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

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**SYNOPSIS**

We describe long-term ocular complications of congenital insensitivity to pain, an inherited condition associated with impaired corneal sensation. Early recognition of this condition and close follow up may prevent vision loss due to corneal opacities in these patients.

**ABSTRACT**

PURPOSE: To describe ocular manifestations in children with congenital insensitivity to pain with and without anhidrosis (CIPA and CIP).

DESIGN: Retrospective observational case series of 39 children.

METHODS: We reviewed medical records of patients followed in ophthalmology clinic and diagnosed with CIPA or CIP. We collected clinical data, with particular attention on ocular surface findings. Corneal sensitivity was tested by a blink reflex upon touching the cornea. Statistical analysis assessed differences in the manifestations between the two conditions and relationships among corneal sensitivity, presence of corneal opacities and visual acuity (VA).

RESULTS: CIPA was diagnosed in 32 children and CIP in seven. Median follow-up period was 50 months for CIPA group and 94 for CIP. Corneal opacities were seen in 23% of CIPA eyes and 57% with CIP. Blink reflex was positive in 52% of CIPA eyes and 33% with CIP. VA ≥20/25 was recorded in 36% of CIPA eyes whereas all CIP patients had VA 20/30 or less. For the whole cohort, we found negative correlation between preserved blink reflex and presence of corneal opacities, and positive correlation between preserved blink reflex and good VA.

CONCLUSION: Children with congenital insensitivity to pain are prone to develop corneal scarring. CIP patients tend to have more severe ocular surface disease than those with CIPA, likely due to more prevalent loss of corneal sensation. In both groups, preserved blink reflex correlated with good vision. Affected children should have close follow-up to identify and treat ocular surface disease and prevent vision loss.

**INTRODUCTION**

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 unknown, 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 of CIP as 1 in 2,200,000–4,200,000.2 Patients with CIPA and CIP are predisposed to self-inflicted injuries that may cause permanent devastating disabilities.3

CIPA is characterized by reduced sensitivity to pain, anhidrosis and mental retardation. Clinically CIP patients differ from those with CIPA by normal intelligence and sweat production.3 Mutations in 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.4Mutations in several genes can lead to CIP. Among them are mutations in SCN9A that cause loss of function of voltage-gated sodium channels in sensory neurons,5 and mutations in *PRDM12* that lead to CIP through a defect in the normal development of nociceptive sensory neurons.6

The ocular manifestations of CIPA and CIP are related to impaired corneal innervation due to loss of NGF-dependent neurons and may include dry eye syndrome, superficial punctate keratitis (SPK), corneal opacities, neurotrophic keratopathy, and corneal ulcers.7 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 ten and corneal ulcers in seven.8 Amano et al examined 18 Japanese patients with CIPA in whom the most frequent abnormality was SPKs with no corneal ulcerations.9 Ocular findings reported in patients with CIP include reduced lacrimation, corneal abrasions, and possibly absent blink reflex leading to keratitis and corneal scarring.6,10 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 these diseases.

# METHODS

This study was conducted at the Soroka University Medical Center (SUMC) in Southern Israel and included 39 patients with a clinical or genetic diagnosis of CIPA or CIP (32 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.

We performed a retrospective review of the electronic medical records of all patients followed in the CIPA outpatient unit at SUMC during 2008–2019 who have been examined by an ophthalmologist at least once. All patients had pediatric evaluation, which included assessment of sensitivity to painful stimuli, thermal sensation, sweat production, and intelligence level. Demographic data and medical history were obtained from patients’ records. The collected ophthalmic data included best corrected visual acuity (VA), cycloplegic refraction, presence of corneal opacities, SPK, corneal sensitivity, tear breakup time (TBUT), Schirmer test results, and posterior segment findings. The findings were collected from the records of the most recent eye exam, and when not found, from the records of the previous visit. Usually, ocular surface and vision assessment were done at each visit, unless patients’ cooperation (due to developmental delay or young age) did not allow to complete the exam. Three of the enrolled patients were previously described by Yagev et al in 1999,8 (CIPA patients2,4,6, Appendix TABLE 1), but only their recent results collected after 2008 are included in the current study.

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. Superficial punctate keratitis was assessed according to the SPK grading method described by Miyata and co-workers,11 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 by recording a blink reflex following touching the cornea with a cotton thread while patient was viewing a distant target. Cotton thread was applied from the temporal side of the eye and the sensitivity was assessed in several places on the cornea. The corneal sensitivity was not tested on top of corneal ulcers or scars unless the cornea was completely scarred. If the blink was observed, the reflex was defined as positive. The Schirmer test was performed to patients who could cooperate with it. We employed Schirmer with anaesthetic following the methodology of Amano et al, used for patients with insensitivity to pain.9 Tear Flow test strip (TearFlo®) was inserted in the lower fornix after local anesthesia with oxybuprocaine hydrochloride 0.4% drops. The length of the wet strip was measured after five minutes and the normal cutoff was defined as 10mm.9 Corneal opacities were assessed by three 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 and some of them 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 using the same criteria, except for anhidrosis and reduced intelligence.

Seventeen patients (11 with CIPA and six with CIP) had genetic analysis, which was performed on their blood samples at the Institute of Human Genetics at SUMC by a real-time polymerase chain reaction technique.

***Statistical analyses***

We used nonparametric tests to check relationships between visual acuity, corneal opacities and corneal sensitivity (Spearman’s rank correlation test) and to trace differences between the two study groups (CIPA and CIP) in age and length of follow up (Mann-Whitney U Test). We also performed a Chi-square or Fisher’s exact test for comparisons between the groups in dichotomous variables such as gender, consanguinity, and presence of corneal opacities. Patient’s age and follow-up period are reported as medians and interquartile ranges. Categorical variables (such as gender, consanguinity, corneal opacities, visual acuity) are expressed as numbers (percentages). All statistical analyses were performed using IBM SPSS Statistics, version 26. Results were considered statistically significant at p≤0.05.

# RESULTS

The study included 39 patients, 32 with CIPA from 26 unrelated families and seven with CIP from four unrelated families. Patients' demographic data are shown in TABLE 1. All patients were of Bedouin Arab origin, except Patient CIP1 of Jewish origin (Appendix table 1). All 11 genetically tested CIPA patients had mutations in *NTRK1* (1926Tins), three CIP patients had mutations in *PRDM12*, and another three in *SCN9A*. All except seven patients had more than one eye exam reported during the study period. Pedigrees of two families enrolled in the study are shown in Figure 1, Family 2 with three children affected with CIPA, one of whom has died of sepsis, and Family 7 with three children with CIP. (Appendix table 1)

**TABLE 1.** Demographic data of patients with congenital insensitivity to pain with and without anhidrosis

|  |  |  |  |
| --- | --- | --- | --- |
|  | **CIPA (n= 32)** | **CIP (n= 7)** | **p value** |
| Female, n (%) | 13 (40.6) | 5 (71.4) | 0.14 |
| Age median (IQR)\_First visit | 10 (4.1; 15.6) | 2.1 (1.1; 6.1) | 0.03 |
| Age median (IQR)\_Last visit | 15 (7.5; 23) | 11 (4; 16) | 0.22 |
| Consanguinity, n (%) | 13 (40.6) | 5 (71.4) | 0.28 |
| Family history, n (%)  (> 1 affected member) | 11 (34.4) | 5 (71.4) | 0.08 |
| Follow-up period (mo)  median (IQR) | 50 (3; 90) | 94 (35; 128) | 0.07 |

CIPA= congenital insensitivity to pain with anhidrosis; CIP= congenital insensitivity to pain without anhidrosis; n= number of patients, mo= months, IQR=interquartile range

Patients’ best corrected VA at the last follow-up visit is presented in TABLE 2.

**TABLE 2.** Visual acuity at last visit

|  |  |  |  |
| --- | --- | --- | --- |
| **Visual Acuity** | **CIPA no. eyes (%)** | **CIP no. eyes (%)** | **p value** |
| ≥20/25 | 23 (35.9) | 0 (0.0) | 0.01 |
| 20/30-20/50 | 12 (18.7) | 7 (50.0) | 0.03 |
| 20/80-20/200 | 3 (4.6) | 3(21.4) | 0.07 |
| ≤ FC 0.5m | 2 (3.1) | 3 (21.4) | 0.04 |
| CSM | 22 (34.4) | 0 (0.0) | 0.01 |
| NA | 2 (3.1) | 1 (7.1) | 0.15 |

CIPA= congenital insensitivity to pain with anhidrosis; CIP = congenital insensitivity to pain without anhidrosis; CSM = central, steady, maintained fixation; FC = finger counting; m= meters; NA= not available

Thirty six percent of the eyes in the CIPA group had VA of 20/25 or better, whereas no patient reached this acuity level in the CIP group (p=0.01), where patients’ VA was 20/30 or less. Due to developmental delay of the CIPA patients, in some of them VA could only be assessed using CSM method. The acuity could not be determined in patient CIPA10, with severe developmental delay and in one eye of young patient CIP2 with corneal opacities (Appendix table 1).

Ocular surface findings revealed no active corneal ulceration at the most recent visit in any patient, although eight CIPA patients and five CIP patients had at least one episode of corneal ulceration during the entire follow-up period. In the CIP patients the ulcers were more prevalent, more difficult to treat and commonly required surgical interventions. Four patients had corneal ulcers in both eyes (CIPA5 and 6, CIP2 and 7) and four had recurrent ulcers (CIPA4 and 6, CIP2 and 3). Corneal ulcers were more frequent during early childhood (age≤10 years) in both groups. All patients presenting with corneal ulcers were treated initially by topical fortified antibiotics (Ceftazidime and Vancomycin) after cultures were obtained. One patient was treated with Photo Activated Chromophore for Keratitis cross linking (PACK CXL) with good ulcer resolution.12 For patients with dry eye signs lubricating eye drops were used. Surgical interventions such as lateral tarsorrhaphy and amniotic membrane transplantation were required due to nonhealing corneal ulcers in four eyes of CIPA patients and 7 eyes of CIP patients. One patient (CIP2, Appendix table 1) had multiple surgeries in both eyes to treat non-healing recurrent corneal erosions and melting, including several amniotic membrane transplantations, lateral and central tarsorrhaphy, tectonic corneal graft and a permanent punctal occlusion.

Main ocular findings of the CIPA and CIP patients are detailed in TABLE 3.

**TABLE 3** Ocular Findings in Patients with Congenital Insensitivity to Pain with and without Anhidrosis

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ocular Finding** | **No. (%) Patients** | | **No. (%) Eyes** | | **p value** |
|  | **CIPA** | **CIP** | **CIPA** | **CIP** |  |
| **Corneal opacities**  1 eye  2 eyes | 5/32 (15.6)  5/32 (15.6) | 4/7 (57.0)  2/7 (28.5) | 15 (23.4) | 8 (57) | **0.01** |
| Location  Diffuse  Central  Eccentric |  |  | 1/15 (6.7)  6/15 (40.0)  8/15 (53.0) | 2/8 (25.0)  6/8 (75.0)  0 | 0.27 |
| 0.19 |
| **0.02** |
| Depth  Subepithelial  Superficial stromal  Deep stromal |  |  | 2/15 (13.3)  6/15 (40.0)  7/15 (46.6) | 1/8 (12.5)  2/8 (25.0)  5/8 (62.5) | 0.9 |
| 0.65 |
| 0.66 |
| Diameter, mm  <2  2–4  >4 |  |  | 5/15 (33.3)  4/15 (26.6)  6/15 (40.0) | 1/8 (12.5)  3/8 (37.5)  4/8 (50.0) | 0.36 |
| 0.65 |
| 0.68 |
| **Corneal sensitivity**  NA  Positive  Negative | 6/32 (18.8) | 1/7 (14.2) | 12/64 (18.8)  27/52 (52.0)  25/52 (48.0) | 2/14 (14.2)  4/12 (33.3)  8/12 (66.6) | 0.9 |
| 0.34 |
| 0.34 |
| **Schirmer**  NA  >10  ≤10 | 14/32 (43.8) | 3/7 (42.8) | 28/64 (43.8)  30/36 (83.3)  6/36 (16.6) | 6/14 (42.8)  2/8 (25.0)  6/8 (75.0) | 0.99 |
| **0.003** |
| **0.003** |
| **Superficial punctate keratitis**  NA  A0D0  A1D1  A1D2  A1D3  A2D1  A2D3  A3D1  A3D2  A3D3 | 6/32 (18.75) | 1/7 (14.0) | 12/64 (18.75)  22/52 (42.3)  9/52 (17.3)  2/52 (3.8)  2/52 (3.8)  2/52 (3.8)  4/52 (7.7)  1/52 (1.9)  3/52 (5.7)  7/52 (13.4) | 2/14 (14.0)  2/12 (16.5)  1/12 (8.3)  1/12 (8.3)  3/12 (25)  0/12 (0)  1/12 (8.3)  0/12 (0)  0/12(0)  4/12 (33.3) |  |
| 0.99 |
| 0.18 |
| 0.67 |
| 1.0 |
| 1.0 |
| 0.47 |
| 1.0 |
| **0.04** |
| 1.0 |
| 0.19 |

CIPA= congenital insensitivity to pain with anhidrosis; CIP= congenital insensitivity to pain without anhidrosis; Superficial punctate keratitis (SPK) area and density of the lesions were used as parameters to quantify SPK.11 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). NA = results not available. p values, reflecting statistically significant differences between the CIPA and CIP groups are highlighted in bold.

Corneal opacities were found in 23.4% of CIPA eyes versus 57% of the CIP eyes (p=0.01) (Figure 2). Most corneal opacities extended from the superficial to the deep stroma and measured more than 4 mm in diameter. The location of corneal opacities varied among the two groups. In the CIPA group peripheral corneal opacities were more prevalent than in the CIP group (53.0 % of eyes versus 0%, p= 0.02), while in the CIP group central opacities were more common than in CIPA (75.0% of the eyes vs 40%, p=0.19).

Blink reflex to evaluate corneal sensitivity was assessed in 26 CIPA patients and six CIP patients, and found positive in 52.0% and 33.3% of eyes, respectively. The three CIPA patients who were included in the study by Yagev et al all had a negative blink reflex, and corneal opacities were present in four of the six eyes. 8(Appendix table1: CIPA2,4,6)

We investigated the relationships among corneal sensitivity, development of corneal opacities and visual acuity in the eyes of patients in the whole cohort and in the CIPA group (because of the small number of the CIP patients, their results were not assessed separately). The results of the Spearman’s rank correlation test yielded a moderate negative correlation between the preserved corneal sensitivity and the development of corneal opacities in the whole cohort and in the CIPA group specifically (r= -0.41, p= 0.001 and r= -0.49, p<0.001, respectively. Appendix tables 2 and 3). We also examined relationships between the corneal sensitivity, evidence of corneal opacities and VA at the last visit. We found that eyes with preserved corneal sensitivity tended to have good VA (correlation between positive blink response and VA≥ 20/25: r= 0.38, p= 0.002 for the whole cohort and r= 0.39, p= 0.004 for the CIPA group). In addition, the eyes with corneal opacities had a decreased visual acuity (correlation between the presence of corneal opacities and VA 20/80-20/200: r=0.34, p=0.002 in the whole cohort) and this relationship was even stronger in eyes with central corneal opacities (r=0.47, p<0.001 for the whole cohort and r=0.44, p<0.001 for the CIPA group), whereas the eyes with poor VA tended to have a negative blink reflex. (Appendix tables 2 and 3).

Schirmer test with anaesthetic was performed to patients who were cooperative enough for the testing (Table 3). The results were within the normal range in 83.3% of CIPA eyes, whereas in the CIP group they were below the normal limit in 75% of eyes (p= 0.003). TBUT was measured in 24 CIPA patients and four CIP patients and was above the lower limit of normal (5 seconds) in 73% and 63% of eyes, respectively (Appendix table 1).

Forty two percent of CIPA eyes showed no SPK findings (A0D0) and 17% had mild and localized SPK (A1D1). In the CIP group, SPK was more prevalent and severe, being very dense and localized to at least one third of the cornea (A1D3) in 25% and very dense and diffuse (A3D3) in 33% of the eyes.

Strabismus was found in four CIPA patients and one CIP patient (Appendix table 1). Four patients had esotropia and one exotropia. In all but one patient it was likely a sensory strabismus related to corneal opacities. Patient CIPA12 with exotropia and no corneal opacity had eyelid ptosis in one eye which caused astigmatism and amblyopia. Very high astigmatism (≥4.50D) was found in one eye of one patient CIPA32 who had keratoconus with corneal hydrops which was possibly related to corneal exposure and thinning. In the CIP group, two patients presented with high astigmatism without keratoconus, which was likely due to their corneal opacities (CIP4 and CIP5). Posterior segment of the eye was normal in all patients.

# DISCUSSION

Our study included patients with CIPA and CIP syndromes. Several studies reported ocular findings in CIPA patients, but to the best of our knowledge, the ocular manifestations in CIP have not been specifically addressed in the literature. The two groups presented with unique but similar ocular manifestations that are mainly restricted to the ocular surface. Some patients in both groups developed corneal ulcers at least once during their lifetime, especially during early childhood. In CIP patients the ulcers were more prevalent and difficult to treat and commonly required surgical interventions. Thus, CIP patients exhibited more severe ocular surface disease than those with CIPA, likely due to more prevalent loss of corneal sensation. Moreover, VA in the CIP patients was lower than in the CIPA group. It has been shown that mutations in *NTRK1* and *PRDM12* cause CIPA and CIP syndromes, respectively, through absence of nociceptive sensory neurons, and in CIPA also through the lack of sympathetic innervation of sweat glands.4,6 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.13 Thus both CIPA and PRDM12-related CIP syndromes have the same common final pathway of abnormal development of nociceptive sensory neurons. Given the same pathophysiological mechanism, ocular manifestations in both diseases are expected to be similar. It is unclear, therefore, why in our study CIP patients tended to have poorer outcome than those with CIPA, and it is possible that the bias was caused by there being a small number of CIP patients in the study. It is also possible that longer follow-up time of the CIP patients in our study (median follow-up period of 94 months versus 50 in the CIPA group) played a role, as the chances of developing ocular complications increase with longer duration of the disease. Further studies involving larger series of CIP patients are needed to confirm the differences in the severity between the two entities and elucidate their mechanism.

Among CIPA patients included in our study, half of the examined eyes had positive blink reflex, and corneal opacities were present in only ten of 32 patients. Interestingly, these results somewhat differ from those in a previous series of 15 Bedouin CIPA patients who tended to have a more frequent corneal involvement (negative blink reflex in all eyes and corneal opacities in ten out of 15 patients).8 The reasons for these differences might be accounted by several factors, one of which could be a limited and possibly not entirely representative patients’ sample in the previous study.8 The three patients in the current study who were also included in the previous series, all had negative blink reflex and corneal opacities present in four of the six eyes. Also, patients enrolled in the previous study were younger than in the current one, and the blink reflex results could be variable in young children. Shatzky et al reported that some CIPA patients have conserved sensitivity, as a pain-sensation response to pinpricks was elicited in patchy areas on the head, neck and palms.14 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. This could account for a variable presentation of the disease, even in patients with the same genetic defect. In agreement with that, other authors also reported variable results in CIPA patients. In a study of 18 Japanese CIPA patients, blink reflex was positive in one patient, diminished in seven, and absent in three patients.9 According to Jarade et al, only 14 patients out of 52 worldwide showed corneal involvement; normal lacrimation with lack of corneal sensitivity and no blink reflex were observed in most patients. Neurotrophic corneal ulcers with poor healing, which predispose to repeated corneal infections and subsequent scarring, were also reported.15 A relatively less frequent corneal scarring observed in the current study compared to the previous one by Yagev et al. conducted two decades ago on the same population, could also reflect the experience accumulated during the years with recognition and managing this condition. Thus, taken together, the results of the two studies may indicate that an earlier diagnosis of the disease and its more aggressive treatment led to a more favorable outcome.

Tear production as evidenced by a Schirmer test results was normal in the majority of CIPA patients and reduced in CIP, in agreement with previous reports .6,9,10 TBUT measurements, however, were within the normal range in both groups. Yagev et al also reported that TBUT was normal,8 whereas Amano et al found a decreased TBUT in CIPA patients.9 It should be noted that both Schirmer test and TBUT may be of limited value for assessment of dry eye signs in children. According to recent study by Ong Tone et al, the only reliable method for that is by corneal fluorescein staining.16

Congenital insensitivity to pain is a group of rare disorders. Long-term prognosis of CIPA patients has not been established, and little data exist regarding ocular manifestations of CIP. Our study is unique in its large number of patients and long follow-up period, which allows us to expand our understanding of the natural history of these disorders and draw conclusions about their management. According to our results patients with CIPA and CIP may present with or without ocular involvement. In general, significant corneal opacities were noticed mostly in patients who lack blink reflex. Our statistical analysis confirmed a negative correlation between presence of the blink response and corneal opacities, such that a preserved corneal sensitivity serves as a protective factor against the development of corneal scarring. Moreover, we show that in most eyes with preserved corneal sensitivity, good vision was maintained.Yet, there is a 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. Although CIP patients had more frequent ocular involvement than those with CIPA, individuals in both groups may develop normal vision, especially if corneal sensitivity is not severely affected. However, children with these conditions should be closely monitored 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 children who lack blink reflex, for whom a prophylactic lateral tarsorrhaphy should be considered. A study by Lambley et al on children with corneal anesthesia from different causes showed beneficial role of early tarsorrhaphy to prevent corneal scaring and microbial keratitis.17 The children with positive blink reflex have a better prognosis and therefore may have less frequent follow up and no need for prophylactic intervention.

# Contributors BE, RY and ET designed the study and initiated the project. BE, AI, RY, AB, GL, and ET examined the patients and collected the data. LG monitored data acquisition, critically analyzed the data and interpreted the results. BE and LG wrote the manuscript and revised it. CB contributed to data acquisition and writing. MAT performed statistical analysis and participated in revising the paper. All authors approved the submitted version. BE and LG contributed equally.

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**Patient consent for publication** Parents consented for Figure 2.

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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) (See Appendix table 1). Filled symbols indicate affected individuals. Small round filled symbols indicate abortions. Squares indicate males; circles indicate females. A diagonal line across a symbol indicates a deceased individual. Please note that in Family 7 both marriages are consanguineous, among first cousins.

FIGURE 2: External eye photographs of patient CIPA 5 showing permanent

lateral tarsorrhaphy and central corneal opacity in the left eye, while the right

eye is with clear cornea and appears normal.