Topical review

Congenital insensitivity to pain: an update

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1. Introduction

The description of individuals with congenital insensitivity and indifference to pain provided one of the bases for Melzack and Casey’s (1968) seminal distinction between the sensory and affective components of pain. In addition, the observation that these people often die in childhood because they fail to notice injuries and illnesses has been viewed as compelling evidence that the ability to perceive pain has great survival value. That is, the sensation of pain protects humans (and other species) from the tissue-damaging effects of dangerous stimuli, and appears to be critical for survival of the organism.

Despite this widespread recognition of the significance of congenital insensitivity to pain in early theory, research, and clinical observations, attention to this phenomenon in current pain scholarship appears to have diminished. There are no references to congenital insensitivity or indifference to pain in the index of the third edition of Bonica’s Management of Pain (Loeser et al., 2001), and in the index of the fourth edition of Wall and Melzack’s (1999) Textbook of Pain only two such references appear, one in a section on biological functions of pain and the other in a section on polyneuropathies with selective loss of pain sensation. This relative lack of interest in recent years in congenital insensitivity to pain among pain specialists is not universal. For example, Wood (1996) observed that insensitivity to pain accompanied by profound small-fiber loss provides evidence of the role of small fibers in pain transduction and transmission, and Mogil (1999) has noted that congenital insensitivity to pain demonstrates that genetic factors can contribute to pain sensitivity.

In this article, we review the conditions that are currently considered types of congenital insensitivity to pain, provide an update on current knowledge about their etiology, and discuss implications of these disorders for understanding pain. We emphasize congenital pain insensitivity, and only briefly mention conditions in which insensitivity to pain is required – for example, from cerebral lesions (Schilder and Stengel, 1931), and in schizophrenia and other psychiatric disorders, poorly characterized phenomena with obscure pathophysiology (Dworkin, 1994).

2. Historical background

Reports of individuals who appeared insensitive to pain from birth onwards have a long history, but it was not until the 1930s that this condition attracted medical attention. Initially, various terms were used to describe these individuals, including ‘congenital general pure analgesia’ (Dearborn, 1932), ‘congenital universal insensitiveness to pain’ (Ford and Wilkins, 1938), ‘congenital universal indifference to pain’ (Boyd and Nie, 1949), and ‘congenital absence of pain’ (Winkelmann et al., 1962). As these labels show, the phenomenon encompasses diverse abnormal responses to pain. Some patients have an absence of response to injury, abnormal autonomic responses to painful stimuli, and difficulties in distinguishing various types of stimuli, whereas others exhibit lack of responsiveness to the stimuli but retain the ability to identify stimulus presence and modality.

Over time, two terms began to predominate in descriptions of these individuals – ‘congenital insensitivity to pain’ (McMurray, 1950) and ‘congenital indifference to pain’ (Jewesbury, 1970). Although these terms were often used interchangeably, in recent years they have acquired distinct meanings and careful authors now use them to distinguish two groups of individuals (Jewesbury, 1970; Landrieu et al., 1990). Patients with congenital insensitivity to pain seem
not to perceive sensations of pain; that is, they have mark-
edly impaired ability to perceive the type, intensity, and
quality of painful stimuli. In those with congenital indiffer-
ence to pain, however, painful stimuli are perceived but
there is an absence of the affective response to pain, rather
than a lack of signal transmission. These individuals report
experiencing sensations of pain but exhibit no aversion to or
withdrawal from painful stimuli.

As soon as careful clinical assessments of congenital
insensitivity to pain were made, attention was drawn to
the role of nervous system lesions in explaining the
phenomenon (Ogden et al., 1959). Criteria were proposed
for congenital insensitivity to pain that excluded individu-
als with acquired lesions that could account for the clinical
presentation. For example, McMurray (1975) proposed
that impairment of pain perception caused by mental retar-
dation or by peripheral neuropathies, infection, trauma, or
toxic agents should not be considered ‘congenital universal
insensitivity to pain’.

With the advent of more sophisticated histological,
microscopic, and morphometric methods for the assess-
ment of nerve fiber pathology, the presence of peripheral
neuropathy became a criterion for diagnosing congenital insensi-
tivity to pain and distinguishing it from congenital
indifference to pain (Dyck et al., 1983). Individuals with
abnormal sensory nerves are now classified as cases of congenital pain insensitivity arising from peripheral neu-
ropathies of various types (Dyck et al., 1983). Many of these
individuals would have been considered to have congenital
indifference to pain in the past.

3. Dimensions of pain

It is widely appreciated that the perception of pain can be
divided into multiple components – including sensory-
discriminative, affective-motivational, and cognitive-
evaluative (Melzack and Casey, 1968; Price, 1999; Treede
et al., 1999). Given these different dimensions of pain, it is
not surprising that insensitivity to pain encompasses a range
of deficits, which include the loss of pain discrimination as
well as the loss of the affective-motivational response. In
the former instance, for example, sharp and dull stimuli or hot
and cold objects cannot be distinguished. Indeed, such indi-
viduals may be able to describe an unpleasant emotional
reaction to a stimulus while being unable to specify the
site of stimulus application (Ploner et al., 1999). The loss
of the affective-motivational response to pain is demon-
strated by patients who are able to perceive the presence
of a painful stimulus, but who show a lack of concern
about it (Ford and Wilkins, 1938; Aguayo et al., 1971;
Berthier et al., 1988), a deficit that is now more commonly
termed ‘indifference to pain’ (Ogden et al., 1959). Such
patients demonstrate no withdrawal response to normally
painful stimuli and may sustain burns or other injuries with-
out noticeable reaction. Alternatively, a patient may display
a negative emotional response to a stimulus, but not object
to repeated stimulus application (Landrieu et al., 1990).

There are two major ascending pathways that make
different contributions to the various components of pain
perception; the lateral pain system that projects through
specific lateral thalamic nuclei to the somatosensory cortex
and the medial pain system that projects through medio-
thalamic nuclei to the anterior cingulate cortex and insula
(Treede et al., 1999). The lateral system subserves the
sensory-discriminative component of pain, whereas the
medial system is associated with the affective response to
a painful stimulus, as suggested by the results of imaging
studies in which stimulus unpleasantness is manipulated
while intensity is held constant. Lesions will therefore
have different effects on pain perception depending on
their location. Loss of peripheral afferents would be
expected to cause deficits in both the sensory discrimination
of pain and in the affective response to it. A relatively loca-
lized abnormality, such as a lesion to a specific brain region,
might selectively impair only one component of the proces-
sing of a painful stimulus and cause a more subtle deficit in
pain perception.

4. Current understanding of hereditary and congenital
pain insensitivity syndromes

Children with underlying peripheral neuropathies have
impairment in both the sensory-discriminative and affective-
motivational components of pain perception. The majority of
them have a type of hereditary sensory and autonomic neuro-
pathy (HSAN). These disorders are characterized by loss of
pain sensation and other sensory or autonomic abnormalities
(Dyck et al., 1983; Thomas, 1993). At present, five types of
HSAN have been identified (see Table 1). All HSAN that
produce abnormalities of pain sensation have involvement
of the small-diameter C and A-delta fibers that transmit pain
sensation. Although each HSAN is characterized by a different
pattern of sensory and autonomic dysfunction, the field is
currently moving away from classification based on clinical
presentation toward classification based on underlying genetic
abnormality.

Across the HSAN spectrum, patients have remarkable
features, such as painless burns (Aguayo et al., 1971), finger
and toe mutilation (Van Epps and Kerr, 1940), and joint
injuries (Swanson, 1963). Case reports suggest a loss of
multiple aspects of pain perception – patients often have
difficulty judging stimulus type and intensity, do not express
an aversion to painful stimuli, and do not attempt to prevent
painful stimuli from recurring. In many cases, the gene
responsible has been localized and candidate genes have
been investigated. Unfortunately, there are currently no
cures for these conditions.

4.1. HSAN I (hereditary sensory radicular neuropathy)

HSAN I, the most prevalent type, is an autosomal domi-
<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Sensory deficits</th>
<th>Autonomic deficits</th>
<th>Reflexes</th>
<th>Tissue damage</th>
<th>Nerve fibers affected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HSAN I</strong> Hereditary sensory radicular neuropathy</td>
<td>Distal loss of pain sensitivity Distal loss of thermal sensitivity Distal proprioceptive deficits Distal light touch deficits</td>
<td>None known</td>
<td>Absent/weak</td>
<td>Severe ulceration of extremities Painless injuries</td>
<td>All (smaller diameters affected more)</td>
</tr>
<tr>
<td><strong>HSAN II</strong></td>
<td>Distal loss of pain sensitivity Distal loss of thermal sensitivity Distal proprioceptive deficits Distal light touch deficits</td>
<td>None known</td>
<td>Absent/weak</td>
<td>Severe ulceration of extremities Painless injuries</td>
<td>Myelinated fibers</td>
</tr>
<tr>
<td><strong>HSAN III</strong> Riley-Day syndrome Familial dysautonomia</td>
<td>Diffuse pain insensitivity Diffuse thermal insensitivity</td>
<td>Excessive sweating Absent/weak Defective lacrimation Postural hypotension Recurrent fevers Feeding problems</td>
<td>Corneal ulceration Painless injuries</td>
<td>Unmyelinated fibers Large myelinated fibers</td>
<td></td>
</tr>
<tr>
<td><strong>HSAN IV</strong> Congenital pain insensitivity w/ anhidrosis</td>
<td>Diffuse pain insensitivity Diffuse thermal insensitivity</td>
<td>Anhidrosis Recurrent fevers</td>
<td>Weak/normal Ulceration of extremities Painless injuries Self-mutilation</td>
<td>Unmyelinated fibers Small myelinated fibers</td>
<td></td>
</tr>
<tr>
<td><strong>HSAN V</strong></td>
<td>Distal pain insensitivity Distal thermal insensitivity</td>
<td>None known</td>
<td>Normal</td>
<td>Ulceration of extremities Painless injuries</td>
<td>Small myelinated fibers</td>
</tr>
</tbody>
</table>

nant neuropathy that begins with a distal loss of pain and temperature sensation that can progress to impairment across all sensory modalities (Wright and Dyck, 1995). Loss of sensation is greatest in the lower limbs, and patients often develop recurring foot ulcerations, beginning in the second through fourth decades of life. This late onset helps distinguish it from other HSANs that present in infancy. Bone fragments may be shed through the ulcer and the amputation of toes may be necessary. Loss of temperature sensation can lead to painless burns. Reflexes are absent in affected areas and deficits in touch and pressure sensation may also develop as the disease progresses. In some kinships, deafness (Wright and Dyck, 1995) and lancinating pain (Denny-Brown, 1951) are also present. Autonomic involvement is usually minor and limited to urinary dysfunction and reduced sweating in the feet.

Examination of peripheral nerves shows losses of all diameters of axons, with the greatest loss being C and A-delta fibers, as one would predict (Lambert and Dyck, 1975). There is degeneration of the dorsal root ganglia and dorsal columns (Denny-Brown, 1951). Nerve conduction studies show reduced (Lambert and Dyck, 1975) or absent (Wright and Dyck, 1995) sensory nerve action potentials. HSAN I maps to human chromosome 9q22, and the gene encoding a subunit of serine palmitoyltransferase is mutated in patients with the disorder (Bejaoui et al., 2001).

4.2. **HSAN II**

HSAN II presents with diffuse impairment of discriminative touch and pressure sensation (Ohta et al., 1973), with variable involvement of other sensory modalities (Parks and Staples, 1945; Ogryzlo, 1946). Onset is in infancy, with deficits appearing in a glove-and-stocking pattern. Patients with HSAN II may be unable to manipulate small objects, lace shoes, or retrieve objects from pockets in clothing (Ogryzlo, 1946; Ohta et al., 1973). Lack of pain perception can lead to ulcers, painless fractures, and joint injuries. Although the extremities show the most severe deficits in all modalities, loss of touch may extend outside of these areas. Pain insensitivity is evident, varying from complete loss of sensation, typically in the lower extremities (Ogryzlo, 1946), to diminished, but present, sensation (Parks and Staples, 1945). Complaints of chronic pain are rare in HSAN II (but can occur in patients with HSAN I).

In HSAN II, sural nerve biopsies show a severe loss of myelinated fibers with relative preservation of unmyelinated fibers (Winkelmann et al., 1962), correlating with greater clinical loss of touch rather than pain. Compound action potential measurements from the sural nerve show absent A-beta and A-delta potentials and a diminished C potential (Ohta et al., 1973). HSAN II is believed to have an autosomal recessive mode of inheritance. HSAN II has also been
called ‘Morvan’s syndrome of uncertain cause’ (Parks and Staples, 1945).

4.3. HSAN III (familial dysautonomia, Riley-Day syndrome)

Patients with HSAN III display widespread autonomic dysfunction combined with loss of pain and temperature perception (Axelrod et al., 1974; Axelrod and Pearson, 1984). Abnormalities are evident in infancy, beginning with difficulties in feeding and incidents of elevated body temperature. Hypoactive tendon reflexes, abnormal tearing, and pain insensitivity also appear early. Fungiform papillae on the tongue are absent. This, along with an Ashkenazi Jewish ancestry, allows a clinical diagnosis to be made. Autonomic abnormalities are numerous, including lack of a flare in response to intradermal administration of histamine or scratching, pupil contracture in response to methacholine, and postural hypotension. Although the ability to produce overflow tears is lacking, increased sweating may be observed.

Individuals with HSAN III may manifest the painless injuries common to pain insensitivity syndromes, but self-mutilation is less evident than in HSAN II, IV, and V (Dyck et al., 1983; Axelrod and Pearson, 1984). There is a severe loss of unmyelinated fibers but total absence of large-diameter myelinated neurons (Aguayo et al., 1971) in HSAN III patients. HSAN III is an autosomal recessive disorder occurring primarily in Ashkenazi Jewish populations, and approximately half of all patients die before age 30 (Axelrod and Abularrage, 1982).

4.4. HSAN IV (congenital insensitivity to pain with anhidrosis)

HSAN IV is an extremely rare autosomal recessive disorder. Pain insensitivity and autonomic deficits are present, but touch and pressure sensitivity are unimpaired. The first sign of this disorder is recurrent episodes of elevated body temperature in infancy (Swanson, 1963). Mental retardation is usually present. Pain insensitivity is manifested in biting of the tongue and hands or in painless fractures, bruises, and cuts. Autonomic abnormalities include the inability to sweat in response to heat or chemical stimuli (e.g. pilocarpine) and the production of a wheal but not a flare after intradermal histamine injection (Swanson, 1963).

Individuals with HSAN IV show an absence of unmyelinated fibers and losses of small myelinated fibers (Rosenberg et al., 1994). Skin biopsy has demonstrated absence of epidermal innervation and loss of most dermal innervation as well as accompanying loss of unmyelinated and thinly myelinated fibers from the sural nerve; sweat glands show no innervation (Nolano et al., 2000). The condition is caused by autosomal recessive mutations and polymorphisms in the TRKA gene on chromosome 1 that encodes the receptor tyrosine kinase for nerve growth factor (NGF) (Indo et al., 1996). Inability to transduce NGF into growing sympathetic and sensory neurons leads to death of this subset of neurons of neural crest origin that is NGF dependent.

4.5. HSAN V

In HSAN V, pain and temperature insensitivity are evident in childhood, with the occurrence of painless fractures, ulcers, and burns (Dyck et al., 1983). Self-mutilation, typically manifesting as biting of the lips and tongue, has also been observed in these patients. Although pain and temperature sensitivity are deficient, proprioception and sensitivity to touch, pressure, and vibration are unaffected (Low et al., 1978). The autonomic manifestations are variable, with minimal autonomic abnormalities in one case (Low et al., 1978) and blotching, abnormal sweating, difficulties with feeding, and elevated temperatures in another (Dyck et al., 1983).

There is a severe loss of small myelinated fibers with a possible decrease in the number of unmyelinated fibers (Low et al., 1978; Dyck et al., 1983). Because of the selectivity of the deficits in HSAN V, it has been argued that these individuals would have been considered cases of congenital indifference to pain prior to the ability to assess peripheral nerve morphology (Dyck et al., 1983). Other individuals with similar characteristics have been reported (Axelrod and Pearson, 1984).

5. Congenital indifference to pain

With these insights into the basis of pain insensitivity, stoics will patiently await the unravelling of the genetic basis of the clinically less pressing, but philosophically more interesting problem of congenital indifference to pain. – John Wood, 1996

Congenital indifference to pain, also referred to as congenital universal insensitivity to pain, has been reported since the early 1930s (Dearborn, 1932; Ford and Wilkins, 1938; Boyd and Nie, 1949; McMurray, 1950; Ogden et al., 1959; Landrieu et al., 1990; Davis et al., 1998). These individuals typically have painless injuries beginning in infancy, but normal sensory responses on examination. Perception of passive movement, joint position, and vibration is normal, as are tactile thresholds and light touch perception. The ability to distinguish sharp and dull stimuli and detect differences in temperature seems to be intact (McMurray, 1950; Ogden et al., 1959). Reflexes and autonomic responses are also normal.

Peripheral nerve samples were obtained from several of the earlier cases of congenital indifference to pain, and no abnormalities were observed (Ogden et al., 1959). Because of their seemingly normal neurologic examinations, these individuals were considered to have a deficit in the affective response to pain rather than in the sensory discrimination of painful stimuli. However, because morphometric analysis of nerve fiber size density had not been performed, it is unclear
whether selective loss of nerve fibers was present. There have been mixed results with some biopsies reported as abnormal (Low et al., 1978; Dyck et al., 1983) and it is possible that some cases are HSAN V. Because of the possibility of peripheral neuropathy, these cases are therefore not considered definitive examples of indifference to pain (Dyck et al., 1983; Thomas, 1993).

A case of congenital indifference to pain with normal nerve morphology has been described by Landrieu et al. (1990). The patient was a 5-year-old girl with painless fractures and indifference to 'casual injuries'. Withdrawal reflexes and grimacing were present to pinprick and hot water (43°C), but she was indifferent to prolonged or repeated application of the painful stimuli anywhere on her body. Subcutaneous injection of histamine yielded normal results. She had an otherwise normal neurological examination. She detected pinprick, heat, and cold, and responded normally to light touch, joint position, vibration, and pressure. Her reflexes were normal, no autonomic abnormalities were observed, and cortical sensory evoked potentials were normal. A sural nerve biopsy appeared normal using electron microscopy, and the size density distributions appeared normal for both myelinated and unmyelinated fibers. In addition, she was reported to have normal psychomotor development.

The normal electron microscopic nerve morphometry rules out the possibility of a selective absence of unmyelinated nociceptors, although it does not exclude the possibility of other structural or neurochemical abnormalities. This patient demonstrates that congenital indifference to pain does not require the same type of peripheral nerve abnormalities associated with the hereditary sensory neuropathies. As Thomas (1993) has suggested, such patients 'could represent a disturbance affecting neurotransmitters that did not involve loss of nerve fibers, or ... the differences could be due to an abnormality of the central sensory pathways or processing'. Additionally, the case suggests that abnormal pain responses can occur even though pain discrimination, affect, and withdrawal responses appear preserved.

Davis et al. (1998) described a subject with normal perception of pinprick, light touch, and vibration. In addition to lifelong lack of pain perception with accompanying painless injuries, she had gait disturbance and spasticity. Sural nerve biopsy and electrophysiologic studies were normal. At age 56, she had progressive decline in cognitive abilities. Autopsy conducted at age 62 showed evidence of Alzheimer's disease and thalamic gliosis at multiple levels, including both ventral and midline nuclei. The amount of gliosis exceeded that found in age-matched normal brains and in an Alzheimer's disease control brain. Other family members were reported to have similar symptoms, including a lack of response to painful stimuli. Although complicated by the presence of other neurologic symptoms, this report suggests that deficits present in hereditary pain insensitivity and indifference disorders can have central as well as peripheral origins.

6. Asymbolia for pain and related conditions

When lesions occur in the areas of the brain that subserve the processing of painful stimuli, deficits in one or more of the components of pain perception can occur, and disorders similar to congenital pain insensitivity can result. Lesions in the anterior cingulate cortex or insular cortex impact the medial pain system and, thus, might be expected to cause a loss of the affective-motivational component. Lesions in the primary and secondary somatosensory cortex affect the lateral pain system; their expected major effect would be loss of sensory-discriminative components of pain.

Loss of the affective-motivational component of pain has been called 'asymbolia for pain'. An early report described a patient who showed a lack of responsiveness to strong electrical currents and physically threatening gestures (Schilder and Stengel, 1931). Although there was some reaction to pain, no withdrawal responses occurred, and the patient at times 'even seemed to derive some pleasure' from the painful stimuli. The authors described both the 'pain reaction' and the 'appreciation of pain' as inadequate, and attributed pain asymbolia to findings of parietal lobe lesions in this patient and two others who were studied.

Later authors restricted use of the term 'asymbolia for pain' to patients with deficits in the affective-motivational component of pain but preserved sensory discrimination. Such patients perceive painful stimuli but lack emotional responses and withdrawal movements (Berthier et al., 1988). As in the earlier descriptions, some patients reportedly smiled or laughed in response to noxious stimuli. Computed tomography demonstrated insular cortex lesions in all patients in a series of six such patients (Berthier et al., 1988). Lesions in the secondary somatosensory cortex could have explained a lack of response to painful stimuli, but no such abnormalities were found in two of these patients.

It is also possible that central lesions could impair the sensory-discriminative components of pain while sparing affective-motivational components. Ploner et al. (1999) describe a patient with a lesion in the primary and secondary somatosensory areas subserving the left hand. He had normal heat pain thresholds in the right hand, but did not perceive pain in the left hand, even at temperatures much higher than those used on his unaffected side. He showed deficits in the assessment of both stimulus localization and quality in the left hand. When offered a list of prompts including both painful and non-painful thermal descriptors, the patient would not use any of them to describe the stimulus, nor could he locate the stimulus more specifically than 'between fingertips and shoulder'.

However, when stimulus intensities equal to and greater than what he considered painful on the unaffected side were administered to the left hand, the patient described a 'clearly unpleasant' feeling that he wanted to avoid. This finding suggests that the affective-motivational component of pain was intact and is consistent with the lateral pain system,
which includes the somatosensory cortex, being more involved in the sensory-discriminative component of pain than in pain affect. This case also illustrates that it is possible for pain responses to occur without an intact sensory-discriminative system.

7. Conclusions

The deficits present in the different pain insensitivity syndromes provide insight into the complex anatomical and physiological nature of pain perception. Reports of pain insensitivity and related cortical conditions illustrate that there can be losses that independently involve either the sensory-discriminative component or the affective-motivational component of pain perception, thus highlighting their different anatomical localization. The presentations of congenital indifference to pain and pain insensitivity overlap, which suggests that indifference to pain — whether congenital or acquired — may involve one or more deficits preferentially affecting the components of the medial pain system, which includes the anterior cingulate cortex.

By affecting both the lateral and medial pain systems, the peripheral nerve abnormalities observed in individuals with the various types of HSAN cause deficits in both components of pain perception. The case of Pioner et al. (1999) demonstrates that the affective-motivational component can be retained even in the absence of the sensory-discriminative component. Importantly, this suggests that the absence of affective responses in individuals with HSAN is not simply a consequence of loss of sensory discrimination but also involves loss of input to the medial pain system caused by the peripheral neuropathy.

It has been proposed that the affective component of pain is not unitary and consists of at least two stages, an immediate primary stage and a cognitively-mediated second stage (Price, 1999). In the cases reviewed, it is unclear at which stage the observed deficits originate. Careful assessment of the separate components of pain sensory intensity and unpleasantness in patients with various congenital pain insensitivity and indifference disorders will help to further clarify the pathways underlying the different components of pain perception. In addition, mapping genetic defects in HSAN patients will provide important clues about molecular mechanisms of pain, and the promise of new, more effective and selective therapies.

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References


