We present a case study of a 10-year-old child with severe burns that were misinterpreted as inflicted burns. Because of multiple injuries since early life, the family was under suspicion of child abuse and therefore under supervision of the Child Care Board for 2 years before the boy was burned. Because the boy incurred the burns without feeling pain, we conducted a thorough medical examination and laboratory testing, evaluated detection and pain thresholds, and used MRI to study brain morphology and brain activation patterns during pain between this patient and 3 healthy age- and gender-matched controls. We found elevated detection and pain thresholds and lower brain activation during pain in the patient compared with the healthy controls and reference values. The patient received the diagnosis of hereditary sensory and autonomic neuropathy type IV on the basis of clinical findings and the laboratory testing, complemented with the altered pain and detection thresholds and MRI findings. Hereditary sensory and autonomic neuropathy IV is a very rare congenital pain insensitivity syndrome characterized by the absence of pain and temperature sensation combined with oral mutilation due to unawareness, fractures, and anhidrosis caused by abnormalities in the peripheral nerves. Health care workers should be aware of the potential presence of this disease to prevent false accusations of child abuse.

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**Key words:** abuse, anhidrosis, congenital insensitivity to pain with anhidrosis (CIPA), hereditary sensory and autonomic neuropathy (HSAN), neuroimaging, pain insensitivity syndrome

**Abbreviations:**
- CIPA—congenital insensitivity to pain with anhidrosis
- HSAN—hereditary sensory and autonomic neuropathy
- NGF—nerve growth factor
- QST—quantitative sensory testing

Dr van den Bosch conducted the literature search, collected the Thermal Sensory Analyzer and MRI data, performed all the data analysis, performed the data interpretation, and wrote the first draft of the manuscript; Dr Baartmans conducted the literature search, collected the clinical data, performed the data interpretation, and wrote the first draft of the manuscript; Drs Vos and Dokter collected clinical data, interpreted the data, and reviewed the draft version of the manuscript; Dr White supervised MRI data collection and analyses and interpreted the data; Dr Tibboel designed the study, interpreted the data, and reviewed the draft version of the manuscript; and all authors approved the final manuscript as submitted.


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Insensitivity to pain can be caused by neuropathies due to diabetes or diseases such as leprosy. It can also be inherited and caused by congenital pain insensitivity syndromes. These congenital diseases are associated with a loss of sensory and pain discrimination and a loss of the affective-motivational response to pain. The majority of these syndromes are caused by hereditary sensory and autonomic neuropathies (HSANs), of which 5 different types are recognized. HSAN IV, or congenital insensitivity to pain with anhidrosis (CIPA), is an extremely rare autosomal recessive disease characterized by diffuse thermal and pain insensitivity and anhidrosis. Patients with HSAN IV suffer from oral mutilation, fractures, bruises, and ulcerations of extremities caused by pain insensitivity. These symptoms are a consequence of the absence of unmyelinated nerve fibers and a loss of small myelinated fibers in the peripheral nerves. The diagnosis of HSAN IV is made primarily clinically on the basis of impaired pain and temperature perception in combination with anhidrosis. Additionally, an intradermal histamine test can be conducted, because a lack of a normal axon flare response is consistent with HSAN. The diagnosis may be confirmed by a genetic test, because the related mutations and polymorphisms of the TRKA gene on chromosome 1 are identified. In this case study we present a boy who presented with severe burns on his buttocks that were caused by an impaired temperature and pain perception.

CASE REPORT
Patient Presentation
A 10-year-old boy was admitted to the Maasstad Hospital Burn Center in Rotterdam, The Netherlands, with severe contact burns on his buttocks. He had played computer games while sitting on top of a central heating system. After a few hours he noticed severe blisters on his buttocks without experiencing pain. The parents sought medical help and were referred to our burn center. The referring hospital suspected inflicted burns, because the blisters had not been cooled and both parents and the patient did not have an explanation for the burns. After extensive questioning on what he had done before the blisters on his buttocks appeared, the central heating system was identified as the possible cause of his burns. Physical examination revealed a cooperative healthy boy with a total body surface area burn of 4%. The burns were deep dermal and surgery was needed to close the wound (Fig 1). His tongue and lips showed several scars from earlier lacerations caused by tongue biting and burns caused by drinking very hot liquids while not detecting heat or pain sensations (Fig 2). Neurologic examination pointed to normal cranial nerve function, sensation of vibration, stature, proprioception, and cold/warm differentiation. His deep tendon reflexes were low.

This boy is the youngest child of non-consanguineous parents of Turkish ethnicity. During infancy he had no feeding or respiratory problems. After the first tooth eruptions he had lingual lacerations. Developmental milestones in the early years and learning abilities were normal, but his hyperactivity was noteworthy. After he started walking, he frequently had painless bruises, skin lacerations, and bone fractures of his legs and ankles. Furthermore, his parents noted that he did not sweat normally, that is, anhidrosis.

Due to 2 separate fractures of his lower extremities, which were unexplained at that time, the parents were already suspected of child abuse and under the supervision of the Child Care Board for 2 years before he was burned. The Child Care Board did not find evidence...
for psychosocial problems in the family, which are often associated with child abuse. Furthermore, the injuries occurred at different places (ie, at school and at home). Because the boy felt no pain during the development of the burns and during admission, we looked deeper into this case and reevaluated the diagnosis of child abuse. On the basis of his medical history we considered the diagnosis of HSAN IV.

Medical Tests and Comparison With Healthy Controls

We performed a histamine flare test with an intradermal injection of histamine (0.1 mg/mL, 0.3 mL), which showed no flare. Furthermore, an electromyogram showed no abnormalities and DNA tests revealed no gene mutations for HSAN II or for HSAN III (Riley Day syndrome).

Furthermore, we compared this patient with 3 healthy age-matched boys and conducted quantitative sensory testing (QST) to measure thermal detection and pain thresholds and compared brain morphology and brain functioning during pain by using structural and functional MRI. (For extended information regarding the methods of the QST and MRI tests, see the Supplemental Information.)

The patient’s mean detection temperatures for cold were lower than reference values and mean detection temperatures for warmth were higher in comparison with reference values generated from 9-to-12-year-old boys and compared with the 3 matched control children (Table 1 and Fig 3), suggesting hyposensitivity. We also found a lower mean threshold for the cold pain in the case in comparison with reference values and the 3 controls. The heat pain threshold temperature of the case was also higher in comparison with the reference values, but it was lower than the mean threshold of the control group (Table 1, Fig 3).

With regard to brain morphology, no evidence for gross brain abnormalities was found, and the total brain volume and the volumes of specific pain-related brain areas (thalamus, amygdala, anterior cingulate cortex, and the insula) were slightly smaller in the patient in comparison with the 3 controls (Table 2). A painful stimulus of 46°C induced minimal significant
brain activation in the patient (Fig 4). Furthermore, the activation pattern was not located in pain-related brain areas, such as the insula, and there was more significant brain activation in the controls during pain compared with the case (Fig 4). A warm stimulus of 41°C induced no significant brain activation in the case, although of the 3 controls, only 1 showed substantial significant brain activation (Fig 5).

**DISCUSSION**

The diagnosis of HSAN IV or CIPA requires 3 clinical criteria: anhidrosis, decreased pain and temperature perception, and mental retardation.7 However, there is wide variability in intellectual performance in these children, and mental retardation does not occur in all patients.2,10 Furthermore, low deep tendon reflexes and hyperactivity, as in our case, are common in patients with HSAN IV.25 In addition to the clinical characteristics, the absence of axon flare after intradermal histamine injection is consistent with HSAN, as in our case.

HSAN IV is caused by mutations in the *NTRK1 (TRKA)* gene. This gene is located...
on chromosome 1 (1q21–q22) and encodes for neurotropic tyrosine kinase receptor type 1, which is auto-phosphorylated in response to nerve growth factor (NGF). As previously described by Axelrod and Gold-von Simson, signal transduction at the NGF receptor is impeded and NGF dependent neurons, such as the small sensory and sympathetic neurons, fail to survive as a result of mutations. The numerous mutations do not allow for a straightforward diagnosis of HSAN IV. Gene expression is highly variable and may be related to the site of the mutation on the NGF receptor or whether there is genetic homo- or heterozygocity. Unfortunately, HSAN III (Riley-Day syndrome) is the only HSAN type for which commercially available genetic testing is available. The gene mutations of \textit{NTRK1} could not be determined in Dutch neurogenetic laboratories.

In our patient, medical history, clinical signs of anhidrosis, pain insensitivity, elevated detection and pain thresholds, low brain activation during warm and painful stimuli, and a negative histamine flare test sufficed to confirm the diagnosis of HSAN IV or CIPA. Even though the child appears to be hypo-sensitive to cold and warm detection and pain, he was able to notice pain during the QST procedure. Unfortunately, we were unable to test possible habituation for pain. It is possible that habituation for pain in combination with hyposensitivity and distraction (computer games) contributed to the severe burns in his case, especially because video games are found to reduce behavioral distress during pain in children. Furthermore, his brain activation during warm and painful stimuli was low in comparison with healthy age- and gender-matched controls. In general, more activation is visible in the brain when the stimuli are rated as more painful. Low brain

### TABLE 2 Global Brain Volumes and Volumes of Pain-Related Brain Regions

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Controls (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global brain volumes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total brain volume, cm³</td>
<td>1172</td>
<td>1246 (76)</td>
</tr>
<tr>
<td>Cerebral white matter, cm³</td>
<td>392</td>
<td>442 (27)</td>
</tr>
<tr>
<td>Total gray volume, cm³</td>
<td>744</td>
<td>758 (47)</td>
</tr>
<tr>
<td>Cerebellum (white matter), mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>11 461</td>
<td>15 460 (891)</td>
</tr>
<tr>
<td>Right</td>
<td>13 142</td>
<td>16 231 (888)</td>
</tr>
<tr>
<td>Cerebellum (cortex), mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>57 673</td>
<td>59 100 (2339)</td>
</tr>
<tr>
<td>Right</td>
<td>53 351</td>
<td>57 751 (4185)</td>
</tr>
<tr>
<td>Pain-related brain regions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus, mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>5956</td>
<td>7745 (678)</td>
</tr>
<tr>
<td>Right</td>
<td>6350</td>
<td>7303 (656)</td>
</tr>
<tr>
<td>Amygdala, mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>1738</td>
<td>1986 (130)</td>
</tr>
<tr>
<td>Right</td>
<td>1859</td>
<td>1968 (191)</td>
</tr>
<tr>
<td>Anterior cingulate cortex, mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>2258</td>
<td>2752 (1034)</td>
</tr>
<tr>
<td>Right</td>
<td>2906</td>
<td>2858 (619)</td>
</tr>
<tr>
<td>Insula, mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>7722</td>
<td>7696 (387)</td>
</tr>
<tr>
<td>Right</td>
<td>7159</td>
<td>7421 (523)</td>
</tr>
</tbody>
</table>

* Data are presented as means (SD).
activation during pain in combination with greater difficulties in detecting temperature variations and pain also supported our suspicion of a pain insensitivity syndrome. On the basis of clinical findings and the histamine test, the diagnosis of HSAN IV was confirmed. We then informed the family about the illness and referred the patient to a rehabilitation physician. However, it is always possible that the child has both HSAN and is a victim of child abuse, although the inspection by the Child Care Board and his medical condition did not suggest child abuse.

Makari et al14 described 2 siblings with HSAN V with a medical history of severe lacerations, fractures, and injuries. Child abuse was suggested when the girl presented with severe burns. The girl was placed in special care because of suspected child abuse. Fortunately, she was allowed to return home after the diagnosis of HSAN was confirmed in both children. Another rare disease that could be mistaken for child abuse is osteogenesis imperfecta, which should also be kept in mind with children with frequent bone fractures.15

CONCLUSIONS
Child abuse has a much higher occurrence rate than rare neuropathies. However, in selected cases with oral mucosal laceration and scars, multiple fractures, anhidrosis, and infrequently, mental retardation, a diagnosis of HSAN should be considered and thoroughly evaluated. Future diagnostic approaches may include systematic measurements of detection and pain thresholds. Health care workers should be aware of the potential existence of this illness.

REFERENCES


**Pain Insensitivity Syndrome Misinterpreted as Inflicted Burns**
Gerbrich E. van den Bosch, Martin G. A. Baartmans, Paul Vos, Jan Dokter, Tonya White and Dick Tibboel

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