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ORIGINAL ARTICLES

The Association of Olfactory Impairment with Charcot Neuroarthropathy and Possible Links to Causation

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Background: Charcot neuroarthropathy (CN) is a devastating complication of some diseases affecting the peripheral nervous system. Initial subjective and objective presentation of the disease can be variable. Common among all presentations seems to be uncontrolled inflammation yielding dislocations and/or fractures. The exact cause remains the subject of much debate.

Methods: Our study retrospectively looks at the function of olfactory function in consecutive patients with CN and compares the findings with a nonaffected population. The University of Pennsylvania Smell Identification Test was used to assess olfaction and document microsomia.

Results: Twenty consecutive patients presenting with CN demonstrated significant ($P < .0001$) microsomia when compared to an unaffected population with diabetes.

Conclusions: Microsomia is strongly associated with CN. This finding may be correlated to voltage-gated sodium 1.7 channel impairment and appears to be a candidate precursor for the development of CN. (J Am Podiatr Med Assoc 112(5), 2022)

Charcot neuroarthropathy (CN) is a relatively rare yet devastating complication of some diseases affecting peripheral nerve function. It is a progressive condition of the musculoskeletal system characterized by joint dislocations, pathologic fractures, and potentially debilitating deformities. Syphilis was believed to be the primary cause until 1936, when diabetes was recognized as another causative factor.[1] Diabetes is now considered to be the most common disease associated with CN.[2] Charcot neuroarthropathy manifests as progressive destruction of bone and soft tissues typically in weightbearing joints but also in nonweightbearing joints such as carpal bones, shoulders, knees, and spine.

The initiating event leading to onset of CN appears to be varied. Patients in our clinics have variously reported minor trauma, major trauma including surgery, no trauma, chronic arthralgia, increased activity, infection, and acute arthralgia as the initiating events. When referred acutely, we have again recognized varied objective initial findings including isolated dislocation of a single foot bone without any significant bone edema on magnetic resonance imaging; global bone edema on magnetic resonance imaging within the majority of the tarsus with or without preservation of cortices; localized bone edema with loss of cortices in the metatarsal phalangeal, midtarsal, tarsal, and talotibial joints; or combinations of the above.

Multiple families have at least two generations with confirmed CN affecting between two and four individuals over those generations. The pathogenesis of CN has been the subject of much research. Repetitive microtrauma, autonomic dysregulation, receptor activator of nuclear factor kappa-B ligand (RANKL) activation,[3] and small fiber neuropathy[4] have been discussed as possible precursors.

Several years ago, we were approached by two families with children aged 5 and 12 years diagnosed with CN, and their clinical information did not seem to fit into any of the existing theories. One child had a diagnosis of congenital indifference to pain (CIP),[5] and the other had a hereditary sensory and autonomic neuropathy (HSAN), which also renders them insensitive or indifferent to pain.[6]

A thorough review of current literature revealed 18 recognized gene mutations that may lead to either CIP or one of the HSANs. Two of these mutations are also associated with short lifespans and the presence of CN is not reported. Fifteen of the

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mutations result in CN at some point in the child's early life.[6-16] One mutation has never been associated with CN. That curious fact has led to this current study and subsequent theory for the pathogenesis of CN. Based on experience treating CN in over 1,200 patients with ages ranging from 5 to 82 years, we now question the role of voltage-gated sodium 1.7 channels ($Na_v1.7$) in the pathogenesis of CN.

Sodium channels are membrane proteins made up of a large α subunit and smaller β subunits. The α subunit forms the voltage-sensitive and ion-selective port in the membrane. Currently, nine isoforms of the sodium channel α subunit are recognized ($Na_v1.1$–$Na_v1.9$). $Na_v1.7$ is encoded by the gene *SCN9A* and is of critical importance in the role of pain sensation.[17]

$Na_v1.7$ is predominantly expressed in the dorsal root ganglion (DRG) and sympathetic ganglion neurons. The majority of DRG neurons that express $Na_v1.7$ are pain-sensitive or nociceptive neurons. The $Na_v1.7$ channels seem to act as a sort of amplifier of voltage from pain signals sent from the peripheral sensory axons, enabling a relatively weak signal from a painful stimulus to be amplified adequately to transmit along pain pathways to the central cortex. In this way, $Na_v1.7$ serves as a molecular gatekeeper of pain detection from peripheral nociceptors.[17-19]

The inflammatory mediators prostaglandin, adenosine, and serotonin affect the electrophysiologic properties of $Na_v1.7$. These mediators increase the magnitude of the pain current, leading to the recognition that inflammation can sensitize nociceptive neurons. Experimental deletion of $Na_v1.7$ in nociceptors results in minimally altered heat-induced pain, mechanical pain, and cold-evoked pain. However, in those same models, there is a failure to produce pain in response to inflammatory stimuli, whereas neuropathic pain remains intact.[17,20]

Also associated with loss of $Na_v1.7$ expression is an up-regulation of an endogenous opioid system, leading to increased pain thresholds. Correspondingly, naloxone significantly reduces analgesia in CIP patients.[21]

Although the Nav1.7 channel is primarily expressed in the DRG and sympathetic ganglia, it has also been discovered in more noncanonical roles in the so-called nonexcitable cells, including chondrocytes, islet β-cells, fibroblasts/keratinocytes, and blood cells. Experimental models inhibiting $Na_v1.7$ function in these types of cells produces decreased insulin release from the islet β-cells, decreased adenosine triphosphatase in keratinocytes, decreased macrophage phagocytosis, and impaired migration of lymphocytes, all of which play important roles in inflammatory and proliferative phases of wound healing.[22,23]

The CIP and HSAN literature encompasses study of children and adults afflicted worldwide. Congenital indifference to pain was first associated with a missense mutation of the *SCN9A* gene causing a complete loss of function of $Na_v1.7$.[24] Interestingly, these children have an inability to discern smells or anosmia. Another site at which the $Na_v1.7$ channel is predominantly expressed was subsequently recognized, and it is in the olfactory bulbs, where it is integral to smell discernment.[25] A validated test for this loss of smell is the University of Pennsylvania Smell Identification Test (UPSIT) that has normalized values for all ages[26] and has been studied in diabetes and insulin resistance.[27]

In this study, we examine the correlation of smell impairment in patients presenting with CN and compare that function to patients without CN. Our hypothesis is that impairment of smell discernment (microsomia) is a precursor to development of CN. The primary aim of the study was to determine whether there was microsomia in CN patients. Our secondary goal was to compare that result to a population of people with diabetes but without CN. An observational study of 20 consecutive patients referred to our clinic with confirmed Eichenholtz stage 0 to 2 CN was undertaken and was compared to existing normative data.

Methods

Institutional review board approval was obtained through the Memorial Hospital and Healthcare System (Jasper, Indiana) for an observational study of 20 consecutive patients referred to our clinics with confirmed Eichenholtz stage 0 to 2. Informed consent was obtained.

All patients were subjected to our standard history and physical examination. The neurologic portion of our examination includes deep tendon reflexes, sharp/dull, hot/cold, Wartenberg wheel, Babinski reflex, clonus, dysmetria, dysdiadochokinesia, cranial nerves, Tinel sign, Mulder sign, straight leg raise, 10-g monofilament, and allodynia evaluation. Laboratory studies ordered included complete blood cell count with differential, chemistry panel, hemoglobin A1c, antinuclear antibodies, rheumatoid factor, serum B_{12} and folate, serum protein electrophoresis, and erythrocyte sedimentation

rate. Neuropathy was diagnosed based on a multiplicity of signs and symptoms. No control group was possible, as there is no current mechanism to predict who will and will not form CN in the future.

All patients were administered the 40-item UPSIT evaluation within their initial treatment course. Exclusion criteria included recent nasal trauma or inability to perform the test unassisted (n = 0). The UPSIT published testing and scoring protocols were followed. Results were tabulated at the completion of enrollment. Test subjects had various causes for their peripheral neuropathy, including diabetes, alcoholism, and idiopathic causation. Active and historical tobacco smoking, duration of diabetes, type of diabetes, height, weight, body mass index, hemoglobin A1c, and location of CN were also documented.

Statistical Analysis

Statistical analysis was performed using MedCalc statistical software (MedCalc Software Ltd, Ostend, Belgium). Mean and standard deviation with 95% confidence level were computed. Significance was defined as $P < .05$.

Results

Ages ranged from 42 to 71 years, with a mean of 57.88 ± 6.77 years. Seventeen subjects had diabetes of 2 to 30 years' duration, with a mean of 14.71 ± 4.36 years. Those same patients had a hemoglobin A1c value of 6.2 to 11.6 mg/dL, with a mean of 8.26 ± 0.79 mg/dL. Heights of all subjects ranged from 61 to 74 inches, with a mean of 67.69 ± 1.82

Table 1. Compiled Reported CIP and HSAN Findings

Type	Subtype	Gene	Onset Age	CN?	NCV/EMG	ENFD	QST	Autonomic	Motor	Sural Biopsy	Nerve Description
CIP		*SCN9A*	Early	Yes	N	N[a]	V	N	N	N	Normal myelinated and unmyelinated
HSAN	1A	*SPTLC1*	20–40	Yes	A	A	N*	V	A	A	Normal myelinated, ↓ unmyelinated
	1B	NR	20s	NR	NR	NR	NR	V	NR	A	—
	1C	*SPTLC2*	50+	NR	A	A	A	V	A	A	↓ myelinated, normal unmyelinated
	1D	*ALT1*	20+	NR	NR	NR	NR	V	NR	NR	NR
	1E	*DNMT1*	20–30	NR	A	NR	A	V	V	V	NR
	1F	*ALT3*	14–35	Yes	A	NR	A	V	N	A	NR
HSAN	2A	*WNK1*	Early	Yes	[b]	N	A	V	N	A	Normal myelinated, ↓ unmyelinated
	2B	*FAM134B*	Early	Yes	[b]	NR	NR	V	N	A	Normal myelinated, ↓ unmyelinated
	2C	*KIF1A*	Early	Yes	[b]	NR	NR	V	N	A	Normal myelinated, ↓ unmyelinated
	2D	*SCN9A*	Early	Yes	[b]	NR	NR	V	N	A	Normal myelinated, ↓ unmyelinated
HSAN	3[c]	*ELP1*	Early	Yes	A	NR	A	A	A	A	↓myelinated, ↓ unmyelinated
HSAN	4	*NTRK1*	Early	Yes	A	A	A	A	N	A	Normal myelinated, ↓ unmyelinated
HSAN	5	*NGFB*	Early	Yes	A	NR	N[e]	V	N	A	Abnormal small fiber
HSAN	6	*DST*	Early	[d]	A	NR	NR	A	NR	NR	NR
HSAN	7	*SCN11A*	Early	Yes	N	NR	N	A	N	A	Normal myelinated, ↓ unmyelinated
HSAN	8	*PRDM12*	Early	No	A	A	N	N	A	A	Loss of A delta fibers
NR	NR	*CLTCL1*	NR	Yes	NR	NR	N	NR	N	NR	NR

Abbreviations: A, abnormal; CIP, congenital indifference to pain; CN, Charcot neuroarthropathy; ENFD, epidermal nerve fiber density; HSAN, hereditary sensory and autonomic neuropathy; N, normal; NCV/EMG, nerve conduction velocity/electromyography; NR, not reported; QST, quantitative sensory testing; V, variable.

[a]One case with decreased findings.

[b]Preserved motor but reduced sensory potentials.

[c]Neuropathy spares palms, soles, genitalia.

[d]Not reported because of early death.

[e]Mechanical and vibration normal, hot/cold abnormal.

inches; and weight ranged from 148 to 305 pounds, with a mean of 215.25 ± 19.25 pounds. That yielded a body mass index range of 24.4 to 47.8 kg/m^2, with a mean of 33.17 ± 3.16 kg/m^2. The location of CN on initial presentation was in the midtarsus (n = 15), tarsus (n = 2), and ankle (n = 3).

All patients were diagnosed with neuropathy based on a multiplicity of signs and symptoms. The existing cause for their neuropathy was taken from primary care medical records and our laboratory and physical examination. It was as follows: diabetes type 2 (n = 16), alcoholism (n = 2), idiopathic (n = 1), and diabetes type 1 (n = 1).

Smell discernment was evaluated with the UPSIT. Of the 20 test subjects, 19 of 20 demonstrated microsomia ranging from mild to severe on the UPSIT evaluation. One patient scored at the lowest level to still be considered normosmia. The CN patients scored 30.75 ± 1.564 on the UPSIT test. This correlates with mild to moderate microsomia. The patients with diabetes (n = 1,215) scored 37 ± 3, indicating normosmia. A comparison of means between all patients with CN and patients with diabetes but without CN yields a difference of 6.25 (95% CI, 4.96 to 7.56; $P < .0001$).

Discussion

Olfactory impairment is one of the signs of $Na_v1.7$ loss. There is no available test to examine the DRG of living patients for loss of $Na_v1.7$ channels. However, the presence of microsomia seems to point to this particular sodium channel as a possible precursor for CN. In addition, other voltage-gated sodium channels may be impaired, as demonstrated by patients with HSAN1 to HSAN8, so a thorough review of their unique disease was undertaken. Our extensive literature review regarding CIP and HSAN1 to HSAN8 objective and clinical findings is summarized in Table 1. T1

The effects on the nervous system are varied. Some have autonomic dysfunction, whereas others do not, yet they all develop CN. Nerve conduction velocity/electromyography, epidermal nerve fiber density, sural biopsy, and quantitative sensory testing (QST) evaluation when performed yields a widely variable picture across the different gene mutations. For example, the *SCN9A* mutation preserves all nerve conduction velocity/electromyography, epidermal nerve fiber density, autonomic, sural biopsy, and QST normal findings.[28] However, some of the HSAN types will have pathologic findings in one or all of those same studies. This leads us to conclude that the peripheral axon damage seen in neuropathies is not a necessary precursor to CN.

Many of the gene mutations produce an anatomical effect yet unrecognized. Of those that are recognized, a discussion of HSAN7 and HSAN8 seems paramount to the understanding of CN pathogenesis.

HSAN8 children do not develop CN.[29] They have a *PRDM12* gene mutation. The *PRDM12* gene directs nociceptive sensory neuron development by regulation of nerve growth factor receptor tropomyosin receptor kinase A. All nociceptors require tropomyosin receptor kinase A and its ligand nerve growth factor for their survival and maturation during development.[30] These children have normal olfaction, quantitative sensory testing evaluations (yet unable to recognize painful extremity temperatures), autonomic function, but absent corneal reflexes and inability to sense pain.[31]

HSAN7 children do develop CN and have a mutation of *SCN11A*, causing a gain of function or upregulation of $Na_v1.9$. They have no loss of $Na_v1.7$ channels. No clinical or neurophysiologic signs of peripheral neuropathy are observed, yet no peripheral pain is perceived. This seems contradictory to our findings, because HSAN7 children do develop CN.[28] The specific variant (p.L811P) of *SCN11A* causes gain of function of $Na_v1.9$, leading to hyperexcitability. This hyperexcitability of $Na_v1.9$ floods

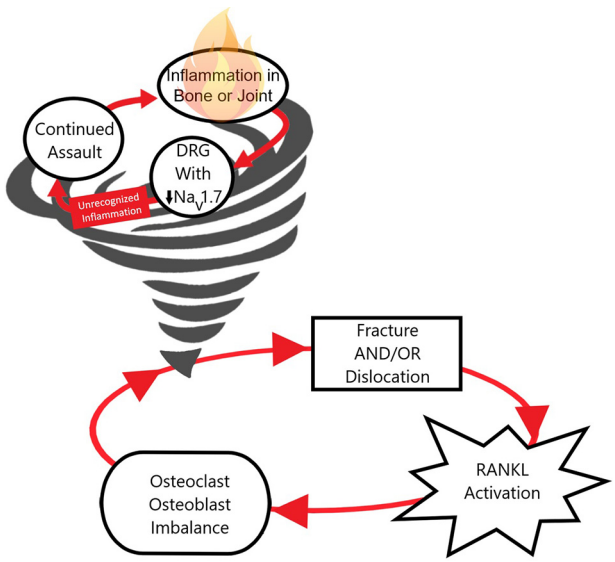

Figure 1. Unrecognized inflammation caused by impaired $Na_v1.7$ function activates receptor activator of nuclear factor kappa-B ligand, leading to progressive destruction in Charcot neuroarthropathy. DRG, dorsal root ganglia; $Na_v1.7$, voltage-gated sodium 1.7 channel; RANKL, activator of nuclear factor kappa-B ligand.

the $Na_v1.7$ channel with input, rendering it constantly depolarized and unable to respond to inflammatory stimuli in the DRG. In that way, the up-regulation of $Na_v1.9$ renders the $Na_v1.7$ unable to respond, so again the $Na_v1.7$ seems to be a viable precursor candidate site for damage leading to CN.[32]

Early unremitting inflammation seems to be a hallmark of CN. It features elevated levels of cytokine production with an emphasis on tumor necrosis factor-α and interleukin-1β. This triggers an overproduction of RANKL. Receptor activator of nuclear factor kappa-B ligand is an essential cytokine in the formation and activation of osteoclasts, which are found in abundance in CN. Osteoprotegerin (OPG) has been identified as a key regulator of bone remodeling acting as a decoy receptor for RANKL. In this way, OPG helps balance osteoclastic activity. The theory is that in times of unremitting inflammation, an overproduction of RANKL exceeds the capacity of OPG to limit osteoclast production.

It has also been theorized that there may be a genetic predisposition to forming CN. In fact, a single nucleotide polymorphism (SNP) altering OPG has been identified in CN, potentially creating an imbalance in the RANKL/OPG system. However, real-time quantitative polymerase chain reaction evaluation of subjects having diabetes with and without CN divided into with and without neuropathy and healthy control was published that demonstrated no significant relation between RANKL/OPG gene expression ratio and CN. It was suggested that "an alternative pathway for osteoclastogenesis exists" and that there is a "need for a broader genetic study into the molecular mechanism of CN."[3]

A study of *SCN9A* gene mutations in a general population of asymptomatic individuals is also important to consider. Three hundred nine Han Chinese women with matched age, education, and socioeconomic backgrounds were studied to investigate the association of SNP in *SCN9A* and the relation of these to pain perception. The assays captured 100% of the allelic variations in 119 SNPs across the gene. A second replication group of 260 subjects confirmed the findings. The identified allele frequency (prevalence, 5.5%) associated with SNP rs16851778 resulted in lower pain sensitivity ($P = .003$).[33]

Conclusions

Our observations lead us to the following candidate theory for the precursor to CN: A predisposed population with hereditary SNPs of *SCN9A* resulting in decreased function of $Na_v1.7$[33,34] can be critically impaired by various disease states that additively harm the $Na_v1.7$ channels. That combination of factors depleting $Na_v1.7$ combined with any inflammation-causing event may lead to unrecognized progression of injury. The unremittent inflammatory cascade up-regulates the RANKL pathway (Fig. 1). F1

This explanation may explain how various initial presentations of CN are found, from isolated dislocations (soft-tissue pathology only) to global bone edema and progressive bone destruction. It also may explain various initiating events, such as minor or major trauma or any condition causing inflammatory abnormality in or near joints.

This theory assumes a homogeneous cause for CN, and this may be a serious limitation. Furthermore, olfactory impairment may have causes other than $Na_v1.7$ impairment. Follow-up study looking for SNPs of *SCN9A* consistently associated with CN are planned in a retrospective and prospective fashion in a U.S., Ecuadorian, and Colombian population.

As CN is associated with diminished ability to discern smells, the UPSIT protocol may be a viable screening test for at-risk patients having diseases causing peripheral neuropathy. Microsomia would be an indication of a person at risk for CN, and patient counseling could be initiated.

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