Congenital Insensitivity to Pain Syndrome with Anhidrosis. Review of Literature

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Abstract

The congenital insensitivity to pain with anhidrosis (CIPA) is a rare autosomal recessive disease caused by mutations in NTRK1 gene (neurotrophic tyrosine kinase receptor 1) located in chromosome 1q21-22, encoding the tyrosinase domain receptor high affinity nerve growth factor. It is characterized by anhidrosis, insensitivity to painful stimuli and mental retardation. Given their low prevalence and the few reported cases, it is important to know its main features to be considered in the differential diagnosis in pediatric practice. The therapeutic approach of CIPA remains unclear. The preventive approach remains the only possible treatment of CIPA. Early surgical treatment for long bone fractures to prevent pseudo arthrosis and to allow early weightbearing decreasing the risk of further osteopenia. The choice of appropriate antibiotics and surgical debridement in cases of infection might prevent further destruction of joints.

Keywords
Congenital insensitivity to pain
Pain insensitivity
Anhidrosis
Sensory Neuropathy
Charcot joint
Anthropathy
Osteomyelitis

Introduction

Congenital insensitivity to pain and anhidrosis (CIPA), also known as hereditary sensory and autonomic neuropathy type IV, is an extremely rare syndrome1, 2. According to literature, the first step in the diagnosis of CIPA syndrome is consideration of the clinical presentation based on the combination of three basic signs: insensitivity to pain, anhidrosis, and mental retardation2,3. The first reference to a similar pathology was mentioned by Dearborn in the early 1900s2, and it was published in 1963 by Swanson 4. Other possible signs may be associated: impaired temperature sensation5, mandibular osteolysis 6, facial alterations 7, growth disturbances 8; heterotopic ossification 9, repetitive soft tissue and osseous infections of hematogenous origin10, self-mutilating behavior6. This condition occurs with an incidence of 1 in 125 million newborns6. All clinical manifestation shown as Table 1.

The pathogenesis of CIPA is characterized by a genetic loss-of-function mutation of the NTRK1 gene (locus 1q 21- 22)11-13. Multiple new mutations have been progressively described12,14. NTRK1 mutations imply an alteration in TrkA, an NGF receptor. 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 of15,16 the afferent somatic sensory
system for pain and temperature, located in the dorsal root ganglion sensory neurons and the autonomic sympathetic neuronal system, which implies loss of the innervation of eccrine sweat glands by sympathetic neurons, the central nervous system, and the nervous system. NGF has a relevant role in the signal pathway of B lymphocytes through three processes: Trk A phosphorylation, cytoskeleton assemblage, and MAP kinase activation. The molecular alteration in the NGF in turn also alters the normal processes: Trk A phosphorylation, cytoskeleton assemblage, and MAP kinase activation.

Orthopedic Clinical Manifestations

Musculoskeletal manifestations are frequent in HSAN-IV, and include repeated fractures and joint dislocations (Figure 3 a,c), arthritis and osteomyelitis (Figure 3 c,d,e,f), avascular necrosis, and Charcot arthropathy (Figure 2 and 3 a,b), in both upper and the lower extremities. A review of literature with HSAN-IV showed that fractures are frequent between 1 and 7 years of age, here as other complications have no apparent age relationship. Fractures and dislocations develop in HSAN-IV, even without any apparent trauma or following minor trauma, such as short falls (Figure 1 a,b).

Although the reason for these fractures and dislocations has not been clarified, decreased sensation, including deep sensation, intellectual disability, and mutilating behavior, may be related. Video gait analysis for patients with HSAN-IV, especially those who experience pain, may provide additional information. Short-latency somatosensory evoked potentials show marked prolongation of the central conduction time and microneurography reveals abnormal activity of somatic A-delta and C fibers in the nerves of the skin. A negative sympathetic skin response may also be helpful in the diagnosis due to the lack of sudomotor nerves in skin biopsy. Neurological laboratory tests may provide additional information. Plasma norepinephrine levels were very low or undetectable and failed to increase in the upright posture despite normal blood pressure. Plasma epinephrine levels were normal and increased when patient was upright. Plasma renin activity also increased appropriately with upright posture. Patients with pure autonomic failure also had very low levels of plasma norepinephrine both supine and when upright, but in contrast to patients with CIPA failed to maintain blood pressure upright.

Laboratory Findings

Plasma norepinephrine levels were very low or undetectable and failed to increase in the upright posture despite normal blood pressure. Plasma epinephrine levels were normal and increased when patient was upright. Plasma renin activity also increased appropriately with upright posture. Patients with pure autonomic failure also had very low levels of plasma norepinephrine both supine and when upright, but in contrast to patients with CIPA failed to maintain blood pressure upright.

Diagnosis is mainly clinical, plus some laboratory tests. Symptoms necessary for diagnosis are insensitivity to pain, anhidrosis, and intellectual disability. However, the severity of these symptoms is highly variable. Skin biopsy may reveal a lack of eccrine sweat gland innervation. A biopsy of the sural nerve may reveal characteristic findings including reduced numbers of myelinated and unmyelinated small-diameter fibers with normal numbers of large diameter fibers. An axonal flare test with a small amount of diluted histamine injected under the skin, fails to cause the normal flare around the site of injection. Molecular genetic testing can confirm the diagnosis but is not available on many occasions.

Table 1: Table summarizing the common clinical manifestations.

<table>
<thead>
<tr>
<th>Sensory Nervous System</th>
<th>Autonomic Nervous System</th>
<th>Cognition</th>
<th>Gastrointestinal</th>
<th>Respiratory</th>
<th>Cardiovascular</th>
<th>Musculoskeletal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lip biting, corneal scarring, and autoamputation of digits</td>
<td>• Anhidrosis</td>
<td>• Intellectual disability</td>
<td>• Uncoordinated swallowing</td>
<td>• Repeated aspiration pneumonia</td>
<td>• Cardiovascular lability</td>
<td>• Delayed cutaneous healing</td>
</tr>
<tr>
<td>• Temperature sensation (i.e. perception of hot and cold)</td>
<td>• Hyperpyrexia</td>
<td>• Impulsivity, hyperactivity, reckless behaviors</td>
<td>• Recurrent misdirection</td>
<td>• Postural hypotension</td>
<td>• Postural hypotension</td>
<td>• Early loss of teeth</td>
</tr>
<tr>
<td>• Hypoalgesia</td>
<td>• Blotchy erythema</td>
<td></td>
<td>• Nausea and vomiting</td>
<td>• Blotchy erythema</td>
<td>• Blotchy erythema</td>
<td>• Fractures caused by minor traumas</td>
</tr>
</tbody>
</table>

Diagnostic Tests

Diagnosis is mainly clinical, plus some laboratory tests. Symptoms necessary for diagnosis are insensitivity to pain, anhidrosis, and intellectual disability. However, the severity of these symptoms is highly variable. Skin biopsy may reveal a lack of eccrine sweat gland innervation. A biopsy of the sural nerve may reveal characteristic findings including reduced numbers of myelinated and unmyelinated small-diameter fibers with normal numbers of large diameter fibers. An axonal flare test with a small amount of diluted histamine injected under the skin, fails to cause the normal flare around the site of injection. Molecular genetic testing can confirm the diagnosis but is not available on many occasions.
IV has shown that younger patients walk faster with a longer stride length and higher heel contact angular velocity than controls. This finding may explain the high incidence of musculoskeletal trauma in the lower extremities. Charcot arthropathy may develop following malunion of fractures (Figure 4 c,e) avascular necrosis, and unreduced/recurrent dislocations in the absence of pain sensation.

Kawashima et al. measured grip force and acceleration of a held object in patients with HSAN-IV. They found greater grip force during the object grasp-lift-holding task and greater fluctuation in acceleration of the object. Such impaired motor control ability may lead to overuse and/or misuse of the extremities and cause joint destruction (Figure 2 a,b,f).

The best therapeutic approach to patients with CIPA appears to be based on prophylactic measures such as braces for early weight bearing in nonsurgical fractures and accurate follow-up to avoid missing complications because of loss of pain sensation and intellectual disability. These may also lead to development of pressure sores. Even after surgical treatments, some patients cannot maintain non-weight bearing status and the fixation of fractures or reduction of dislocations can break down (Figure 3 a,b). Because surgical and conservative treatments have their...

The high incidence of infections in patients with CIPA is also problematic. Skin and deep bone infections are the most common types, and Staphylococcus aureus is the most commonly involved pathogen. Resistance to antibiotics is a frequently occurring limitation in the treatment of these patients. Temperature deregulation may cause recurrent fever, which may lead to death if not recognized early. Other complications such as trauma or soft tissue/bone infection may decrease condition of the survival rate, although all are treatable conditions if diagnosed in a timely manner.

Wide surgical debridement and antibiotic therapy, corrective osteotomies, shoe raises or epiphysiodesis for shortening may be needed. These patients need regular follow-up with anticipation of complications and hospital re-admissions in the management of this rare syndrome.

Discussion

Congenital insensitivity to pain with anhidrosis is caused by a mutation in the gene neurotrophic receptor tyrosinase 1 (NTRK1), which is located on chromosome 1q21-22, which encodes the tyrosinase domain of the receptor high affinity of nerve growth factor. This gene alteration determines the failure of the differentiation and migration of cells the neural crest and, consequently, the absence complete of small myelinated fibers and not myelinated responsible for the perception of pain and temperature, as well as the absence of innervation of the sweat glands. Infection in the fingers and toes, lips and tongue and scarring are observed commonly. Keratoderma palmoplantaris is a typical finding in the advanced period. Other problems include chronic bone and joint infections. The first sign of this syndrome is fever secondary to anhidrosis, which has recurrent presentation since the period neonatal or from the first months of life. Due to the infrequency of this disorder and the absence of other signs that guide to its diagnosis, initially, they are described recurrent febrile episodes, such as fever of origin to be determined. The febrile seizures occur frequently and described that 20% of the cases of death in the three first years of life are produced by hyperpyrexia. As a consequence of the absence of painful and thermal sensitivity, are produced injuries at different levels. Common are alterations of the skin (lacerations, ulcers, infections, burns) and orthopedic (fractures multiple with hyperplastic bone formation, affecting femur and tibia; Charcot joints; limb dysmetria; scoliosis progressive osteomyelitis; septic arthritis; dislocations; amputations and self-mutilations). The differential diagnosis among others hereditary neuropathies were mainly based at the age of onset of the clinical picture, in the marked insensitivity to pain and in the absence of sweating. Other important data for take into account for the differential diagnosis are the normal reflex response deep tendons and developmental delay maturity. Clinical suspicion is confirmed with the result of skin biopsy. Malignancy was eventually ruled out based on histologic sampling. Inflammatory arthropathy is also a consideration, as
in our case, when inflammatory changes predominate on imaging or there is polyarticular involvement\(^2\), an additional consideration is neuropathic joint disease secondary to chronic neuropathy caused by a long standing illness such as diabetes or vascular disease. Eventually, after excluding all other possibilities, the correct diagnosis of congenital insensitivity to pain was confirmed by gene testing\(^3\).

Conservative management can be useful in cases of mild deformities and disease consequences, thermoregulation is imperative in the management of CIPA and should include treatment of pyrexia with fanning, cooling blankets, cold drinks, paracetamol and/or non-steroidal anti-inflammatory drugs, and appropriate clothing advice\(^4\). Therapeutic approach with pamidronate as a representative treatment requires expertise in managing this disease.

Skeletal-system complications are more common in the lower limbs, almost all bones and joints may be affected. Szoke et al. reported that 58% of patients with CIPA had osteoarticular disorders of the feet and ankles, 53% of the knees, and 26% of the hips\(^5\). Bar-On et al. reported that in 31 fractures in patients with congenital insensitivity to pain, 28 occurred in the lower limbs\(^6\). Fractures occurred in the early years of life, especially between the ages of 4 and 6 years. Fractures occur frequently at these ages because young children are very active. As children get older and become less active, the frequency of fractures decreases\(^7\). Furthermore, cardiovascular complications such as bradycardia, and hypotension following anesthesia, are common in patients with CIPA\(^8,9\). Therefore, surgical treatment of these patients may not always be advisable. Conservative therapy was used more frequently than surgery to manage fractures. On the other hand, use of casts, a representative conservative treatment, has drawbacks. First, the intellectual disability and loss of pain sensation of CIPA patients promotes instability. Second, there is a risk of developing pressure sores because of the sensory disturbance. Patients wore high-top sneakers and knee pads, and the parents covered the floor with sheets of soft material to prevent injuries. In addition, a few patients even used wheelchairs for locomotion to prevent accidental falls despite their walking ability. Some of published articles are described as Table 2.

**Conclusion**

HSAN are a very rare disorder with many diagnostic and treatment challenges. Data compilation of affected patients could provide a valuable resource of diagnosing and managing this disease.

A specialized and multidisciplinary approach is necessary to promote better development, reduce risks, treat complications and sequelae adequately. The participation and collaboration of parents and family members is fundamental, and they must be continuously trained to avoid all events that pose a possible risk to the patient. In the case presented, the dedication and affection of the family environment have been key in its favorable evolution.

**References**


**Table 2:** Table summarizing the published cases.

<table>
<thead>
<tr>
<th>Published cases</th>
<th>Year of publication</th>
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<tbody>
<tr>
<td>Dearborn [2]</td>
<td>1932</td>
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<td>Rosenberg et al. [5] rew</td>
<td>1994</td>
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<tr>
<td>Weier et al. [13]</td>
<td>1995</td>
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<tr>
<td>Indo et al. [14]</td>
<td>1997</td>
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<tr>
<td>Grills and Schuifers [22]</td>
<td>1998</td>
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<tr>
<td>Jarade et al. [9] review</td>
<td>2002</td>
</tr>
<tr>
<td>Bonkowski et al. [39]</td>
<td>2003</td>
</tr>
<tr>
<td>Melamed et al. [19]</td>
<td>2004</td>
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<tr>
<td>Tunc_bilek et al. [18]</td>
<td>2005</td>
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<tr>
<td>Schwarzkopf et al. [39] review</td>
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<td>Brandes and Stuth [44]</td>
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<td>Oliveira et al. [45]</td>
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<td>Lin et al. [12]</td>
<td>2010</td>
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<tr>
<td>Indo [15]</td>
<td>2010</td>
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<tr>
<td>Daneshjou et al. [6]</td>
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<tr>
<td>Indo [26]</td>
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<tr>
<td>Gao et al. [7]</td>
<td>2013</td>
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<tr>
<td>Fruchtman et al. [41]</td>
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<td>Yang et al. [45]</td>
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<td>Abdulla et al. [10]</td>
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<tr>
<td>Pérez-López et al. [43]</td>
<td>2015</td>
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<tr>
<td>Nabiye et al. [8]</td>
<td>2016</td>
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