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Review

Congenital insensitivity to pain with anhidrosis: a literature review and the advocacy for stem cell therapeutic interventions

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***Abstract*:** Congenital Insensitivity to Pain with Anhidrosis (CIPA) is a rare genetic disorder affecting the autonomic nervous system, leading to an inability to feel pain, temperature, or sweat1. This condition is caused by mutations in the NTRK1 gene, which encodes a receptor for nerve growth factor (NGF). The lack of NGF signaling results in the improper development and function of sensory and sympathetic neurons. Patients with CIPA often suffer from repeated injuries, infections, and hyperthermia due to their inability to sense pain and regulate body temperature. Management focuses on preventing injuries, controlling infections, and providing supportive care, as there is no definitive cure for CIPA. We present several hypotheses for treating CIPA using stem cells and modern genetic techniques. One approach involves using induced pluripotent stem cells (iPSCs) to replace defective neurons. Another hypothesis suggests in vivo gene editing of neural progenitors to restore TrkA function. Additionally, mesenchymal stem cells (MSCs) genetically modified to overexpress NGF could provide trophic support. Other strategies include epigenetic modulation of NTRK1 expression and exosome-mediated gene therapy. These innovative approaches aim to address the underlying genetic defects and restore normal cellular functions in CIPA patients.

Plain language summary

Living without pain: a superpower or a disease?

Congenital Insensitivity to Pain with Anhidrosis (CIPA) is a rare genetic disorder where people can't feel pain or temperature and don't sweat. This can lead to serious health issues like infections and overheating. The condition is caused by mutations in the NTRK1 gene, which affects nerve growth.

Symptoms include frequent injuries, inability to regulate body temperature, and intellectual disabilities. There is no cure, but management focuses on preventing injuries, controlling fever, and providing supportive care.

Stem cell therapy and gene editing are being explored as potential treatments to restore normal nerve function. These advanced techniques aim to correct the genetic mutations and improve the quality of life for those affected by CIPA.

Keywords: CIPA, congenital insensitivity to pain with anhidrosis, congenital sensory neuropathies, HSAN type IV, stem cells

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Introduction

Congenital Insensitivity to Pain with Anhidrosis (CIPA) is an extremely uncommon disorder that affects the nervous system, particularly the autonomic nervous system.[1] People with CIPA are unable to feel pain, temperature, or sweat. This condition can lead to serious health problems and complications, such as infections, injuries, and hyperthermia.[2] It is also called Hereditary Sensory and Autonomic Neuropathy IV (HSAN IV).[3]

A mutation in the NTRK1 (neurotrophic tyrosine kinase receptor I) gene, which encodes a receptor for nerve growth factor (NGF), causes CIPA.[4,5] NGF plays an essential role in the growth and survival of sympathetic and sensory neurons, which are responsible for transmitting pain, heat, and cold signals to the brain.[6,7] The mutation in NTRK1 prevents NGF from binding properly, resulting in defects in the formation and function of these neurons.[4]

Due to the autosomal recessive pattern of inheritance, each cell must have two copies of the mutations to cause the disease.[8] Each parent of the affected patient carries one copy of the mutated gene, but they are typically asymptomatic.[9]

Symptoms usually appear quite early in life, often during infancy.[10] The primary symptoms of anhidrosis (loss of sweating) and insensitivity to pain are the central features of CIPA. Other clinical manifestations observed in affected individuals are either direct consequences or indirect outcomes stemming from these primary hallmarks. CIPA has no definitive cure; however, the management focuses on preventing injuries and infections, controlling fever and seizures, and providing supportive care.[11,12] People with CIPA need to be monitored closely by a team of medical professionals, including neurologists, dermatologists, orthopedists, ophthalmologists, dentists, and psychologists. Moreover, certain precautions need to be taken to avoid exposure to extreme temperatures or potential sources of injury.

CIPA is a very rare disorder that affects only a few hundred people worldwide.[13] The exact prevalence of this disease is unknown, but it is more common among certain populations, such as Negev Arabs in Israel and Japanese people.[14,15] Approximately one in five patients with CIPA die of hyperthermia by the third year of life.[1,16] However, with proper medical attention and education, patients with CIPA can live longer and have a better quality of life.

Reviewing CIPA is crucial for uncovering precise genetic variations, exploring neuro-immunological connections, and evaluating advanced imaging techniques, as well as for offering insights into personalized medicine, disease modifiers, and innovative therapeutic interventions. We provide insights into the multidisciplinary management of CIPA and offer a current review of the literature while advocating for utilizing stem cells as a potential treatment option for this condition.

Genetics and pathophysiology

A mutation in the NTRK1/TrkA gene, which codes for an NGF receptor, results in CIPA. With 17 exons, the NTRK1 gene is found on chromosome 1q23.1.[17] In CIPA patients, the NTRK1 gene has been found to have more than 100 distinct mutations, the majority of which are missense or nonsense mutations affecting the NTRK1 protein's intracellular tyrosine kinase domain.[18–20] This domain is essential for signal transduction; mutations in this region result in the production of abnormal proteins that do not function properly and thus do not transmit signals that are necessary for the growth and survival of neurons. Some of the common mutations in the NTRK1 gene are as follows:

c.1860-1861insT: This is a founder mutation that is prevalent among Negev Arabs in Israel and Palestinian Bedouins. This mutation inserts a T nucleotide in exon 15, causing a frameshift and a premature stop codon. This mutation leads to a truncated NTRK1 protein that lacks the intracellular tyrosine kinase domain, which is important for signal transduction.[21]

c.2170G>A: This is a missense mutation that changes a glycine to a serine at position 724 in exon 16. This mutation affects the ATP-binding site of the tyrosine kinase domain, impairing its catalytic activity and reducing its affinity for NGF.[22]

Other genes that have been associated with CIPA are NGF, which encodes the ligand for NTRK1, and SCN9A, which encodes a sodium channel subunit that is involved in pain perception.[23]

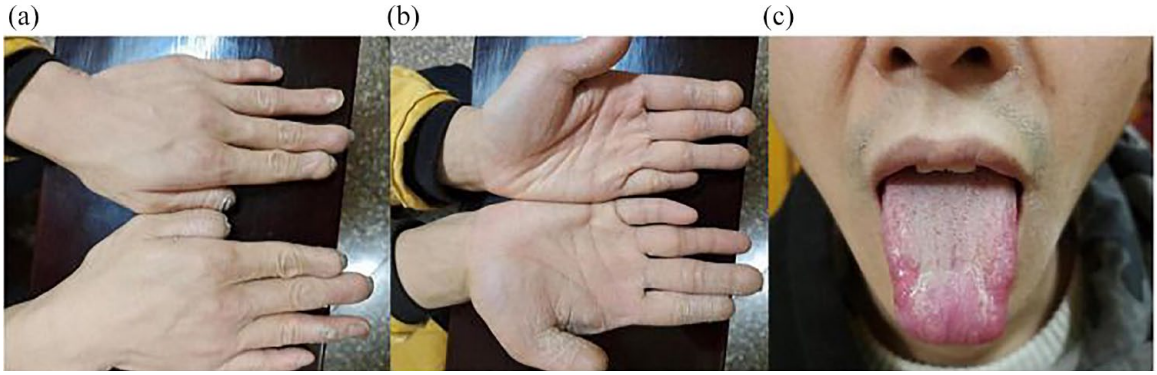

Figure 1. Adapted from Rong Zhu et al.[33] Systemic manifestations. Clinical symptoms of the patient: Spontaneous amputation of fingertips (a), dry and hyperkeratotic skin of the palm (b), and damaged tongue (c).

Mutations in these genes are less common and have variable effects on the phenotype of CIPA patients.

The loss of pain and temperature sensation in these patients is due to the absence or dysfunction of small-diameter sensory neurons that express the NTRK1 protein.[3] These neurons normally convey nociceptive (painful) and thermosensitive stimuli from the skin and other tissues to the central nervous system. Without NGF signaling, these neurons undergo apoptosis (programmed cell death) during embryonic development or early childhood, leaving CIPA patients with a decreased number of sensory nerve fibers and a lack of pain perception.[24]

Anhidrosis in CIPA patients is due to the impairment of sympathetic neurons that also express the NTRK1 protein. These neurons normally innervate sweat glands and regulate sweating in response to changes in body temperature or emotional stress. Without NGF signaling, these neurons also undergo apoptosis or fail to develop properly, leaving CIPA patients with a reduced number of sweat glands and a lack of thermoregulation.[24,25]

NGF is known to be elevated in systemic lupus erythematosus, which is characterized by abnormal B cell and immunoglobulin production1. Similarly, multiple sclerosis, which involves abnormal T cell and B cell activity, has been associated with NGF activity. CIPA has shown aberrant humoral and cell-mediated immune functions, suggesting a potential overlap in immune symptomology with autoimmune diseases. Given the NGF defects in CIPA and the shared immune characteristics with autoimmune conditions, it's plausible to consider autoimmune phenomena within the spectrum of CIPA-related issues.[26,27]

Clinical features

Symptoms usually appear quite early in life, often during infancy.[10] The inability to feel temperature and pain, along with diminished or even non-existent sweating (anhidrosis), are the most distinctive characteristics of CIPA.[4] People with CIPA often suffer from repeated injuries, such as burns, cuts, fractures, and infections, without even noticing them.[22,28,29] They may also bite their tongue, lips, or fingers, causing ulcers or amputations (See Figure 1).[30] These patients heal slowly from skin and bone wounds, and may develop chronic bone infections (osteomyelitis) or joint damage (Charcot joints).[31,32]

Another major problem for people with CIPA is the inability to regulate their body temperature. Since they do not sweat, they cannot cool when they are hot. This can cause recurrent episodes of very high fever (hyperpyrexia) and seizures triggered by high temperature.[34,35] These episodes can be life-threatening if not treated promptly.

Many patients with CIPA have generalized xerosis, malformed fingernails or toenails, and thickened skin (lichenification) on the palms of their hands.[36] Additionally, they may have hypotrichosis, or areas of hair loss, on their scalps.[30] Many

CIPA patients have intellectual disabilities, and around half of them exhibit hyperactivity or emotional instability. When they are younger, some individuals with CIPA have hypotonia or weak muscular tone; however, as they age, their muscle strength and tone return to normal.[10,29] Corneal ulcers can occur in some CIPA patients as a result of a lack of protective impulse.[25,36–39]

Cases

A few diverse cases of CIPA are discussed here, this is not at all an exhaustive list of cases, we have selected those cases that represent the different manifestations of the disease:

1. *10-Year-old with CIPA*: 10-year-old Iranian girl diagnosed with CIPA exhibited self-mutilation, and mental retardation, and had injuries from biting, leading to tooth loss and oral ulcers. The patient received a prosthetic treatment to prevent further oral injuries and improve function and aesthetics, which showed improvement after a 6-month follow-up. The case emphasizes the need for specialized dental management for CIPA patients based on individual conditions and advocates for conservative treatments over radical ones like full mouth teeth extraction.[40]
2. *Family case study*: A family case study details the cases of two sisters with CIPA, born to consanguineous parents, and mentions a brother with ataxia telangiectasia and IgA deficiency. The patients exhibited symptoms like hyperpyrexia without sweating, self-mutilation, and orthopedic complications due to repeated trauma. While immunoglobulin deficiency has been reported in CIPA, the article notes only a transient IgA deficiency in one case, suggesting that immune deficiency may not be central to the syndrome[41]
3. *Anesthesia in CIPA*: A 6-year-old boy with CIPA presented unique challenges for anesthesia during a surgical procedure, due to his inability to feel pain, lack of sweat production, and potential for autonomic dysfunction. Bispectral index monitoring was utilized to maintain an appropriate anesthesia depth, with lower sevoflurane concentrations required for the patient. The case emphasized the importance of controlling body temperature, managing psychological stress, and avoiding deep anesthesia to prevent complications.[42]
4. Autoimmune considerations: A case reports the development of a cervical mass following a viral illness, in a CIPA patient, who responded to steroid therapy, this suggests an autoimmune link. In CIPA patients, abnormalities in the neural and immune systems, along with endocrine dysfunction, indicate the involvement of these three systems, which are critical for autoimmune phenomena. The defect in NGF in CIPA and its regulatory role over the neural, immune, and endocrine systems further link it to autoimmunity. Additionally, reports of lupus anticoagulant and ischemic stroke in CIPA patients, along with rare instances of immune-mediated vasculitis and immunoglobulin deposition, support an immune connection.[26]
5. *Radiological observations*: In a radiological case study of 20 individuals with CIPA, it was observed that fractures in the extremities were present in all patients. Close to 50% of these patients also exhibited osteomyelitis and Charcot joints, particularly in older children. Dislocations were less common, occurring in fewer than 15% of the cases.[29]
6. *CIPA and ASD*: A case report discusses a boy with CIPA who developed autism spectrum disorder (ASD). Diagnosed with CIPA at 48 months, the boy later showed developmental delays and was diagnosed with ASD at 5 years old. After the ASD diagnosis, interventions improved his communication, social skills, and reduced maladaptive behaviors. This case suggests that children with CIPA should be screened for ASD to ensure timely diagnosis and treatment.[13]
7. *33-Year-Old CIPA patient*: The longevity of a 33-year-old woman with CIPA is indeed remarkable, given the typically early mortality associated with the condition. This case report chronicles the patient's journey, marked by a lifetime of recurrent infections, fractures in various body parts, growth disturbances, and avascular necrosis. The elbow and hip joints were particularly affected, resulting in Charcot arthropathies and repeated dislocations. At 33, she faced

Table 1. Major clinical manifestations of CIPA.

System	Features
Sensory System	- Unable to feel pain and temperature – Self-mutilation
Integumentary System (Skin)	- Decreased or absent sweating – Repeated injuries and infections – Slow wound healing – Thickened skin – Abnormal nails – Hair loss
Musculoskeletal System	- Acro-osteolysis – Chronic bone infections (osteomyelitis) – Joint damage (Charcot joints)
Neurological System	- Seizures – Hyperactivity – Emotional instability – Intellectual disability – Hypotonia
miscellaneous	ASD – Corneal ulceration – Hyperthermia – Recurrent fever – Tooth loss – Oral Ulcers

obesity and a constrained social life. Her left arm's functionality was severely limited due to a Charcot elbow, and her walking distance was curtailed by dislocated hips and unstable ankles.[43]

Major clinical manifestations of CIPA are listed in Table 1.

Diagnosis

CIPA is diagnosed based on a combination of genetic testing, clinical evaluations, and specialized assessments. The diagnosis process is as follows:

Genetic testing: Genetic testing can confirm the presence of mutations in the NTRK1 gene in people with suspected CIPA.[44]
Clinical evaluations: Clinical evaluations can identify the signs and symptoms of CIPA in people with suspected CIPA.
Radiology: Radiology as discussed earlier is an important tool in establishing the diagnosis of CIPA.[29]
Specialized assessments: CIPA also affects other aspects of the nervous system, such as the skin, the eyes, the muscles, and the brain. Specialized assessments can detect these additional features of CIPA in people with suspected CIPA. These assessments may include skin biopsies, eye examinations, axonal flare testing (failure to cause normal flare around the site of histamine injection), biopsy of nerve, and muscle tests (e.g., electromyography (EMG)).[44–47]

By using these methods, CIPA can be diagnosed early in life. This can help prevent further complications and provide appropriate treatment and care for people with CIPA.

Associated conditions

There are some conditions or symptoms that may mimic or overlap with CIPA. These include:

Other types of HSANs, which are a group of disorders that affect the sensory and autonomic nervous systems are summarized in Table 2. There are eight types of HSANs (I-VIII), each with different genetic causes and clinical features.[48] Some of the features that may overlap with CIPA are insensitivity to pain, anhidrosis, self-mutilation, slow wound healing, osteomyelitis, Charcot joints, hypotonia, intellectual disability, and corneal ulceration.

Congenital indifference to pain (CIP) is a condition that causes a person to not react emotionally or behaviorally to pain stimuli. Unlike CIPA, people with CIP can feel pain and temperature sensations but do not perceive them as unpleasant or distressing. They also do not have anhidrosis or other autonomic problems. CIP is not caused by a mutation in the NTRK1 gene but by other genetic or environmental factors that affect the brain's processing of pain signals.[49]

Familial dysautonomia (FD) is a genetic disorder that affects the development and function of the autonomic nervous system. People with FD have reduced sensitivity to pain and temperature stimuli but not complete insensitivity. They also have

Table 2. HSAN classification.

Type	Name	Features
HSAN I	Hereditary Sensory and Autonomic Neuropathy I	Progressive degeneration of motor neurons and dorsal root ganglia, loss of distal sensory perception, weakening and wasting of muscles, and variable neural deafness.
HSAN II	Hereditary Sensory and Autonomic Neuropathy II	Characterized by onset at birth, marked sensory loss, self-mutilating behavior, and variable autonomic dysfunction.
HSAN III	Riley-Day syndrome or Familial Dysautonomia	Autonomic dysfunction, including reflux esophagitis, postural hypotension, excessive perspiration, and sensory dysfunction are nearly exclusively observed in individuals of Eastern European Jewish descent.
HSAN IV	Congenital Insensitivity to Pain with Anhidrosis	Autosomal recessive inheritance, insensitivity to pain, anhidrosis, and intellectual disability.
HSAN V	—	Less is known, similar to HSAN IV but with normal sweating.
HSAN VI	—	Neonatal hypotonia, breathing and eating issues, impaired psychomotor development, and anomalies related to the autonomic nervous system.

abnormal sweating patterns but not complete anhidrosis. They may have other features that are similar to CIPA, such as recurrent fever, infections, hypotonia, intellectual disability, corneal ulceration, optic atrophy, and hearing loss. FD is caused by a mutation in the IKBKAP gene.[50–53]

Management

There is no cure for CIPA, so the management of this condition focuses on preventing injuries and infections, controlling fever and seizures, and providing supportive care. Some of the current approaches to managing CIPA are:

Pain management: People with CIPA do not feel pain, but they still need to be protected from potential sources of injury, such as hot or cold objects, sharp or pointed items, or electrical appliances. They also need to be educated about the importance of avoiding self-mutilation, such as biting or scratching themselves. They may need to wear protective clothing, gloves, shoes, or eyewear to prevent skin or eye damage.

Corneal ulcer treatment: The management of corneal conditions may involve the use of regular eye moisturizers, performing a lateral tarsorrhaphy, applying a corneal patch graft, or conducting a penetrating keratoplasty. Additionally, specialized topical treatments with nerve growth factors can be taken into account.[39]

Orthopedic interventions: People with CIPA may develop orthopedic problems due to their repeated trauma or delayed healing of injuries. They may have deformities or fractures of the bones, especially in the lower limbs. They may also have destruction of the bones and tissues surrounding joints, which can cause painless swelling, instability, and loss of function. They may need to undergo surgery to correct these problems or to prevent further complications. They may also need to use braces, splints, casts, or crutches to support their limbs or joints.[54]

Infection prevention: People with CIPA are prone to infections due to their lack of pain sensation, which prevents them from seeking medical attention or taking preventive measures. They may also have impaired immune responses due to their defective NGF signaling.[24] They need to be monitored closely for signs of infection, such as fever, redness, swelling, pus, or foul odor. They need to receive prompt and appropriate antibiotic treatment for any suspected infection. They may also need to receive prophylactic antibiotics before any surgical procedure or dental work.

Wound care: People with CIPA heal slowly from skin and bone wounds. They need to have regular wound care to prevent infection and promote healing. They need to keep their wounds clean and dry and apply antiseptic creams or dressings as prescribed. They may also need to have debridement or irrigation of their wounds to remove dead tissue or foreign material. They may also need to have skin grafts or flaps to cover large or deep wounds.[55,56]

Hyperthermia management: People with CIPA need to avoid exposure to extreme temperatures and stay hydrated. They need to seek medical attention if they develop symptoms of hyperthermia, such as high fever, confusion, seizures, or coma. They may need to receive cooling measures, such as ice packs, fans, or intravenous fluids.[31,57]

Neurological interventions: People with CIPA may need to receive treatments for their neurological problems, such as medications, surgery, hearing aids, glasses, eye drops, or cognitive rehabilitation. They may also need to undergo regular assessments of their cognitive, sensory, motor, and functional abilities.

Psychological support: People with CIPA and their families may benefit from psychological support to cope with the emotional and social challenges of living with the condition. They may need counseling and psychotherapy.

A *multidisciplinary approach* to treating such rare disorders is not only advantageous for the patients but also for the healthcare community as a whole. The involvement of more professionals from various fields in the management process can lead to the discovery of new and innovative treatment methods.[47]

Theoretical approaches to CIPA treatment using stem cells and modern genetic techniques

Recent advancements in stem cell technology and gene editing techniques offer promising avenues for developing novel therapies for CIPA. While these approaches remain theoretical, they are grounded in current scientific understanding and ongoing research in related fields. Stem cell therapy aims to replace or repair defective cells, potentially restoring normal function. Induced pluripotent stem cells (iPSCs), neural stem cells (NSCs), and embryonic stem cells are considered viable options, with iPSCs being particularly promising due to reduced immune rejection risks.[58,59] Genetic modification techniques, such as CRISPR-Cas9, can correct NTRK1 mutations in iPSCs, while engineered stem cells can overexpress functional TrkA receptors.[60] Stem cells can be directed to differentiate into nociceptive neurons, autonomic neurons, and Schwann cells, addressing CIPA's primary symptoms. Delivery methods include direct injection, systemic administration, and biomaterial scaffolds, enhancing cell survival and integration.[58] Potential mechanisms of action include direct cell replacement, trophic support, and immunomodulation, offering a multifaceted approach to CIPA treatment.

Here, we present several hypothetical treatment strategies, discussing their potential mechanisms, challenges, and future research directions.

iPSC-derived nociceptor replacement therapy

The hypothesis here is that patient-specific iPSCs can be gene-edited to correct NTRK1 mutations and differentiated into functional nociceptors for autologous transplantation. The methodology involves generating iPSCs from patient fibroblasts using non-integrating reprogramming methods like Sendai virus or episomal vectors.[61,62] Then, CRISPR-Cas9 may be employed to correct the NTRK1 mutation in the iPSCs. These corrected iPSCs can be differentiated into nociceptor progenitors using a defined protocol that mimics neural crest development, and these progenitors may be then transplanted into the dorsal root ganglia of CIPA patients.[63] Potential challenges include ensuring proper integration and synapse formation of transplanted neurons, achieving sufficient engraftment rates for clinical efficacy, and ensuring the long-term survival of transplanted cells in the host environment.

CRISPR-Cas9. The application of gene editing technologies, such as CRISPR-Cas9, holds significant promise in the treatment of CIPA. CRISPR-Cas9 can be utilized to correct the specific genetic mutations responsible for CIPA in patient-derived iPSCs. These corrected iPSCs can then be differentiated into neural cells, potentially restoring normal pain sensation and sweat gland function. CRISPR-Cas9 works by using a guide RNA to target specific DNA sequences in the genome. Once the target site is located, the

Cas9 enzyme creates a double-strand break in the DNA. This break can then be repaired by the cell's natural repair mechanisms, either by non-homologous end joining (NHEJ) or homology-directed repair (HDR).[64] For therapeutic purposes, HDR is particularly useful as it allows for the precise correction of genetic mutations when a template DNA is provided. This means that the mutations causing CIPA can be specifically corrected in the iPSCs derived from the patient, thus creating genetically corrected cells that can then be used for therapy. Once the iPSCs are genetically corrected, they can be differentiated into neural cells, which are the primary cells affected by CIPA. These neural cells can potentially restore normal pain sensation and sweat gland function when transplanted into the patient. Ex vivo transduction involves culturing and editing stem cells, such as iPSCs or NSCs, which can be cultured from the patient's own cells (autologous) or from a donor (allogenic). Using CRISPR-Cas9, these cells can be genetically modified ex vivo to correct the CIPA mutations. Once corrected, these stem cells can be differentiated into the required neural cell types and expanded in culture, ensuring a sufficient number of cells for transplantation. The genetically corrected and differentiated cells can then be implanted into the affected areas of the patient's nervous system. For CIPA, this may involve direct implantation into regions of the peripheral nervous system or central nervous system where neural function needs restoration. In vivo, transduction involves the direct delivery of CRISPR-Cas9 components into the patient's body to target and correct the genetic mutations in situ. This method requires a delivery system capable of targeting the specific neural cells affected by CIPA. Viral vectors, such as adeno-associated virus (AAV) or lentiviruses, can be engineered to deliver CRISPR-Cas9 components specifically to the neural cells.[65] This targeting can be achieved through the use of cell-specific promoters and surface markers. Depending on the approach, the delivery system can be administered systemically (e.g., through intravenous injection) or locally (e.g., direct injection into the nervous system). The choice of administration route depends on the efficiency and safety profile of the delivery system. Using the patient's own cells (autologous) minimizes the risk of immune rejection and ethical concerns. The patient's cells are reprogrammed to iPSCs, genetically corrected, and then differentiated into the required cell types for transplantation. Donor-derived cells (allogenic) offer the advantage of readily available stem cells, potentially accelerating the treatment process. However, there is a risk of immune rejection, and patients may require immunosuppressive therapy to prevent rejection.

In Vivo gene editing of endogenous neural progenitors

This theory posits that direct in vivo gene editing of endogenous neural progenitor cells in the dorsal root ganglia could restore TrkA function without the need for cell transplantation.[62] The proposed approach involves developing a highly specific AAV vector targeting neural progenitor cells in the dorsal root ganglia. This vector is engineered to carry CRISPR-Cas9 components for NTRK1 correction and is administered via intrathecal injection to reach the dorsal root ganglia, where the corrected progenitors are allowed to differentiate naturally into functional nociceptors. Advantages of this method include avoiding the challenges associated with cell transplantation and utilizing the patient's own cells in their native environment. However, limitations include lower editing efficiency compared to ex vivo approaches and potential off-target effects in non-target cells.

Combinatorial approach: gene-modified MSCs and neurotrophic factors

The hypothesis here is that mesenchymal stem cells (MSCs) genetically modified to overexpress NGF could provide trophic support and stimulate the growth of residual TrkA-positive neurons in CIPA patients. The experimental design involves isolating autologous MSCs from CIPA patients, transducing MSCs with a lentiviral vector encoding NGF and a constitutively active TrkA receptor, encapsulating modified MSCs in a biocompatible hydrogel, and implanting the hydrogel construct in proximity to the dorsal root ganglia.[66] Expected outcomes include enhanced survival and potential sprouting of any residual TrkA-positive neurons, paracrine effects promoting a regenerative microenvironment, and potential partial restoration of nociceptive function.

Epigenetic modulation of NTRK1 expression

Epigenetic regulation of NTRK1 gene expression could compensate for loss-of-function mutations by enhancing transcription of the wild-type allele or activating compensatory pathways. The

proposed methodology uses the CRISPR-dCas9 system fused with epigenetic modifiers such as histone acetyltransferases to target the NTRK1 promoter region.[67] The construct could be delivered via viral vectors such as AAV or lentiviruses, to dorsal root ganglia neurons to induce local chromatin remodeling and enhance NTRK1 transcription. The potential impact includes increased expression of functional TrkA receptors from the wild-type allele and activation of compensatory neurotrophic signaling pathways.

Synthetic biology approach: engineered pain-sensing circuits

The hypothesis here is that synthetic biological circuits can be designed to mimic pain-sensing pathways, bypassing the need for TrkA-mediated signaling. The conceptual framework involves engineering iPSC-derived neurons with synthetic gene circuits responsive to noxious stimuli such as heat and mechanical stress, incorporating optogenetic or chemogenetic actuators for controlled activation, and integrating these engineered neurons into existing sensory circuits. Advantages include the potential to create tunable pain responses and bypass the need for correcting endogenous TrkA signaling. Challenges include the complexity of mimicking natural pain-sensing mechanisms and ensuring appropriate integration with central pain-processing pathways.

Exosome-mediated gene therapy

The theory here is that exosomes derived from gene-corrected iPSCs could deliver functional mRNA and proteins to endogenous neurons, temporarily restoring TrkA function.[68] The proposed method involves generating iPSCs from CIPA patients, correcting the NTRK1 mutation, differentiating these corrected iPSCs into sensory neurons, harvesting exosomes from these neurons enriched with TrkA mRNA and protein, and administering the exosomes intrathecally or via direct injection into the dorsal root ganglia. While direct evidence of NTRK1-containing exosomes from healthy cells is currently lacking, this approach is based on the principle of exosome-mediated protein transfer observed with other proteins. Further research would be needed to confirm the feasibility of this method for NTRK1 delivery. Potential benefits include a non-cell-based approach that reduces risks associated with cell transplantation and the potential for repeated administrations to maintain therapeutic effects.

These theoretical approaches leverage cutting-edge stem cell technologies and genetic engineering techniques to address the underlying pathophysiology of CIPA. Each strategy presents unique advantages and challenges, and a combination of these approaches may ultimately yield the most effective treatment. Rigorous preclinical studies in appropriate animal models would be essential to evaluate the safety and efficacy of these proposed therapies before considering human clinical trials.

Limitations

While the section on stem cell therapies and genetic techniques is innovative, it remains largely theoretical at this stage. The absence of experimental data to support these approaches significantly limits the practical applicability and validation of the proposed therapies. This lack of empirical evidence underscores the need for rigorous preclinical and clinical studies to evaluate the efficacy and safety of these potential treatments for CIPA.

Conclusion

CIPA is a rare and complex disorder with significant clinical challenges due to its genetic and pathophysiological underpinnings. Despite the absence of a definitive cure, multidisciplinary management strategies focusing on injury prevention, infection control, and supportive care can significantly improve the quality of life for affected individuals. The exploration of stem cell therapies and advanced genetic techniques offers promising avenues for future research and potential therapeutic interventions. Continued efforts in understanding the genetic variations, neuro-immunological connections, and innovative treatment approaches are essential for advancing the care and outcomes of patients with CIPA.

Declarations

Ethics approval and consent to participate

Not applicable as the study is based exclusively on published literature/medical records, etc.

Consent for publication
Not applicable

Author contributions
Muhammad Ikrama: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Muhammad Usama: Data curation; Formal analysis; Investigation; Methodology; Validation; Writing – original draft; Writing – review & editing.

Muhammad Hassan Haider: Data curation; Investigation; Validation; Writing – original draft; Writing – review & editing.

Shifa Israr: Data curation; Investigation; Supervision; Validation; Writing – original draft; Writing – review & editing.

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During the preparation of this work the authors used GPT 4.0 in order to improve the overall language and check grammatical errors after writing the manuscript. After using this, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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