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Commentary

Development of CRPS after shingles: It's all about location

Although the goal of medicine is to cure disease, effective treatment of the symptoms that the patient notices requires that the clinician identify their underlying cause – namely the diagnosis. Without a diagnosis, clinicians can only palliate the symptoms and hope that the actual disease resolves on its own. The 20th century brought great advances in understanding disease pathophysiology. For instance, we learned that seemingly identical coughs can have causes as diverse as infection, cancer, heart failure, or asthma, each requiring different diagnostic and therapeutic responses. Moving beyond symptoms to pathogenic diagnosis enabled development of diagnostic tests and disease-modifying treatments of such efficacy that prescribing cough syrup became irrelevant. In the 21st century diagnostic accuracy looms even larger as treatment decisions become increasingly complex, factoring in clinical-trial and data-mining results, not to mention cost considerations. As we enter the era of individualized medicine, in which computers will be necessary to perform these multivariate treatment decisions, accurate diagnosis will be paramount (viz. "garbage in (to the computer), garbage out").

However fundamental it may be, diagnosis can be challenging when the major symptom is pain. Given pain's subjective nature and widespread expression, the causes of pain symptoms are often uncertain. The same pain can signal conditions ranging from trivial to fatal. One of the most elusive pain syndromes is complex regional pain syndrome (CRPS), previously known as causalgia and reflex sympathetic dystrophy. CRPS consists of chronic limb pain that is disproportionate in severity and duration to the causal injury. For CRPS, the Freudian-era attribution of unexplained symptoms to psychopathology lingered to the end of the 20th century – surprising given that CRPS includes not only pain but also hard-to-fake objective signs including edema, abnormal bone metabolism, and disordered sweating.

Pathophysiological understanding of CRPS began in the early 21st century with recognition that peripheral nociceptive axons ("small-fibers") have efferent and trophic actions in addition to pain signaling function, as demonstrated in the small-fiber-predominant polyneuropathies [9]. Discovering small-fiber-predominant axonal injuries in CRPS-I patients explicated many of the non-pain as well as pain features of CRPS [1,11,15] and invalidated the distinction between CRPS-II (with known nerve injury) and CRPS-I (without known nerve injury) [10]. Discovering the prevalence of motor-system and brain dysfunction provided additional evidence that CRPS is a neuropathic disorder caused by neurological injury [7,12]. The role of microvasculopathy also came into focus–not only as an independent pain generator, but also for causing tissue hypoxia and malnutrition, which hinders recovery and spreads CRPS. Contributions of inflammation and immunity were also recognized, initially as caused by neurogenic inflammation and microvessel leakiness. The subsequent discovery that surgery (and presumably other traumas as well) can trigger painful autoimmune peripheral neuropathies [13], that some CRPS patients have anti-neuronal antibodies [6], and that immunomodulatory treatments effective for autoimmune polyneuropathies also effectively treat CRPS [4], pointed to a potential contribution of trauma-triggered autoimmune neuropathy.

But why do some patients develop CRPS after injuries while most do not? Insights into this question come from approximately 15 case reports of CRPS caused by shingles (zoster) (reviewed in [2]) and a new detailed study of a patient with multiple CRPS features including bone-scan abnormalities, all caused by shingles affecting the hand and thus part of post-herpetic neuralgia (PHN) [3]. An earlier prospective study reported that among 17 patients with PHN affecting an arm or leg, 8 had 3–5 CRPS symptoms, but no one with PHN of the head or torso had any CRPS symptoms [2]. The literature on PHN/CRPS overlap proves beyond doubt that CRPS is a phenotype, a cluster of signs and symptoms, rather than an actual diagnosis with a single cause, as PHN is. It also informs about the 10% of CRPS patients without a history of external trauma [16]. No doubt mild or inapparent zoster (*sine herpete*) underlies other CRPS-I cases, meaning that patients with acute, atraumatic CRPS, particularly after age 40, should be considered for serological testing for zoster and antiviral treatment. Recognizing PHN when it presents as CRPS enables use of PHN-tested medications [5] and even suggests that this type of CRPS could be prevented by immunizing against zoster. Because shingles does not infect the bone or microvessels, but rather the sensory ganglia, roots, and peripheral nerves, the PHN/CRPS cases additionally establish that nerve injury alone is sufficient to trigger a panoply of CRPS signs.

Last but not least, the PHN/CRPS cases emphasize that anatomical location of the inciting injury influences who develops the CRPS phenotype, or as real-estate agents say –location, location, location. Although zoster and PHN are most common on the torso or head, I suggest that the CRPS endophenotype of PHN does not develop in such cases because these regions have extensive collateral circulation and low hydrostatic pressure. In contrast, the distal limbs have limited, vertical blood vessels. Gravity facilitates blood entry, but fluid must overcome hydrostatic pressure to exit. No wonder the feet are the most common location for edema and microcirculatory disorders of all causes including CRPS and other neuropathies. The anatomic location of a nerve injury is apparently a significant but unrecognized determinant of whether the CRPS or "plain pain" phenotype develops.

Strengthening of the association of CRPS with underlying peripheral-nervous system injuries – zoster in this case – shows the need to recategorize CRPS as a phenotype like cough, rather

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than as an etiologic diagnosis such as tuberculosis, and to dig further to expose CRPS-causal diagnoses, particularly in patients without trauma. Other internal CRPS causes include neuromas, ganglia, and nerve entrapments, which may require surgical treatment [14]. It also highlights the need to eliminate the 4th criterion from the IASP definition of CRPS-I; "diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction" [8]. It is becoming evident that all patients with the CRPS phenotype have underlying and potentially treatable diagnoses if we look hard enough. The patients deserve no less.

Conflict of interest statement

There are no conflicts of interest to report.

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