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Review Article

Roots and fates of congenital insensitivity to pain and anhidrosis: a human phenotype

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ABSTRACT

Congenital insensitivity to pain is a rare neurological disorder characterized by the inability to perceive physical pain. Individuals with CIP lack the typical nociceptive responses to harmful stimuli, which poses significant challenges to their safety and well-being. This condition is often caused by genetic mutations affecting the nervous system's ability to transmit pain signals. Despite the apparent advantage of not experiencing pain, CIP presents severe risks as affected individuals may unknowingly sustain injuries or develop medical complications without timely intervention. The absence of pain perception hinders the learning of protective behaviour and responses to potentially harmful situations, making daily activities fraught with danger. Understanding the genetic basis of CIP has provided valuable insights into pain perception and the functioning of nociceptive pathways. While this knowledge may pave the way for potential therapeutic interventions, managing CIP remains a complex task. This article provides an overview of CIPA, its genetic basis, clinical manifestations, complications, treatment and the challenges associated with managing this complex condition. A multidisciplinary approach involving genetic counselling, pain management, and specialized care is crucial to support individuals with CIPA and improve their overall well-being.

Keywords: CIPA, Hereditary sensory and autonomic neuropathy, Genetics of pain, Paediatric pain, Pain perception

INTRODUCTION

Pain is a sensory modality present in all complex creatures that is used to identify both potential and real tissue damage.[1] An emotional experience, pain triggers the sympathetic nervous system in the body. The "fight-or-flight response" depicts a powerful emotional state linked to high sympathetic nervous system excitement and aids in protecting our physical bodies, frequently leading to a conflict or leading away from a conflict.[2] Despite being an unpleasant sensory and emotional experience, it has a significant impact on our actions and helps us survive.[3] Pain, along with touch, pressure, and position perception, was originally thought of as a sub modality of somatic sensation. However, pain is a complex sensation that the brain must process both cognitively and emotionally. "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damages," said the international association for the study of pain (IASP) (IASP Taxonomy). Because of its fundamental connection to emotion, pain is thereby distinguished from other physical experiences.[4] Normally, a complex network of mechanical and chemical sensors called nociceptors detects pain and transmits information to the brain via spinal inter neuronal pathways.[5] Except for ionising radiation, nociceptors can identify both actual and potential tissue damage.[6] However, parts of the pain-signalling pathway may be damaged or fail to develop in a number of uncommon conditions.[7] Congenital insensitivity to pain (CIP), when people are unable to feel pain from birth, is

one such ailment.[8] The two kinds of CIP are those with and without anhidrosis (the inability to sweat).[9]

Hereditary sensory and autonomic neuropathy type IV (HSAN-IV), also known as congenital insensitivity to pain with anhidrosis (CIPA:MIM 256800), is an autosomal recessive disorder characterised by recurrent episodic fever, anhidrosis (inability to sweat), absence of reaction to noxious (or painful) stimuli, self-mutilating behaviour, and mental retardation.[10] Congenital insensitivity to pain (CIP) is a very uncommon human trait in which no pain of any kind is ever felt by the affected person throughout their lifetime.[6] Due to a lack of afferent neurons stimulated by tissue-damaging stimuli and a reduction in sympathetic innervation of the eccrine sweat glands, respectively, CIPA suffers from abnormal pain, temperature, and anhidrosis.[11] Reduced pain perception affects one's capacity to defend oneself from external or self-inflicted harm. Therefore, injuries to children with CIPA might be severe and go unnoticed. The cause of anhidrosis is loss of sympathetic innervation of the eccrine sweat gland. Anhidrosis impairs homeostasis and increases vulnerability to repeated febrile episodes since sweating is crucial for maintaining normothermia in hot environmental settings. A greater knowledge of nociceptors and their function in the pain perception may result from research on CIP and its various genetic variants.[12] The clinical and genetic diversity of the hereditary sensory and autonomic neuropathies (HSAN) category of illnesses, which affects both sexes, has led Dyck and Ohta to suggest five different types.[13,14] These include familial dysautonomia (FD III), congenital insensitivity to pain with anhidrosis type IV (HSAN IV), congenital indifference to pain associated with intellectual disability type V (HSAN V), and hereditary sensory radicular neuropathy type I (HSAN I).[15]

In the second to fourth decades of life, hereditary sensory radicular neuropathy (HSAN 1) typically manifests. Any type of nerve fibre is impacted by HSAN 1. Reduced or absent reflexes, distal loss of proprioception, light touch, and susceptibility to unpleasant heat stimuli are the clinical and sensory impairments that define this syndrome. The onset of HSAN 2 is in infancy. All myelinated fibres are impacted by HSAN 2. Reduced or absent reflexes, distal loss of proprioception, light touch, and susceptibility to unpleasant heat stimuli are the clinical and sensory impairments that define this syndrome. Due to a variety of deficits, HSAN 3 (Riley-Day syndrome, familial dysautonomia) is often discovered in infancy. Both large myelinated fibres and unmyelinated fibres are impacted by HSAN 3. The sensory deficiencies include a distributed failure to detect noxious stimuli and a diffused thermal insensitivity, and the reflexes may be decreased or nonexistent. A unique presentation of CIP is HSAN 4. Due to autonomic dysfunctions of anhidrosis that cause recurrent pyrexia episodes, HSAN 4 is often diagnosed in infancy. There may occasionally be intellectual disability.[12] HSAN4 is the most frequent cause of developmental CIP. Both tiny myelinated fibres and unmyelinated fibres are impacted by HSAN 4. The sensory deficiencies include a distributed failure to detect noxious stimuli and a diffused thermal insensitivity, and the reflexes may be decreased or nonexistent. Autosomal recessive HSAN 5 is frequently discovered in children who have experienced trauma. HSAN 5 is characterised by distal insensitivities to noxious and heat stimuli and exclusively affects tiny myelinated fibers.[12] Due to the absence of the anticipated emotional reactions connected with actual tissue injury, CIP are frequently diagnosed in infancy or early childhood[16]. One in 125 million infants are born with this condition[17]. Early infancy aberrant abnormalities of the autonomic nerve function, such as anhidrosis, recurrent pyrexia, defective lacrimation, and feeding issues, are used to diagnosis some phenotypes of CIP.[12]

Swanson originally provided a description of CIPA in 1963. The molecular cause of CIP has been discovered for the first time in a human genetic disorder.[9,10] The NTKR1 gene has a genetic loss-of-function mutation that is indicative of the pathophysiology of CIPA[18]. Progressive descriptions of numerous novel mutations have been made.[19] There are two typical variations of CIP. First off, nociceptors are rendered incapable of responding to any unpleasant stimulation by a loss-of-function mutation in the SCN9A. Second, nociceptors are unable to form as a result of a loss-of-function mutation in the NTRK1.[11] Other types of CIP, including CIP caused by abnormalities in NGF itself, have genetic causes that have recently been found by studies.[20] A new kind of CIP that results from mutations in the epigenetic regulator PRDM12 has recently been identified.[21] Rare human genetic abnormalities can provide chances to investigate underlying normal biological processes as well as diseased circumstances in humans.[4]

THE GENES WHICH CAUSE CIP

Sodium voltage-gated channel alpha subunit 9

The protein voltage-gated sodium channel Nav1.7 is encoded by the sodium voltage-gated channel alpha subunit 9 (SCN9A) gene, which is highly expressed in all classes of nociceptor. Both autosomal dominant excessive pain and autosomal recessive painlessness are disorders brought on by mutations in SCN9A.[6] It is thought that the Nav1.7 protein has non-functional alterations as a result of the recessive mutations in CIP people. Even if it was demonstrated to be true in the initial reports, it hasn't always been since. The functional effects of mis-sense mutations, however, cannot be confidently anticipated to be inert, activating, or benign.[6] Additionally, SCN9A has an unusual U12 intron that differs from the standard U2 splicing in terms of the splice acceptor and donor sites.[22] So, without any other clear clinical symptoms, activating mutations in SCN9A only result in paroxysmal neuropathic pain. Congenital painlessness is also a result of bi-allelic non-functional

mutations, with anosmia being the sole other side effect. SCN9A is now a crucial and non-redundant component of pain perception, albeit it is yet unknown how this is accomplished.

NTRK1

NTRK1 was the first gene to be found to induce a CIP in 1996[6]. NTRK1 stands for neurotrophic tyrosine kinase gene 1, which codes for the protein tropomyosin receptor kinase, also known as high affinity nerve growth factor receptor, which was formerly known as TRKA. Mutations in NTRK1 suggest that TrkA, an NGF receptor, has changed. NGF is involved in surveillance of nociceptive sensory neurons and sympathetic autonomic neurons and collaborates in the activation and homeostasis of other cellular types so that a NTRK1 mutation will cause deficient development of: the dorsal root ganglion sensory neurons that make up the afferent somatic sensory system for pain and warmth, the autonomic sympathetic neuronal system, which denotes the lack of sympathetic neurons' innervation of the eccrine sweat glands, the neurological system, the two-way exchange of information between the immune system and the nervous system (Through the processes of Trk A phosphorylation, cytoskeleton assembly, and MAP kinase activation, NGF is relevant in the signal pathway of a B lymphocyte).[9,17]

Nerve growth factor

Nerve growth factor (NGF), which Rita Levi-Montalcini and Stanley Cohen first identified and characterised and for which they were given the 1986 Nobel Prize, is a key ligand for the tyrosine kinase receptor TRKA. A large Swedish family's CIP was found to be caused by a homozygous NGF mutation in 2004.[23] Only a few other families have subsequently been discovered, each with a different mis-sense or frameshift NGF mutation, which is likely the cause of the delay between NGF being detected and the phenotype, its loss caused in humans, being characterised. Functional analyses of these mutations have revealed that either the cysteine knot structure of NGF a structural motif unique to neurotrophins and made up of two disulphide cysteine bonds is destabilised or that NGF's intracellular proteolytic processing is unsuccessful.[24] The p75 neurotrophin receptor (p75NTR), a member of the tumour necrosis factor receptor superfamily, and TrkA are two of the well-known receptors for NGF. NGF and other neurotrophins, such as brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4, bind to the low-affinity p75NTR receptor.[25] Numerous ways of NGF-induced neuronal regulation require p75NTR. But as of yet, no human genetic diseases linked to p75NTR loss-of-function mutations have been reported.[9]

PR domain zinc finger protein 12

A new HSAN4-like phenotype was reported in 2015 and was attributed to bi-allelic mutations in PR domain zinc finger protein 12 (PRDM12) (also known as HSAN6 in the clinical setting).[21] As a transcriptional regulator, PRDM12 has a role. Normal cognition (or occasionally a little cognitive delay) and a reduction in A but not C fibres on nerve biopsy are the clinical characteristics that set this novel illness apart from HSAN4. The second most typical variety of developmental CIP[6] is this disease. Patients with PRDM12 mutations may, however, exhibit non-global pain insensitivity, in contrast to SCN9A and NTRK1 CIP.[26]

Zinc finger homeobox 2

An unusual three-generation family with a heterozygous missense mutation in Zinc finger homeobox 2 (ZFHX2) p.Arg1907Lys has been identified.[27] This putative transcription factor has a homeodomain mutation. The scientists demonstrated that several pain-related genes had altered expression, and the phenotype did not appear to include neuropathy. However, it is now unknown how this ZFHX2 caused a lack of pain perception.

CLINICAL FEATURES

Depending on the temperature of the environment, recurrent episodic fevers, which may appear in infancy or early childhood, are typically the initial clinical symptom. Children get hyperthermia in hot environments because they do not sweat. When exposed to extremely cold temperatures, they can also suffer hypothermia.[10] High ambient temperatures can also cause recurrent febrile convulsions in some people.[28] The palms and soles' surfaces gradually thicken and develop cracks.[28] Significant plantar skin fissures are frequently accompanied by palmoplantar hyperkeratosis.[29] However, in the early stages of infancy, these skin lesions are not visible. The distribution of hair on the body and scalp is normal.[4] Parents may remember that their children did not cry during blood sample, even though the reduced pain sensitivity may not be immediately obvious. After the first teeth sprout, people begin to bite their tongue or lips, which can lead to a bifid or missing tongue. Finger ulcers and finger biting are both rather prevalent. Bruises, wounds, and burns don't cause the typical reactions and can go unnoticed. Accidental wounds from falls or burns leave behind numerous scars, and severe infections like osteomyelitis can worsen fractures of the bone or joint. These problems frequently result in finger or limb amputations. Surgery is commonly required to treat neurogenic arthropathy, an abnormal malformation of the joints. Life expectancy varies.[11] Individuals with PRDM12-CIP are able to taste foods that are frequently linked to unpleasant feelings, such as being able to distinguish between 'hot' and 'spicy' dishes. They have complete access to the normal emotional spectrum, including unpleasant emotions. Individuals with SCN9A and NTRK1 CIP can distinguish a hot flavour and experience emotional pain.[26] Different symptoms and indicators of CIPA may appear, some of which may be deceptive. Radicular hereditary sensory neuropathy (HSN

I), hereditary sensory and autonomic neuropathy (HSN II), familial dysautonomia or Riley-Day syndrome (HSN III), congenital indifference to pain (HSN V), and Lesch-Nyhan syndrome are the differential diagnoses for this pathology.[17] Orthopaedic dental, ophthalmological, dermatological issues are among the various clinical consequences linked to CIPA.[11,29,30]

Orthopaedic clinical manifestations

Repeated fractures and joint dislocations, arthritis and osteomyelitis, avascular necrosis, and Charcot arthropathy, are all common musculoskeletal symptoms of HSAN-IV in both the upper and lower extremities.[31] At the elbow, knee, and ankle joints, orthopaedic abnormalities may be particularly noticeable[11]. Large weight-bearing joints that are frequently injured include the ankles, knees, and femoral joints, which usually result in joint deformity and neurogenic arthropathy (Charcot joints). Due to accidental injuries or self-mutilation, fingers or limbs may be removed. Fractures are more common between 1 and 7 years of age, according to a review of the literature using the HSAN-IV, although other problems don't seem to be age-related.[32] Because young children are so active, fractures are common at these ages. The incidence of fractures declines as kids get older and become less active. In HSAN-IV, fractures and dislocations can form even in the absence of obvious trauma or after minimal trauma like short falls.[33] Reduced sensitivity, particularly profound sensation, intellectual incapacity, and mutilating behaviour may be associated to these fractures and dislocations even when the cause has not been determined. Patients with CIPA may overuse their extremities, resulting in fractures and dislocations, due to their insensitivity to shallow and deep painful stimulation, which is sometimes accompanied by intellectual incapacity and self-mutilating behaviour. Nearly all bones and joints can be impacted, while lower limbs are more frequently afflicted by skeletal-system complications.[32]

Treatment of orthopaedic complications

A daily comprehensive examination of the feet and ankles by the patient and/or a relative is a crucial component of the preventative treatment when treating the lower limb symptoms in order to spot pressure spots early on. The Wagner grading system for neuropathic ulcers should be used to grade newly formed ulcers, and the appropriate treatment should be administered.[34] With pressure-free casts, stringent no-weight-bearing, routine wound reviews, and debridement as needed, conservative care should be the mainstay. Due to the possibility of future antibiotic use and the potential development of multidrug-resistant bacteria, antibiotic use should be avoided wherever possible unless there is evidence of cellulitis or osteomyelitis. If surgery is necessary to remove an infection from a wound or bone, the removal must be thorough and done in coordination with plastic surgeons because these patients frequently need permanent soft tissue coverage. Surgery is most usually used to treat infections, while conservative therapy can be used more frequently to treat fractures, joint dislocations, and Charcot joints.[34] It has been reported that surgically altering the anatomy may not be able to stop CIPA patients' joints from dislocating over time. Additionally, individuals with CIPA frequently experience cardiovascular problems such bradycardia and hypotension after anesthesia.[35] Therefore, it might not always be wise to treat these patients surgically. However, using casts, a typical conservative treatment, has disadvantages. First, instability is encouraged by CIPA patients' intellectual incapacity and loss of pain perception. Second, the sensory disruption increases the chance of getting pressure sores. In this patient population, minimising trauma is crucial because both surgical and conservative therapies have drawbacks.[32]

The timing of surgery is crucial when there is joint instability. In order to ensure that surgery is performed when there are no symptoms of a deep infection, a period of close in-patient rest and monitoring with regular clinical reviews and the help of diagnostic tools such as inflammatory markers, bone scans, and magnetic resonance imaging (MRI) may be planned in advance, if necessary. Additionally, patients should receive early advice regarding the possibility of major limb amputation for two reasons. Major limb amputation is the only option available to treat the persistent lower limb infections and bone destruction because, first, complex mid-foot and hindfoot fusions frequently come with complications, and second, if the patient develops aggressive osteomyelitis close to the ankle joint and/or systemic sepsis. The use of topical emollients on a regular basis and adequate hand cleanliness are advised for the treatment of the upper limb manifestations.[32] The latter's application gives the patients a chance to examine the hand for unintentional injury. Patients should be given rest, elevation in a sling, routine wound cleansing and debridement, and antibiotics if necessary after they develop hand ulcers. Only individuals in whom a strict period of rest, elevation, and wound cleaning has failed to prevent the development of osteomyelitis should undergo surgical debridement. A period of close preoperative monitoring and examination with an MRI scan is advised, similar to the lower limb patients, to guarantee excision of all contaminated bone and soft tissue of questionable viability, followed by appropriate soft-tissue coverage.[34] Preventing significant articular damage and amputation is the primary goal of orthopaedic treatment in CIPA. The most common recommendation is to minimise activity; however, this is impractical because the majority of patients are intellectually retarded and are not shielded by discomfort. Therefore, it is crucial to use braces with extreme caution when treating patients who have decreased sensation.[24]

Dental clinical manifestations

Injury from trauma and self-inflicted wounds are brought about by painlessness. Biting on hands, fingers, or oral

tissues might seriously harm oneself.[36] Cicatrisation and restricted mouth opening are the results of repeated bouts of oral ulcerations and healing.[37] Some syndromes, including Lesch-Nyhan syndrome, Tourette syndrome, and de Lange syndrome, have been linked to impaired pain perception and oral mutilation.[38] Serious oral mutilation frequently ensues from the absence of pain perception.[39] The tongue, lips, and other oral mucosa have been known to become lacerated and ulcerated as a result of bite wounds. Additionally, considerable dental attrition and tooth luxation have been noted. Although the dental aspects have only been characterised in a small number of recorded instances due to the extreme rarity of this condition, the oral manifestations are particularly distinctive in HSAN.[30] An infant with HSAN type IV is more likely to have additional oral trauma, such as biting of the tongue or lips, with the eruption of the upper and mandibular primary incisors. One of the key diagnostic indicators of HSAN IV is uncontrollably and repeatedly biting the tongue with the primary incisors[40]. By mutilating the tongue, one causes serious damage that might lead to tissue laceration, profuse bleeding, infection, fever, or malnutrition.

Treatment of dental complications

Since there is no known cure for this ailment, treating such patients presents difficulties for paediatric dentists. The situation is more challenging to handle due to the absence of pain, developmental and psychological issues, and functional impairment brought on by early tooth loss. The management's goal is to stop people from using their teeth to harm their own oral structures. To do this, various therapeutic approaches are available. Although it can be tried, simple grinding of sharp tooth edges does not always work. Although it is a radical treatment and the final option, it is possible to extract all erupting teeth.[36] A mouth guard is a useful instrument in such situations. They are simple to construct, wear, and clean with low aspiration risk.[38] The mouth guards will safeguard the sensitive tissue and assist in ending the habit of self-mutilation.[36] All dental injuries can be easily avoided using mouth guards.[38] In order to protect the infant from all types of harm, mouth guards are used.[36-40] Up until the patient is old enough to understand and refrain from self-mutilating behaviours, parents' cooperation and routine mouth guard replacement will be required.[38] Long term, it will be necessary to give fresh mouth guards to fit the changing dentition, assure proper oral and appliance care, and promote a diet low in cariogenic foods. This will shield the mouth guard from any potential negative consequences brought on by plague stagnation.[36]

Ophthalmological clinical manifestations

Neurotrophic keratopathy, superficial punctate (SPK), corneal ulcers and opacities, and dry eye syndrome are a few of the ocular signs of CIP.[41] Reduced lacrimation, corneal abrasions, and a weak or non-existent corneal blink reflex are common in people with PRDM12 variations, which can lead to keratitis and corneal scarring.[42] Neurotrophic keratitis (NK), also known as neurotrophic keratopathy or neuroparalytic keratitis, is a clinical condition that affects people who have decreased or absent corneal sensitivity. Regardless of the underlying cause, NK is a rare degenerative disease of the cornea caused by an impairment of corneal sensory innervation, characterised by decreased or absent corneal sensitivity (hypo/anaesthesia), which causes spontaneous epithelial breakdown and reduced corneal healing.[43,44] Systemic, congenital, ocular, or iatrogenic illnesses that harm the fifth cranial nerve can result in NK. Given the exceptional rarity of CIPA, even if we assume that the cornea was affected in every case throughout the patient's lifetime, the effect of CIPA on the overall prevalence of NK can be safely regarded as insignificant.[45]

Treatment of ocular complications

For the purpose of avoiding corneal ulcers and the resulting scarring, early identification is crucial. Children with a history of CIP in their families should get a quick genetic investigation to see if they have the familial genetic variant. Genetic testing for CIP should be requested for patients without a family history of the condition who experience recurrent corneal ulcers at a young age, especially if they also exhibit other symptoms that point to the condition, such as accidental injury without obvious pain, tongue-biting, and lack of pain during blood sampling. A thorough ophthalmologic examination, namely of the ocular surface for dry eye symptoms, corneal abnormalities and opacities, as well as evaluation of corneal sensitivity, should be performed promptly after birth once the diagnosis of CIP is established or suspected. In order to prevent the onset of corneal opacities and vision loss, vigorous therapy should be started as soon as ocular surface illness is identified. We advise ample ocular lubrication using preservative-free eyedrops and punctal occlusion for patients who have dry eye symptoms. A broad-spectrum topical antibiotic should be given if a corneal ulcer appears. Treatment options for corneal ulcers that are expanding or not healing should include early lateral tarsorrhaphy.[43] Although phase 2 clinical trials exploring growth factors and neuropeptides are now active in both Europe and the USA, there are currently no approved pharmaceutical therapies for NK.[46] Although regular lubrication with preservative-free substances needs to be advised, particularly in youngsters, the use of artificial tears without preservatives may help improve the corneal surface at all stages of disease. To avoid secondary NK infections in the eyes, it is frequently advised and encouraged for kids to use topical antibiotic eye drops devoid of preservatives.

Dermatological clinical manifestations

Disorders of temperature and pain perception (CIPA and CIP): Patients with dysplasia of the terminal C fibres of

the sensory nerves are unable to experience pain in reaction to mechanical or chemical stimuli, as well as heat or cold. The likelihood of getting bruises, scratches, bites, burns, and frostbite increases as a result. In addition, failing to get enough rest after an injury might result in serious sickness. Skin wounds frequently progress to deeper organs, resulting in osteomyelitis, meningitis, septicaemia, and encephalitis. Sweating disorder (CIPA only): The absence of C fibres, which are postganglionic fibres that trigger sweat secretion, prevents sweating in CIPA even though the number of sweat glands is normal and their morphology is unaffected. Due to the body's inability to control its temperature, it increases dramatically, causing heat retention and potentially heat stroke. The absence of moisture-retaining perspiration also makes the stratum corneum thicker and causes the skin to dry up more quickly. It cracks easily due to its lack of flexibility, which has a negative impact on the effectiveness of the barrier. This renders patients more susceptible to bruising and abrasions from trauma, and when combined with sensory problems, wounds have a tendency to penetrate the skin more deeply, leading to bacterial infections and slower wound healing.

Treatment of dermatological complications

There are no systematic descriptions of the symptoms or coping mechanisms, despite the fact that skin symptoms are present in CIPA and CIP very frequently and are known to occasionally become severe. The attending physician is now administering their own form of treatment for symptoms. Some of the measures to protect the skin is as follows: Maintain cleanliness: A daily bath or shower wash should be used to maintain the skin's outer layer. Look for even the smallest bruises and scratches on the skin all over the body. Apply a topical antibiotic as soon as you discover them, cover them with gauze or a wound dressing, and prevent infection. Moisturize and protect: Applying moisturisers from early infancy is vital since the skin is prone to dryness. Applying it to the entire body after 20 minutes of taking a bath, while the stratum corneum is still moist, is very helpful. Every time they are washed or cleaned, the easily dirty areas around the lips, hands, and nappy area should be moisturised and protected by applying moisturiser. UV protection: Unprotected exposure to UV radiation for more than 20 minutes on a typical sunny day will result in sunburn and skin damage. To prevent exposure to UV radiation, cover up with sunscreen, hats or umbrellas before going outside, and dress the patient in long sleeves and long pants. Prevention of burns: Keep devices that produce steam out of easy reach and away from high-heat sources like stoves, rice cookers, and hot water kettles. Pay attention to the hot water and shower temperature and keep it at a modest setting. Be careful while eating things that may be hotter inside, such as croquettes, gyoza, and hamburgers, and chill all hot food before placing it nearby. Prevention of frostbite: When it's cold outside during the winter, make sure the patient is wearing gloves, thick socks, and hats to keep their hands and feet from being too chilly. Also, make sure the temperature inside doesn't drop below 20°C. Prevention of falls and trauma: As much as possible, keep the skin covered with clothing and avoid exposing it. To lessen impact, particularly on the knees, shins, elbows, and forearms, it is advised that patients wear padded supporters. To avoid falling, make sure the patient's shoes are comfortable. Use cushioned and rounded-cornered furniture to absorb the shock of bumps.[47]

CONCLUSION

HSAN are a highly uncommon illness that provide numerous diagnostic and therapeutic hurdles. Early detection of this incredibly rare condition is crucial for effective treatment and the avoidance of consequences. Clinically, CIP patients face a myriad of challenges due to their insensitivity to pain, despite the intriguing nature of CIP, managing the condition remains a considerable medical challenge. The lack of effective treatment options underscores the need for further research to unravel the intricate mechanisms underlying pain perception and develop targeted therapies. Recent research suggests that the NGF- TrkA system may be implicated in a number of disease states and that NGF-dependent neurons play critical roles in brain-immune endocrine connections in pain, itch, and inflammation. The development of new analgesics, anti-pruritic, and anti-inflammatory medications may be aided by research that focuses on the molecular processes of NGF- TrkA signal transduction. To encourage better growth, lower risks, and effectively treat problems and sequelae, a specialised and multidisciplinary approach is required. The involvement and cooperation of parents and other family members is essential, and they need to be regularly instructed to avoid any situations that could endanger the patient. This review emphasizes the importance of interdisciplinary collaboration among geneticists, neurologists, and physicians to enhance our understanding of CIP. Additionally, it calls for increased awareness within the medical community to ensure timely identification and support for affected individuals. In conclusion, this review sheds light on the clinical and genetic aspects of Congenital Insensitivity to Pain, underscoring the complexities associated with this rare disorder and the imperative for ongoing research to improve diagnosis and management strategies.

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