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Focus Article

Congenital Insensitivity to Pain: A Misnomer

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Abstract: **Congenital insensitivity to pain is an umbrella term used to describe a group of rare genetic diseases also classified as hereditary sensory autonomic neuropathies. These conditions are intriguing, with the potential to shed light on the poorly understood relationship concerning nociception and the experience of pain. However, the term congenital insensitivity to pain is epistemologically incorrect and is the product of historical circumstances. The term conflates pain and nociception and, thus, prevents researchers and caregivers from grasping the full dimensions of these conditions. The aims of this article were to review the epistemological problems surrounding the term, to demonstrate why the term is inaccurate and to suggest a new term, namely, congenital nociceptor deficiency. The suggested term better reflects the nature of the conditions and incorporates current understandings of nociception.**

Perspective: ***The umbrella term congenital insensitivity to pain conflates pain and nociception, which is epistemologically unacceptable. We suggest a new term, namely, congenital nociceptor deficiency, that overcomes this problem and is concordant with current neurobiological knowledge.***

Key words: *Congenital insensitivity to pain, pain, nociception, nociceptor, experience.*

Congenital insensitivity to pain (CIP) is an umbrella term used to describe a group of rare genetic diseases, also classified as hereditary sensory autonomic neuropathies (HSAN). Studying CIP and its different genetic variants has the potential to advance medical science and promote a better understanding of nociceptors and their role in the pain experience.

Throughout history, there have been many case reports of individuals who exhibited exceptional tolerance to noxious physical stimuli that would be interpreted as painful by most people. The earliest scientific description of a sensory neuropathy appeared in Leplat's medical dictionary in 1846.[13] However, the first true description of CIP appeared nearly a century later in 1932 in a report by Dearborn.[7,17] In that article, Dearborn described a case of a person from Prague named Edward H. Gibson, who was a stage performer also known as the human pin cushion. Throughout his life, Gibson sustained numerous dramatic noxious injuries, such as an axe lodged in his temporal bone, a gunshot wound in his index finger, a burnt hand, and a broken nose, all without apparent vocalizing or showing other evidence of being in pain. In his later life as a stage performer, he was known for performing extreme acts such as asking up to 50 people to stab him with needles and also to be crucified. No doubt Dearborn's case attracted the attention of the medical community, because other case studies followed it identifying various clinical presentations.[5,16,17,21] Although Dearborn used the term congenital pure analgesia, several other terms were being used to describe the same phenomena (eg, congenital universal indifference to pain[21] and congenital absence of pain[16]) until around the 1970s or 1980s, when the term CIP was ultimately assigned to describe a group of distinct congenital neuropathies.

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Aims

The aims of this paper were to identify problems surrounding the current term and to suggest a new term that better reflects the nature of the conditions and does not conflate pain with nociception. A new umbrella term may help to create innovative approaches to studying CIP in an appropriate context.

Clinical Aspects of CIP

CIP are often diagnosed in infancy or early childhood owing to the lack of expected emotional responses associated with actual tissue damage.[11] Some phenotypes of CIP are diagnosed in early infancy by abnormal deficiencies of the autonomic nervous function (ie, anhidrosis, recurrent pyrexia, defective lacrimation, and feeding problems). One remarkable aspect of CIP is that, on clinical examination, the sensory responses seem to be unimpaired.[17]

There are currently 5 different types of HSANs classified under the umbrella term of CIP.[17] Each type is associated with unique pathoanatomical features and varied expression of impairments. However, over the years several methods of classification have been suggested for CIP.[8,18,22] The first generally accepted classification was suggested by Pinsky and DiGeorge in 1966.[18] Developments in genetics owing to the discovery of DNA a decade before and improvement of histologic techniques allowed CIP to be identified as a disease of peripheral and sometimes autonomic nerves. Because other phenotypes of CIP were later identified, the classification required updating. That classification offered by Dyck[8] in 1984 is still accepted and used today. This classification identifies 5 distinct phenotypes of CIP that are all autosomal recessive, apart from HSAN 1, which is autosomal dominant.

Hereditary Sensory Radicular Neuropathy

Hereditary sensory radicular neuropathy (HSAN 1) usually appears between the second and fourth decades of life. HSAN 1 affects all nerve fiber types. The clinical and sensory deficits that characterize this condition are diminished or absent reflexes, distal loss of proprioception, light touch, and sensitivity to noxious thermal stimuli.

HSAN 2

The onset of HSAN 2 is in infancy. HSAN 2 affects all myelinated fibers. The clinical and sensory deficits that characterize this condition are diminished or absent reflexes, distal loss of proprioception, light touch, and sensitivity to noxious thermal stimuli.

HSAN 3

HSAN 3 (Riley-Day syndrome, familial dysautonomia) is typically detected in infancy owing to wide ranges of deficiencies. HSAN 3 affects both unmyelinated fibers and large myelinated fibers. The autonomic deficits include hyperhidrosis, defective lacrimation, postural hypotension, recurrent fevers, and feeding problems. The reflexes might be diminished or absent and the sensory deficits include a diffused inability to detect noxious stimuli and a diffused thermal insensitivity.

HSAN 4

HSAN 4 is a rare presentation of CIP. HSAN 4 is typically diagnosed in infancy owing to autonomic dysfunctions of anhidrosis that leads to repeated episodes of pyrexia. Intellectual disability is sometimes present. HSAN 4 affects both unmyelinated fibers and small myelinated fibers. The reflexes might be diminished or absent and the sensory deficits include a diffused inability to detect noxious stimuli and a diffused thermal insensitivity.

HSAN 5

HSAN 5 is autosomal recessive and is typically diagnosed at childhood after trauma. HSAN 5 affects only the small myelinated fibers and is characterized by distal insensitivities to noxious and thermal stimuli.

The formal medical documentation of CIP case studies in the early twentieth century contributed extensively to the expanding knowledge base of pain science. In their 2003 report, Nagasako et al[17] stated that, "Although the significance of CIP is well acknowledged, unfortunately, it appears that interest in the condition has diminished." That still seems to be the case because the CIP conditions are hardly mentioned in the new editions of the main textbooks of pain science cited by Nagasako et al.[10,14] Reasons for this relative neglect are the rarity of the disorder and the scarcity of patients available for research. The exact prevalence of the disorders categorized under the CIP umbrella is unknown and the current estimate is 1 case in a million people.[19]

Biological Aspects of CIP

It is apparent that the common denominator of all the CIP phenotypes is the deficiency of nerve tissue, either peripheral or autonomic. When examining the known biology of CIP under the microscope of modern neuroscience, it is evident that the underlying problem occurs at the level of the nociceptors.

Life expectancy for patients with CIP is unfortunately very short. This observation was used as an evolutionary and teleological argument by pain theoreticians who declared pain is an "alarm" and "important for survival."[17] We argue here that this conclusion is epistemologically flawed, because nociceptors and spinal reflexes are the actual alarm mechanisms and they are indeed flawed in CIP, which in turn leads to the shortened life expectancy observed.

Pain and the Problem of Language

The problem of language in conveying a person's pain experience is a frequently discussed topic in the pain literature.[4,6,9,15] The use of accurate and nonambiguous

terminology in pain research and science is extremely important and has major implications for patients, caregivers, science, and society and should not be taken lightly.[1,3]

As is made clear in the current definition of the International Association for the Study of Pain, pain is both a sensory and an emotional experience.[2] This experience cannot be reduced to either a sensation or an emotion; moreover, pain should never be conceived of as a stimulus. On these epistemological grounds, we suggest that the term CIP inadvertently conflates pain and nociception. Moreover, on logical grounds, we ask, how can anyone be insensitive to an experience that has never been felt by that person? In our opinion, the literature concerning CIP makes it evident that the term itself is the source of the problem. It causes a circularity that portrays pain as "a thing" that one is obliged to feel or should feel. This same issue is evident in the many articles about CIP that use inaccurate terminology when describing psychophysical tests that refer to the stimuli as painful and to CIP nociceptive deficiencies as a loss of pain sensitivity. This issue is not unique to the CIP literature. Another example is the term pain processing.[20] How can pain, an experience, be processed if it is always the outcome of the processing of all sensory and other inputs that preceded the experience? Finally, another example is that of centralized pain, which suggests an anatomic location of pain within the central nervous system.[12] Because there is no actual pain system in the body and pain is not a thing, how then can it be located anatomically?

In the case of CIP, it seems that early observers of the clinical phenomena biased the understanding of patients with CIP to accord with the then prevalent view of pain neurobiology (ie, the hard-wired nervous system). On the one hand, there are patients with CIP who have never experienced pain associated with nociception and who are now certain that any other of their emotions are not in fact pain. In contrast, some researchers have been led to believe that all that there is to learn about CIP are the physical aspects of these conditions. A testimonial to this situation is the lack of qualitative studies of the experiences of patients with CIP. Without such studies, it is premature to conclude that these people do not experience pain.

Conclusions

We argue that the term CIP is epistemologically incorrect. The term conflates pain and nociception and, thus, prevents researchers and caregivers from grasping the full dimensions of the conditions. Our suggestions for future research are either to refer to the CIP conditions using the generic term HSAN, or to adopt a new umbrella term, namely, congenital nociceptor deficiency. We recommend the former suggestion and believe the proposed term better reflects the nature of the conditions, as well as incorporating the current understandings of nociception and pain.

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