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Letter to the Editor of *Pain* on Jørum et al: Catecholamine-induced excitation of nociceptors in sympathetically maintained pain; *Pain* 2006

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The pearl in this “neuropathic” pain patient, studied by Jørum et al, is activation of three nociceptors in hyperalgesic skin by reflex sympathetic maneuvers and by ID norepinephrine. What does it mean?

The medical nature of this patient

For the authors, this chronic pain patient has “SMP,” a condition which “is first and foremost associated with CRPS.” The reader wants to know what kind of “CRPS.” Was there nerve pathology? This is impossible to resolve because the clinical description is incomplete. Burning pain was reported in peroneal nerve territories, but neurological examination did not include motor system nor reflexes; motor nerve conduction were normal and the electromyogram did not show signs of muscle denervation. Moreover, the area of subjective hyperalgesia was in bilateral stocking; no sensory deficits are described; sensory nerve conduction was normal (correcting for a 1.5°C cooler Left leg) and subjective thermal thresholds by QST were non specifically impaired. Thus, a case cannot be made for neuropathy (nor peripheral inflammation). Could this be a pure small caliber fiber neuropathy? Unlikely because, in acute local compression syndromes, the primary nerve lesion spares small caliber fibers (Ochoa et al, 1971). In sum, the cause of the patient’s symptom complex is not known. Therefore, he officially fits “CRPS I,” a concept disabled by non sequitur, particularly in its criterion #4, one that evades refutability principle when it states: “This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction” (see Ochoa and Verdugo, 2001). The enlightened scholar invited to introduce the latest book on CRPS, edited by Wilson et al (2005) wrote: “The fourth criterion says that CRPS is a diagnosis that can only be made when another diagnosis cannot be established. This means that if we get better at diagnosing something else, we will reduce the frequency of diagnosing CRPS. Either this entity exists on its own criteria, or it does not and is just a repository for patients who cannot be adequately assessed and labeled” (Loeser, 2005). But there must exist a testable medical explanation for this patient’s non specific symptoms. It will not be found unless differential diagnosis is pursued (Ochoa, 2006). The authors did not. It might even be an ill characterized, structurally-based peripheral neuropathy.

The Clinical “SMP”

As per the shallow criterion: “SMP are all pain syndromes that can be relieved by sympathetic blockade” (Treede et al, 1991), this patient qualified as his pain complaint was eliminated for

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1½–21 days following various blocks. But in absence of placebo control, the SMP assumption is scientifically invalid because too many chronic pain patients communicate temporary relief that is demonstrably due to inert or active placebo effect (Verdugo and Ochoa, 1994a; Verdugo et al, 1994; Ramamurthy et al, 1995; Jadad et al, 1995; etc.) and recent work ratifies this (unpublished). At the beginning of Introduction, Jørum et al make a statement that misrepresents cited publications. They write: “the validity of placebo-controlled studies has been questioned.” No, what those articles did question, two of them already in their title, is the concept of sympathetically maintained pain itself (Verdugo and Ochoa, 1994a; Verdugo et al, 1994). In the present case, there was no placebo control for the phentolamine nor the guanethidine blocks. Thus, if SMP exists as a pathophysiological entity, there is no evidence that this patient has it, and he couldn’t possibly if he does not harbor neuropathy.

Psychophysical Evidence of Catecholamine Dependence of this Patient’s Sensory Symptoms

Having adjudicated medical veracity to “SMP,” gratis, Jørum et al briefly analyze prior contradictory publications where (unlike normal volunteers) some patients, with or without prior sympathectomy, labeled with “CRPS-SMP” in absence of rigorous scientific evidential basis, self-reported subjective local pain from ID injection of catecholamines. But there was no placebo/nocebo control and patients of this kind express those twice as frequently as normals (Verdugo and Ochoa 1994b), and a recent article reports absence of catecholamine-evoked pain in painful polyneuropathy (Schattschneider et al, 2006). Contrary to Ali et al (2000), one publication mentions self reported pain following ID catecholamines in the asymptomatic contralateral side (Mailis and Bennett, 2004). Imaginative theories attempt to explain remote spread of pain in “RSD/CRPS I/SMP” on the basis of hypothetical and untestable secondary central neuronal sensitization in those patients (for review, see Ochoa, 2004). But, on what pathophysiological basis do catecholamines injected to asymptomatic contralateral areas evoke contralateral pain and hyperalgesia, if the hypothetical sympathetic/primary nociceptor coupling would require ipsilateral injured and sensitized nerves, and the human brain function of locognosia of nociceptor input is so unilaterally focused (Ochoa and Torebjörk, 1989). Why should there be *de novo* adrenergic sensitivity in a contralateral area without injury to either sympathetic or nociceptor fibers? Self reported symptom spread is only communicated by patients without demonstrable structural pathology underlying their pseudoneurological display (Verdugo et al, 2004). In the present case, there was self reported pain induced ipsilaterally, but there was no control for placebo/nocebo effect either. Therefore, rigorously speaking, the ID catecholamine-induced limb pains are anything but robust evidence in any direction.

Sensitized Nociceptors

The striking finding in the present study was activation by presumed sympathetic reflex discharge, and by ID norepinephrine, of 3 primary nociceptors with receptive fields in the stocking area of self reported hyperalgesia and spontaneous pain. It is easy and necessary to compare this with the effect of inert ID substances in patients, and with ID catecholamines administered to control volunteers, during microneurography. It is also necessary to directly record C sympathetic efferent activity in sites where misbehaving nociceptors are found. In this case, such activity was just not recordable. This is unusual and might reflect ablation of sympathetic post ganglionic C fibers, which would be in keeping with the authors’ final pathophysiological choice, namely denervation supersensitivity of nociceptor fibers to interstitial catecholamines, rather than an effect of local sympathetic neural secretion of catecholamines upon “pain nociceptors.” But it cannot be had both ways. The neural sympathetic reflex secretion that the authors assume in connection with Figure 1, could not

occur in sympathetically denervated areas. Moreover, diagnostic sympathetic blocks could not possibly have abolished SMP in symptomatic areas devoid of blockable sympathetic terminals.

In Summary

The medical nature of this patient remains unknown, and in the possible absence of nerve pathology, he could not have “SMP,” a highly controversial concept anyway. The self reported pain post ID norepinephrine is of debatable significance in this study, and inconsistent in prior studies. If this patient, as the authors propose, has occult nerve pathology and sympathetic denervation supersensitivity behind his painful symptoms, then the sympathetic blocks could not have contributed specifically to symptom relief. Thus, provocative as they are, the refined studies by Jørum et al fail to overcome hurdles that invalidate general resuscitation and individual adjudication of the concept “SMP.”

Perhaps a minority of patients with structural pathology of primary nociceptors might be sensitized to catecholamines, despite Verdugo et al 1994. It is impossible, however, that nociceptors of abundant “CRPS” patients without true nerve fiber dysfunction might express adrenergic sensitization. And yet, many such patients continue to be “treated” with sympathectomy.

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