● History Article

From Neuralgia to Peripheral Neuropathic Pain: Evolution of a Concept

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"A rheumatic affection of the nerves follows the course of the nerves, the pain is numb and of an aching kind, generally constant but occasionally exasperated by paroxysms; this invariably increases by pressure."[1]

During the 19th century, clinicians elucidated the characteristic features of pain of presumed peripheral nerve origin and classified it as "neuralgia." This clinical presentation and pathophysiology have been the subject of heated debate over the past 200 years.[2,3] Though it is now accepted that a primary lesion in the peripheral nervous system can cause persistent diffuse pain and other aberrant sensations when there are no objective neurological deficits or abnormalities found on laboratory tests,[4] some clinicians still infer psychogenesis.[5,6]

In this report we trace the dynamic history of the concept of neuralgia as it has evolved into that of peripheral neuropathic pain. We also show how the seeds of psychogenesis came to be planted in the minds of generations of skeptical physicians, and present historical and current competing constructs.

Neuralgia

Clinical Features

The clinical characteristics that defined neuralgia were described by pioneering neurologists of the 19th century,[7-11] and these descriptions remain accurate.[12] Neuralgias were characterized by spontaneous and/or paroxysmal pain felt in the cutaneous or deep distribution of an involved sensory or mixed nerve, or corresponding to the anatomical course of the nerve trunk or its branches. Pain spread into the distribution of other nerves of the same limb, and even to that of corresponding nerves of the opposite limb.[13] When asked to trace the distribution of their pain, sufferers indicated the affected nerve(s) with reasonable accuracy.[7] Their pain was more severe at those points where nerves passed through fibro-osseous tunnels or around bony prominences.[10]

The descriptors used for pain varied according to its intensity, and included "burning," "aching," "boring," "darting," "shooting," "tearing," and "cutting."[7] In the acute presentation, pain tended to be spontaneous and almost continuous. Accompanying sensations, such as tingling, numbness, and perception of cold were commonly felt in the cutaneous region supplied by a sensory or mixed nerve. Chronic pain tended to be "dull and wearying," and was commonly interspersed with attacks of great severity.[7] In both acute and chronic conditions, body movements or postures likely to cause tension or pressure on the nerves invariably exacerbated the pain.

Numerous other sensory perceptions were also described. Increased cutaneous sensitivity (hyperesthesia) was a very common accompaniment of the pain. In this context, Gowers[7] defined hyperesthesia ("or more properly hyperalgesia") as "the transformation into pain of sensations that are not usually painful" (in current terminology, this phenomenon is known as allodynia[14]). The state of heightened sensitivity could also involve deep structures, such as bone, "so that first attention may not be directed to the nerve."[9]

The coexistence of diminished cutaneous sensation and "violent spontaneous pain and tenderness on pressure" was said to be an early feature of peripheral nerve dysfunction.[10] Vasomotor and trophic disturbances were also frequently noted. Weakness of muscle contraction to avoid pain (an-

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Accepted for publication January 27, 2001.

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1098-7339/01/2604-0017$35.00/0
doi:10.1053/rapm.2001.23676

talgic inhibition) was common, but discernible muscle wasting was rarely detected.

Pain evoked by palpation of a tender nerve trunk in a limb was usually felt locally but could also radiate quite widely, often in both proximal and distal directions. Other more circumscribed "tender points" could be found in locations such as where nerves branched to cutaneous targets, or over the vertebral spinous process at the level of an involved spinal nerve.[8] On occasion, swelling of a tender nerve trunk was detectable.[7]

Innovative hypotheses were offered for the symptoms. Pain and other sensory phenomena that were felt in the cutaneous distribution of a sensory nerve were said to reflect irritation of sensory fibers traveling within the nerve.[7] Explanations were that either an irritative lesion of these fibers intensified sensory impressions passing by it, or that the lesion could "exalt" the irritability of the related part of the cerebral cortex. Pain produced by light touch to the skin (allodynia[14]) was attributed to oversensitive nerves of common sensibility.[7] Interestingly, these ideas are consistent with our current concepts regarding mechanisms of peripheral neuropathic pain,[15] including postaxotomy mechanical sensitivity[16] and spurious neuronal discharge,[17,18] and central sensitization.[19]

Pain and tenderness that extended along the course of nerve trunks was attributed to an inflammatory process spreading from the site of the original pathology (hence the term "interstitial neuritis"). The temporal discovery of the intrinsic innervation of the nerve sheaths (nervi nervorum) supported this concept. The nervi nervorum was observed to possess end organs consistent with sensory and proprioceptive function, which could be localized to the nerve trunk.[20,21] It was subsequently argued that any inflammatory process involving a peripheral nerve could potentially excite the nervi nervorum and produce "true peripheral neuralgia."[11] Henceforth, neuralgia was attributed to "increased sensitiveness" or "irritation" of the nervi nervorum,[7] even though nerve inflammation/irritation was usually an a priori supposition.

It was thought that symptoms propagated to the contralateral nerve trunk(s)[7,10] were caused by an abnormal state of "irritation" of the inflamed nerve that induced subtle changes within the central nervous system of those so predisposed (producing so-called "central neuroses"). The hypothesized state of "increased action of the sensory centres" was thought to assume a "morbid independence," leading not only to cutaneous hyperesthesia but also to persistent pain and tenderness of nerve trunks.[7] While these ideas are also consistent with contemporary concepts,[15] the belief that certain persons were predisposed to neuralgia[7] also planted the seeds of psychogenesis.

Only recently has this symptom complex[22] been subdivided into "nerve trunk pain" and "dysesthetic pain," based on their hypothesized etiological differences;[23] this distinction essentially is made in the early descriptions. Using current taxonomy, nerve trunk pain refers to the deep and aching pain that may extend along the course of nerve trunk, which is invariably tender. As before, the proposed etiology involves the intrinsic innervation of the nerve sheaths, called the nervi nervorum.[24] By contrast, dysesthetic pain is variously described as "burning," "tingling," "raw," "searing," "crawling," "drawing," and "electric," and is felt superficially in the cutaneous area innervated by the involved sensory or mixed nerve. The pathogenesis of these symptoms is thought to be more complex, but is dependent on axonal damage, ectopic axonal sensitivity, and/or central sensitivity changes.

Terminology and the Seeds of Psychogenesis

From the time of its coining in the early 19th century, neuralgia was misused and misunderstood. Literally meaning "pain in a nerve," it was originally used as a descriptive generic term for all painful disorders attributed to peripheral nerves. Neuralgia was classed as a disease and placed in the category of "neuroses" or "nervous affections."[25] This placement was probably related to the concept that certain people were predisposed to neuralgia, implicating the psychological makeup of the sufferer.

In the middle of the 19th century, the German neurologist Romberg classified nervous diseases according to whether they were disorders of sensibility or disorders of motion.[26] The neuralgias were then placed among the "hyperesthesias," but in his later writings Romberg used the terms neuralgia and hyperesthesia interchangeably.[27] Therefore, in addition to its original denotation as a symptom of peripheral neuropathy, the term neuralgia was used to denote a painful "functional" disorder of the nervous system.[7] To make matters worse, the diagnosis was typically one of exclusion, made in the absence of clinical evidence of a primary lesion of the peripheral or central nervous system; thus, most neuralgias were considered idiopathic, though some were linked to amputations and other direct injuries to peripheral nerves.

Perhaps because of the taxonomic schism, neuralgia became a term open to easy abuse. For example, obscure pains in the chest, abdominal, and pelvic regions were grouped together as "neuralgic affections" or "visceral neuralgias," appearing more

frequently in women, and usually as accompaniments of (then-called) hysteria[28] and neurasthenia.[29] It was firmly believed that many of these painful presentations were psychogenic.[30]

Later in the 19th century, neuropathological studies showed that inflammatory processes, both acute and chronic, could involve all components of peripheral nerves. This supported a true organic process underlying symptoms of neuralgia. To separate diseases due to this process, the term "neuritis" was introduced for cases where the symptoms were chronic and localized to the distribution of a certain nerve trunk that was found to be painful and tender.[9] Clinicians conceptualized neuritis as being caused by the extension of extraneural inflammatory processes. Gowers[31] proposed that a sterile inflammatory process of muscles ("fibrositis") could spread and invade the sheaths of adjacent nerve trunks. Such inflammation could remain perineural (involving only the nerve's sheath), or could spread to the interstitium of the nerve and impair its conductivity.[31] Interstitial neuritis became an acceptable diagnosis for idiopathic lesions thought to involve a single peripheral nerve. However, when the diagnosis of "neuritis" began to appear with increasing frequency on medical certificates issued to those with alleged physical incapacity due to pain, the dearth of documented "organic" changes in these patients suggested that their symptoms were really manifestations of a chronic anxiety state.[32]

Of course, nerve inflammation was then, as now, difficult to prove. The clinical diagnosis of neuritis (as opposed to neuralgia) eventually became dependent on the finding of associated neurological deficits indicating organic disease of peripheral nerves.[7] When the existence of interstitial neuritis as a distinct pathological entity was doubted, the term eventually disappeared from clinical usage. Modern use of the term neuritis carries the admonition that it should not be used unless "inflammation is thought to be present"[14]; unfortunately, methods of detection remain rudimentary in practice, and nerve inflammation typically remains a presumption.

In an attempt to correct the error in nomenclature that occurred early in the last century, Wechsler[33] argued that because most cases of "neuritis" were in fact caused by peripheral neural degenerative changes in the absence of inflammation, "neuropathy" was a more appropriate terminology. Neurologists have since adopted this denotation (e.g., mono-, plexo-, or poly-neuropathy) for virtually all diseases of peripheral nerves, with the exception of tumors.[34]

More recently, Fields[35] recommended the use of the term "neuropathic pain" for pain that results from dysfunction within the nervous system, without regard for its site of origin (central or peripheral) or its etiology. Devor and Rappaport[22] then introduced "peripheral neuropathic pain" for pain attributable either to a primary disturbance of nerve function or to pathology involving a peripheral nerve. Because current hypotheses suggest that central neurophysiological changes (central sensitization) frequently accompany peripheral nerve lesions,[12] it may be impossible to make such a distinction when the etiology is unknown. However, the current terminology reflects major advances in neurobiology and a better appreciation for the complexity of the somatosensory system.

Competing Constructs

The often ill-defined nature of the symptoms of peripheral neuropathic pain, as well as the relative lack of objective findings, led to numerous concepts that urged psychologically dependent etiologies. This legacy continues, and the comparison between ideas of the 19th and 20th centuries is illuminating.

Historical

As was the case for many other poorly understood pain syndromes in the 19th century,[3] there were speculative psychogenic explanations for neuralgia. For example, women who were unmarried, or married but barren, were thought predisposed to neuralgia by virtue of their "irritable, hysterical or nervous habit."[25] Neuralgia was said often to be the first indication of an "enfeebled" nervous system.[36] It could be found as a purely psychical condition, called "psychalgia,"[37] which was increased by mental and emotional causes, and relieved by suggestion and distraction.[38] The belief that psychical factors can induce chronic regional pain syndromes and mechanical allodynia remains one that is still widely canvassed.[2]

When Gowers proposed that a sterile inflammatory process of muscles ("muscular rheumatism") could spread and invade the sheath of nearby nerve trunks ("interstitial neuritis"), he united the competing musculoskeletal pain models of the 19th century into that of "fibrositis."[31] Nerve trunk tenderness was still being attributed to involvement of the nervi nervorum in this construct, and diffuse pain and cutaneous hyperesthesia to irritation of the sensory fibers traveling within the nerve.[39] The proposed inflammatory process could also result in degeneration of conducting nerve fibers, producing sensory and motor deficits. Muscles and joints within the sensory area of the involved nerve could also be tender, making it impossible to determine

whether these tissues were primarily involved, or the site of referred pain and tenderness. Notwithstanding this fundamental epistemological problem, it appears that many peripheral neuropathic pain syndromes were subsumed by the construct of "fibrositis."[39] When this diagnosis eventually fell into disrepute,[3] sufferers were left without a credible diagnosis.

Current

A more recent thesis continues the historical tendency to ascribe poorly understood symptoms and responses to psychogenic factors. Ochoa[40] has warned against the indiscriminate use of the term neuropathic pain for symptoms where careful multidisciplinary evaluation provided "evidence of absence of nerve dysfunction, explicit evidence of brain-mind origin for their neuromuscular symptoms, and, often, abnormal psychological profiles." He argued that these patients are best categorized (and treated) as suffering from "psychogenic pseudoneuropathy," a "legitimate disorder" said to be centered in the psyche. While these conclusions are based on clinical observations, there are numerous flaws in interpretation. First, it was proposed that the features suggesting psychogenic pseudoneuropathy include otherwise inexplicable muscle weakness, nondermatomal hypoesthesia, and areas of cutaneous hyperalgesia not confined to nerve or nerve root territories. Many such symptoms can be understood in terms of normal variations of peripheral nerve anatomy, antalgic inhibition, and the current data and concepts regarding convergent projections and physiology of primary afferents. Second, it was suggested that an important feature of regional pain syndromes mimicking neuropathy was the reversal of hypoesthesia by placebo or local anesthetic injection, demonstrable in a diverse group of chronic pain patients where objective neurological tests failed to provide evidence of nerve damage sufficient to explain their often gross and intractable symptoms.[41] While many of these patients may have had psychological bases for their pain, one should remember that conventional electrodiagnostic examinations have many limitations, one being their inability to infer symptoms and neuropathic deficit.[42] Moreover, the pinprick and light-touch tests that manifested the proposed psychogenesis are subjective in both their application and verbal, response-based interpretation. Finally, the patients, doctors, and treatment all carried elements contributing to a potent placebo potential[43] (indeed, the response itself deserves study). We should consider potential ramifications of labeling placebo-responsive symptoms "psychogenic;" while by definition this is always true, it carries a negative connotation and stigma.

Without entering the debate of organic versus psychogenic pathophysiological entities, we make the plea that patients who present with "nerve trunk" pain in the absence of sensory or motor deficit should not be ipso facto categorized as suffering from "psychogenic neuropathy." It is quite possible that we do not as yet have the tools to detect the problem.

Conclusion

The modern concept of peripheral neuropathic pain has ancestral roots in poorly defined clinical presentations and erratically used terminology. However, our forebears, who "stood in much need of the touchstone of pathological anatomy,"[10] are to be applauded for their pathophysiological insights. Relatively recent collaborative efforts between clinicians and scientists have helped remove the hazy nomenclature from symptoms associated with peripheral neuropathy,[14] resulting in rapid advancements in knowledge related to this malady. It is now possible to offer reasonable neurobiological explanations for the long-observed clinical phenomena that can be labeled peripheral neuropathic pain. Thus, peripheral neuropathic pain remains a valid clinical entity and, as such, deserves a rightful place in the deliberations of modern pain medicine. Nonetheless, the topic continues to be the subject of strong and often opposing views.

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