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## The Challenging Task of Erythromelalgia Therapy

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### Commentary

Chronic pain is one of the most common symptom seen in the clinical practice; it affects about 30% of adults in the world [1] leading to a poor quality of life and a higher risk to develop comorbidities such as depression. Available treatments often produce insufficient pain relief; thus the general therapeutic approach is still a stepwise process aimed to identify which drugs or drug combinations provide the greatest pain relief with fewest side-effects. The difficulty in the therapeutic management of chronic pain stems from the complexity of the pain neuraxis. Three are the pivotal mechanisms that concur to persistent pain: i) sensitization of primary nociceptors within the dorsal root ganglion (DRG); ii) enhancement in the function of spinal interneurons; iii) modulation of the nociceptive signal from the brainstem and higher cortical centers descending pathways [2]. Remarkable cellular and molecular events are also involved in pain transmission and among these a huge transcriptional modification [3], thus pain transmission must be viewed as a highly dynamic process where both, epigenetic and genetic component takes part. Lessons from twins [4,5] and population-based studies [6-8] tell us that genetic risk factors may predict the individual differences in pain thresholds and perception or underlie the etiology of chronic pain conditions such primary erythromelalgia (PE). This disease is a rare clinical syndrome caused by gain-of-function mutations in the SCN9A gene encoding for the Nav1.7<sup>+</sup> sodium channel [9]. Nav1.7 is a transmembrane protein highly expressed in rat and human dorsal root ganglia (DRG), sympathetic ganglia and nociceptive neurons [10-13]. This protein responds to small, slow depolarizations and participates to the generation of action potential, thereby affecting the electrophysiological properties of nociceptive unit.

To date, several SCN9A missense mutations in several families have been recognized as causative agents of PE [14]. The PE mutations affect critical, and therefore highly conserved, amino acid residues at the level of cytoplasmic linkers or transmembrane domains (i.e. F216S and N395K) of the Nav1.7<sup>+</sup> protein. The functional consequence is a hyperpolarizing shift of channel activation, allowing Nav1.7<sup>+</sup> to open at lower potentials. Impairment of deactivation and repriming, has also been described for channels having peculiar PE mutations [14] Each of these alterations can participate to the hyper-excitability of DRG neurons expressing these mutant channels, thus leading to hyperalgesia. Clinically, PE is characterized by severe burning

pain, redness and occasionally swelling, more commonly affecting legs and/or hands [15]. Symptoms are worsened by warmth and longtime standing or exercise. The pain attacks are relieved by cooling, which can become compulsive and result in skin lesions [15]. Treatment of PE is still a challenge in the clinical practice and based on small case series. The therapy is based mainly on support and avoidance of trigger factors. While aspirin shows efficacy in patients with secondary Erythromelalgia caused by myeloproliferative disorders [16] most cases of PE are refractory to pharmacotherapy and the response to pain treatments shows a wide heterogeneity [17]. Several classes of drugs, among these local anesthetics (lidocaine), systemic antiarrhythmics (mexiletine), and antiepileptic drugs (phenytoin or carbamazepine) act as sodium channel blockers and they are commonly used for the treatment of chronic pain including some forms of neuropathic pain. All of them do not possess a high degree of specificity as they inhibit many types of sodium channels instead of exerting a selective blockade of Nav1.7<sup>+</sup>; on the other hand the presence of heavy side effects often limits their usefulness in clinical practice. In addition, several of these drugs have shown limited efficacy in patients bearing mutations in Nav1.7<sup>+</sup> sodium channel. The therapeutic inadequacy relies on SCN9A-linked conformational alterations of the binding site of local anaesthetic agents as revealed by a clinical case report and electrophysiological studies performed on HEK293 cell line transfected with wild type and causative mutant variants of Nav1.7<sup>+</sup> protein [18,19]. Remarkably, some PE mutations reduce the effect on sodium channels of lidocaine, while other PE mutations do not, indicating that the pharmacological response to sodium-channel blockers is related with the specific genotype [19]. In a similar way carbamazepine shows efficacy in the context of PE specific mutations as this drug leads to a normalization of the hyperpolarizing shift in the voltage-dependence of activation produced by the V400M or S241T Nav1.7 mutations [20,21]. Of note a novel approach [22] based on genomic analysis, structural modelling and functional profiling could predict pharmacological responsiveness. A frequently used treatment for PE is mexiletine, an antiarrhythmic drug. Compared to lidocaine this non-selective sodium channel inhibitor shows an improved pharmacokinetic profile because of the fast absorption after oral administration, the long plasma half-life, ranging from 8 to 14 h, and low first-pass effect [23]. Mexiletine was reported to have a degree of efficacy in some young patients although the responsiveness to this drug was temporary [24]. However, a study performed on a

patient bearing V872G mutation demonstrated that the positive response to mexiletine led to a long-lasting improvement of symptoms as this causative mutation increased the use-dependent effect of this drug, suggesting a therapeutic mechanism of mexiletine more important than the tonic block effect [25]. Development of several selective blockers of Nav1.7<sup>+</sup> sodium channels is on-going, and PE is a base for proof-of concept trials [14].

Other drugs that have been proven to relieve symptoms in a limited cases of PE include SSRI (selective serotonin reuptake inhibitors), tricyclic antidepressants, benzodiazepines and sodium nitroprusside, which may be useful in children, and local therapy with midodrine, lidocaine patch and botulinum toxin [14].

In a recent case report [26] we shed light on the efficacy Ziconotide (Prialt) in the management of severe burning pain in a patient with PE refractory to the conventional pharmacotherapy. Ziconotide is the synthetic equivalent of a 25-amino-acid polybasic peptide found in the venom of the marine snail *Conus magus*. The drug selectively blocks the neuronal N-type voltage-sensitive calcium channels at the presynaptic level, thereby inhibiting neurotransmission from primary nociceptive afferents. The efficacy of Ziconotide likely relies on its ability to interrupt pain signalling at the level of the spinal cord. As analgesic drug, Ziconotide produces potent and long lasting effects however; the usage of this peptide is limited by undesirable side effects and route of administration. Indeed, intrathecal Ziconotide can result in severe but reversible psychiatric symptoms and neurological impairment including cognitive impairment, hallucinations, and changes in mood and consciousness [27]. However, a low starting (maximum) dose of 0.5 µg/day and a limitation of dose escalations to no more than 0.5 µg/day, as we performed in our patient (starting dose: 0.3 µg/day, to the dose of 1.2 µg/day), may reduce the adverse effects. The requirement that the drug be administered intrathecally is also extremely limiting due to the invasive surgery and high cost associated with implantable pumps. Importantly, prolonged administration of Ziconotide does not produce the development of addiction or tolerance [27]. Taking into consideration all available data on safety, efficacy, and side effects, morphine, hydromorphone, and ziconotide are equal as analgesic drugs with the exception of the neuropathic pain, in such a case ziconotide should be the first choice.

An intriguing aspect illustrated in our case report is also the finding that intrathecal ziconotide administration in PE leads to a net improvement of lower extremities swelling and edema, two disabling symptoms often associated with this disease. The exact mechanism through which the drug exerts this unexpected effect is still unknown. It can be assumed that in some patients, PE is associated to neurogenic inflammation as reported in various chronic pain conditions [28]. As currently accepted, this process is based on the capability of noxious stimuli to activate peripheral nociceptive nerve endings yielding to action potentials that are conducted by their axons to the spinal cord. However, the action potentials can also retrogradely diffuse into the arborizations of the primary afferent neuron, thereby causing depolarization, dorsal root reflexes and additional

antidromic impulses towards the periphery. This antidromic activity results in the release of vasoactive neuropeptides, such as substance P, neurokinin A, and CGRP, from activated C-fiber terminals producing intense protein plasma extravasation, so called edema, and vasodilation [28]. Ziconotide could inhibit the vasoactive response interfering with the neurogenic inflammatory circuit as this drug controls neurotransmission at the level of many synapses. This novel putative effect of Ziconotide deserves attention for the use of the drug also in Complex Regional Pain Syndrome a painful conditions similar to erythromelalgia and often associated to the swelling of the lower extremities. Treatment of PE is still challenging in the clinical practice and there is a need for improving the therapeutic approach. In this context ziconotide could be a new effective drug in the management of unresponsive PE. The costs associated with preparation of the pump and use of the drug must be balanced within the risk–benefit analysis.

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