dense SPK were found in 4/6 eyes and no SPK in both eyes of 1 patient. Schirmer was normal in the first group but reduced among all eyes of the second group. Corneal reflex was absent in all patients of the first group, versus positive in both eyes of 2/3 patients from group 2. Best corrected visual acuity (BCVA) was ≤ 20/40 in most patients from the first group, while among patients from group 2, it was 20/30, except one eye of two patients who had BCVA of 20/80 and 20/200.

**Conclusion:** In conclusion, patients with PRDM12 congenital insensitivity to pain have a poorer prognosis, with severe corneal involvement, and lower BCVA in comparison to patients with mutation at the SCN9A gene.

**Introduction**  
Congenital insensitivity to pain is part of a group of extremely rare autosomal recessive neuropathies characterized by the inability to perceive noxious stimuli as pain and heat. Patients are predisposed to self-inflicted injuries and prone to bone fractures and burns. Other complications including Charcot joints, poorly healing injuries, and abscesses may cause permanent and devastating orthopedic disabilities: intellectual ability and sweat function are preserved.2

Congenital insensitivity to pain The undeterminedIts classification is based on genetic diagnosis.

Several genetic mutations have been found to correlate with congenital insensitivity to pain. Among them is a missense mutation in the voltage-gated sodium channel type IX α subunit (SCN9A), which causes loss of function of voltage-gated sodium channels of the sensory neurons at the dorsal root ganglia and the trigeminal ganglia, phenotypically characterized with insensitivity to pain and anosmia while other sensorial modalities remain intact.3

Another mutation that causes congenital insensitivity to pain affects the epigenetic regulator PR domain zinc finger protein 12 (*PRDM12*), interrupting the development of the Aδ and C nociceptive sensory neurons4. Lack of corneal innervation causes reduced secretion of various neuropeptides, such as NGF and substance P, that play a role in homeostasis and normal regeneration of corneal epithelium. This results in neurotrophic keratopathy and causes epithelial defects, reduced function of the corneal-limbal stem cells, ulceration, and even corneal perforations.10

The ocular manifestations of congenital insensitivity to pain are thought to relate to impaired corneal innervation and include dry eye syndrome, superficial punctate keratopathies (SPKs), corneal opacities, neurotrophic keratopathy, and corneal ulcers.5 *PRDM12* mutation is correlated with reduced lacrimation, corneal abrasions, and reduced or absent corneal reflex, causing keratitis and corneal scarring.4, 6 Current literature regarding ocular manifestations in patients with *SCN9A* is inconclusive and based on small-scale studies.

The aim of this study is to describe ocular findings and compare the natural history of the disease in these two groups of patients**.**

**Methods**

This is a retrospective case series of all patients with confirmed diagnosis of congenital insensitivity to pain who visited the outpatient clinic at Soroka University Medical Center (SUMC), a tertiary referral center located in Southern Israel, between 2009 and 2018. fully e

All patients were genetically diagnosed at the Institute of Human Genetics at SUMC using real-time polymerase chain reaction. They were followed by an ophthalmologist and a pediatrician at the CIPA outpatient unit at SUMC. Demographic data and medical histories were obtained from computerized medical records. Ophthalmic data collected included visual acuity (VA), cycloplegic refraction, presence of corneal opacities, SPKs, corneal sensitivity, tear breakup time (TBUT), Schirmer test, and posterior segment findings. Data from ancillary exams (e.g., corneal tomography, anterior segment photos) were included if performed.

Visual acuity was evaluated by Snellen chart. SPKs were measured according to the SPK grading method,7 in which the area and density of the lesions were used as parameters to quantify SPKs, where 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 and lesions overlap. Corneal sensitivity was assessed by cotton thread. Telling the patient to fixate on a target, it was applied on the cornea from the lateral side of the eye. If a blink reflex was elicited it was recorded as positive corneal reflex.Tear production was evaluated by Schirmer test after instillation of oxybuprocaine hydrochloride 0.4% for local anesthesia. Schirmer strips (TearFlo®) were inserted into the lower fornix without touching the cornea. The length of wetting in millimeters was recorded after 5 minutes.

Corneal opacity was assessed by three parameters: location (central, eccentric, or peripheral), diameter (less than 2 mm, between 2 and 4 mm, or more than 4 mm), and depth (subepithelial, stromal-superficial, or deep). Active corneal ulcer was defined as a corneal infiltrate with epithelial defect and described by location, diameter, and depth.

**Results**

Demographic data and results are summarized in Table 1. Six patients genetically diagnosed with congenital insensitivity to pain were divided into two groups (A and B) of three patients: Group A had *PRDM12* gene mutations and Group B had *SCN9A* gene mutations. Group A consisted of two first-degree siblings (sister, aged 11 years, and brother, 3 years; patients CIP1 and CIP2), offspring from a consanguineous marriage, and a third unrelated patient (patient CIP3; 6 years old). Group B contained three sisters (24, 16, and 13 years old; patients CIP4, CIP5, CIP6) with the same father but two different mothers.

Follow up time was 23–94 months and 121–143 months for groups A and B, respectively.

All patients in group A versus two in group B (CIP4 and CIP6) presented to the outpatient clinic or ophthalmic emergency room with corneal ulcer by the first year of life: they were hospitalized and treated aggressively with topical and sub-conjunctival fortified antibiotics and by lateral tarsorrhaphy (LT). CIP5 presented at 6 years of age with dry eye complaints and was followed up because of dry-eye syndrome.

In group A, CIP2 had repeated LT and amniotic membrane (AM) transplant due to non-healing corneal ulcers: six LT, five AM in the right eye and seven LT, eight AM in the left eye. He also required two corneal-covering graft transplantations due to descemetocele on his left eye.

All patients had signs of dry eye syndrome with variable severity. In group B, two patients (CIP5 and CIP6) had short TBUT and abnormal Schirmer test results. Moderate dry eye syndrome with localized and dense SPK was observed in CIP4 and CIP6, whereas no dry eye syndrome was observed in CIP5. All patients required constant eye lubrication. CIP1 and CIP2, who are siblings, underwent therapeutic punctal occlusion.

Corneal reflex was negative (four of six eyes) or not tested (two of six eyes) in group A. A positive corneal reflex was present in CIP4 and CIP6 (four of six eyes) and negative (two of six eyes) in CIP5 in group B.

Corneal opacities were observed in five of six eyes in group A versus two of six eyes in group B.

In group A, visual acuity at the last follow-up visit was 20/30 in both eyes for CIP1; CIP2 had light perception in his right eye and visual acuity could not be determined in the left. CIP3 had a visual acuity of 20/200 in his right eye and 20/40 in the left. In group B, CIP4 and CIP6 had developed amblyopia: visual acuity at the last follow-up visit was 20/200 and 20/80 in their amblyopic eyes, respectively, versus 20/30 in the non-amblyopic eye. Both had corneal opacities and astigmatism in the amblyopic eye (Figure 2). CIP5 had a visual acuity of 20/30 in both eyes at the last follow-up visit, with bilateral clear corneas and no signs of dry-eye syndrome.

**Discussion**

Congenital insensitivity to pain is a rare disorder and little is known about its ocular manifestations. Patients with different genetic mutations have not been compared yet. In this study we compared ocular manifestations in patients with *PRDM12* mutations with those in patients with *SCN9A* mutations.

We found that patients with *PRDM12* mutations (group A) tended to have a poorer ocular prognosis and visual acuity than patients with *SCN9A* mutations (group B). All in group A had absent corneal reflex, versus one patient in group B.

Corneal opacities and SPK grade were higher in all patients in group A: two patients in group B had milder SPK grade and one had no SPK. Tear production was decreased among all patients in group B, but normal in the only patient for which it was measured in group A.

Refractory non-healing corneal ulcers that required surgery were more frequent and tended to be more severe and difficult to treat in group A than group B.

Similar results regarding corneal reflex and corneal opacities have been reported previously in patients with *PRDM12* mutations. In one study of affected individuals from 11 families, absent corneal reflex led to progressive corneal scarring in many cases. They also tended to have reduced tear function.4 In another study of five individuals (23–57 years of age), all with decreased tear production and no corneal reflex, two had no useful vision in one eye.6

Ocular findings vary among patients with *SCN9A* mutation. The corneal reflex was intact in three studied patients (31, 34, and 44 years old),8 whereas in a previous study of four patients, three of whom are also included here, all had decreased or absent corneal reflex but normal lacrimal production.3 One reported case had absent corneal reflex and developed bilateral sterile corneal ulcers that were attributed to neurotrophic keratopathy.9

We think the phenotypic expression varies due to variable penetrance of the mutation.

In our study, all but one case of corneal ulcer occurred before the age of 2 years. These could have been prevented if parents were aware of such complications and of ways to prevent them.

In conclusion, we note that patients with *PRDM12* mutations have a more serious ocular involvement than patients with *SCN9A* mutations, but both can develop corneal ulcers at an early age. Outcomes tend to be better among patients with *SCN9A* mutation, which is probably because of some degree of preserved corneal sensitivity compared with patients with *PRDM12* mutation.

Ocular manifestations in both groups may represent variable degrees of neurotrophic keratopathy and the different manifestations are due to a variable degree of corneal hypoesthesia or anesthesia. Our case series is highly limited due to the small number of patients, lack of control subjects, and by its retrospective nature. More studies are required in order to determine the genotype phenotype correlation in these disorders.

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**Figure legends**

**FIG 1.** Pedigree of family with congenital insensitivity to pain. Filled symbols indicate affected individuals. Small round filled symbols indicate abortions. Squares indicate males and circles females. Diagonal line across a symbol = deceased individual.



**FIG 2.** Right eye of patient CIP5 showing central corneal opacity. Note the notch in upper and lower eyelids where tarsorrhaphy was made.

**FIG 3.** PENTACAM® tomography, right eyes of patients CIP4 and CIP5 showing high with-the-rule astigmatism.