Medical Hypotheses 73 (2009) 927–929

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Post herpetic neuralgia, schwann cell activation and vitamin D

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ARTICLE INFO

Article history:
Received 17 June 2009
Accepted 18 June 2009

SUMMARY

While the underlying pathophysiology of herpes zoster infection has been well characterised, many of the mechanisms relating to the subsequent development of post herpetic neuralgia (PHN) remain uncertain. The dorsal horn atrophy and reduction in skin innervation seen in PHN patients does not adequately explain many clinical features or the efficacy of a number of topical treatments. In the central nervous system the glia, their receptors and their secreted signalling factors are now known to have a major influence on neural function. In the peripheral nervous system, schwann cell activation in response to infection and trauma releases a number of neuroexcitatory substances. Activation of the nervi nervorum in the peripheral nervous system also leads to the release of calcitonin gene related peptide, substance P and nitric oxide. Schwann cell and/or nervi nervorum activation could be an additional mechanism of pain generation in PHN. Such a paradigm shift would mean that drugs useful in the treatment of glial cell activation such as naloxone, naltrexone, minocycline, pentoxifyllline, propentofylline, AV411 (ibudilast) and interleukin 10 could be useful in PHN. These drugs could be used systemically or even topically. High dose topical vitamin D would appear to offer particular promise because vitamin D has the ability to both reduce glial inflammation and reduce nitric oxide production.

Background

The management of post herpetic neuralgia (PHN) following the recurrence of a herpes zoster viral infection can be challenging. The underlying pathophysiology of the initial herpes zoster (HZ) reactivation has been well characterized [1]. Initially viral replication causes inflammation in the dorsal root ganglion (DRG) with consequent infection of the corresponding nerves and skin dermatome. Inflammatory processes can involve the dorsal horn of the spinal cord [2]. Necrosis and scarring of the DRG is followed by secondary degeneration and fibrosis of the associated motor and sensory nerve roots. Axonal and myelin damage extends peripherally from the DRG. A decrease in the number of nerve endings in the associated skin dermatome occurs [3,4].

A number of PHN syndromes can then develop:

- A constant, spontaneous, deep-aching, or burning pain.
- A brief recurrent, piercing or electrical-shock-type pain often described as a spasmodic shooting, tic-like pain.
- Allodynia (pain occurring in response to normally innocuous stimuli) and hyperalgesia [5,6].

Chronic itch can also be problematic in some patients [4].

A single mechanism unifying these pain syndromes may prove elusive. The pathophysiology of PHN may involve both peripheral and central mechanisms. Traditional gate-control pain theory teaches that reduced sensory input from large A-β fibre nerves in the skin then allows increased firing from C and A-δ nerves reaching the dorsal horn of the spinal cord which in turn "opens the gate" to a deafferentation type pain. Degeneration of peripheral neurons with resultant hyperexcitability of spinal cord neurons has also been posited. Dorsal horn atrophy is a major feature of PHN patients [2,7]. A reduction in skin innervation density using axonal markers has also been shown to be a feature of HZ [3,4], and these changes are more dramatic in patients with PHN [3]. Histamine responses are reduced or abolished within areas of allodynia and impairment of C nerve fibre function has been correlated with the intensity of post herpetic pain [8].

On the other hand, axonal and myelin loss in the peripheral nerves is similar regardless of whether patients have PHN or not [9]. No difference in substance P, calcitonin gene related peptide, a norepinephrine marker or in opioid receptor binding sites has been found between affected and non-affected spinal cord levels [10]. Moreover the severity of allodynic pain has been correlated with preservation of thermal sensory function [11]. A significant correlation has been found between the intensity of ongoing pain and mechanical allodynia in patients with short lasting (<1 year) PHN, but not in patients with long lasting PHN [12]. Oaklander et al. [13] have also shown bilateral segmental damage to primary sensory neurons with unilateral HZ. Changes in contralateral unaffected skin innervation in patients with PHN correlate with the presence and severity of pain, yet these patients report no pain on the contralateral side.

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doi:10.1016/j.mehy.2009.06.039

Despite the severity of the underlying structural neurological changes, many PHN patients improve by themselves. One prospective long-term follow-up study reported that at one month 19% of the patients had pain, at 3 months 7% and at one year 3%. Once a patient becomes pain free after a zoster episode there is practically no risk of pain recurrence [14]. Another prospective community study reported that at 6 weeks 30% of the patients had pain, at 3 months 27%, at 6 months 16% and at one year 9% [15]. The epidemiological data indicates that despite extensive neural damage not all patients proceed to PHN, and the damage is not irreversible.

Schwann cell activation

Traditional pain research has focused largely on the neurons and the transmission of neural signals. In the central nervous system the glia (oligodendrocytes and astrocytes), their receptors and their secreted signalling factors also influence neural function. Persisting glial inflammation has been implicated in the initiation and maintenance of a number of pain states [16]. In the peripheral nervous system the schwann cells and the satellite cells in the DRG are now recognized as "peripheral glia" sharing many of the characteristics with oligodendrocytes and astrocytes in the CNS (17). Injury to a myelinated axon results in Schwann and satellite cell activation and the release of a number of neuroexcitatory substances, including TNF-α [18–21]. Nerve injury as well as increasing the number of Na^+ channels in injured nerves may also increase in Na^+ channels in schwann cells [22]. The release of these inflammatory mediators is blocked by treatment with anti-inflammatory drugs including dexamethasone [23] and thalidomide [24]. Interestingly in nerve ventral root transection, TNF-α concentrations on both sides of the spinal dorsal horn are increased [24]. This might be a factor in the as yet unexplained reduced innervation on the contralateral side seen in patients with PHN [13].

Nervi and vasa nervorum

All peripheral nerves have an intrinsic nerve and vascular supply. All layers of the nerve are innervated and have a thin, but potentially important plexus of nociceptors. The "nervi nervorum" have the potential to induce neurogenic inflammation [25–27]. Peripheral nerve injury leads to the release of calcitonin gene related peptide, substance P and nitric oxide from the nervi nervorum which upregulates the vascular permeability of the vasa nervorum and neighbouring blood vessels [26]. Activation of the nervi nervorum has been implicated in peripheral nerve pain [27].

Current treatment modalities

Psychotropic drugs and anticonvulsant medications are a cornerstone of PHN treatment. Opioid medication has also been advocated [28]. Tricyclic antidepressants have been utilized either alone, or in combination with other therapies including neuroleptic agents. More recently, gabapentin and pregabalin have been shown to be effective. However the elderly, a group of patients typically affected by PHN, tolerate these medications poorly and the long-term efficacy of these interventions remains unknown [28]. The clinical reality is that as many as half of all patients fail to respond to these medications (alone or in combination) or cannot tolerate their side effects [29].

The efficacy of a number of topical agents indicates that peripheral as well as central mechanisms are important in PHN. Topical lignocaine when used as a 5% gel under an occlusive dressing partially reduces pain and allodynia in PHN. Blood lidocaine level measurements indicate minimal systemic absorption. EMLA cream, an acronym for eutectic mixture of the local anaesthetics lidocaine and prilocaine, is also beneficial in some patients with PHN [28]. Both agents are thought to block upregulated nerve sodium channels thereby reducing pain. These agents could also block the activated Na^+ channels in Schwann cells [22] after nerve injury.

Capsaicin cream has also been shown to be beneficial in both PHN as well as diabetic neuralgia [30], however the cream induces a burning sensation in the skin which makes it difficult to use. This has been interpreted as evidence that nociceptive peripheral axons contribute to PHN pain and allodynia. Capsaicin reduces the levels of substance P, a potent pro-inflammatory peptide, and possibly other neurotransmitters in peripheral sensory nerves. Reduction of substance P levels would also reduce schwann cell and nervi nervorum inflammation. A topical aspirin/diethyl ether mixture has also been shown to be useful in the treatment of PHN [31]. Similar results have been noted with aspirin in chloroform [32]. The analgesic mechanisms remain unexplained using conventional neurological pain theory. However a reduction in schwann cell and possibly nervi nervorum inflammation offers a potential mechanism. Aspirin influences cyclooxygenase mechanisms, which have been implicated in glial cell activation [17].

Vitamin D

Sunlight, particularly ultraviolet B rays, can damage skin setting up an inflammatory reaction. When this is excessive, we experience this as sunburn with a corresponding hyperalgesia. The skin has mechanisms to counter this. The skin creates molecules called proopiomelanocortin derived peptides, which then break down into other hormones, which include melanocyte stimulating hormones (MSH), and β-endorphins which act as a natural painkillers [33]. MSH has powerful anti-inflammatory effects. Alpha-MSH downregulates the production of proinflammatory and immunomodulating cytokines as well upregulating the production of the cytokine synthesis inhibitor IL-10 [34] which is important in reducing glial inflammation. Vitamin D also has similar anti-inflammatory actions. Vitamin D also has an important role in astrocyte "detoxification" pathways. Vitamin D receptors have been located within glial cells. Vitamin D inhibits the synthesis of inducible nitric oxide and increases glutathione and γ-glutamyl peptidase levels in astrocytes. Gamma-glutamyl peptidase is thought to participate in the scavenging of reactive oxygen species [35]. Vitamin D could potentially reduce Schwann cell inflammation. UVB phototherapy in the acute stage of zoster rash reduces the incidence and severity of PHN, however treatment of PHN with UVB radiation after 3 months does not have a significant beneficial effect.

Vitamin D also upregulates nerve growth factor gene expression [35]. Nerve growth factor is produced both in keratinocytes and Schwann cells. In diabetic peripheral neuropathy there is degeneration of Schwann cells and myelinated neuronal fibres as well as a loss of cells within the DRG [36]. The pathological findings are similar to PHN. Animal models of diabetic neuropathy have shown nerve growth factor effective against measures of neuropathy. Phase 1–2 and HIV trials have demonstrated improvements in pain symptoms when recombinant human nerve growth factor has been used, however the phase 3 trial did not demonstrate any therapeutic benefit. The recombinant human nerve growth factor was delivered by subcutaneous injections [37].

Both PHN and diabetic neuropathy respond to topical capsaicin cream. High dose oral Vitamin D has been shown to be effective in the treatment of diabetic neuropathy [38]. Quantitative sensory testing reveals decreased pain sensibility (with or without decreased touch sensibility). The author has also had one vitamin D deficient patient whose post herpetic neuralgia pain was significantly reduced when he was treated for his vitamin D deficiency.

The hypothesis

The hypothesis is that peripheral nerve (schwann cell and/or nervi nervorum) activation and the subsequent release of proinflammatory mediators is a factor in PHN. Such a hypothesis could mean that drugs that block glial cell activation could potentially be useful in the treatment of PHN. These drugs include naloxone, naltrexone, minocycline, pentoxifyllline, propentofylline, AV411 (ibudilast) and interleukin 10 [39].

Vitamin D would appear to have considerable potential. Parallels can be drawn with diabetic neuropathy, which responds to high dose oral vitamin D as well as topical capsaicin. The potential production of NGF in the keratinocytes and possibly the Schwann cells is an additional advantage. From an evolutionary perspective we were designed to get most of our vitamin D through the skin. Sun exposure produces vitamin D levels in the blood equivalent to a daily oral intake of 10,000–25,000 IU vitamin D. Current recommended dietary allowances vary widely but range from 200–400 IU/day [40]. A trial of a high potency topical vitamin D cream would appear to offer particular promise.

Evaluation of the hypothesis

The hypothesis can be simply evaluated by formulating a high potency vitamin D cream and initially trialing it in an open label study on a cohort of patients with PHN before submitting it to more rigorous evaluation. Patients would apply the cream to the affected area twice a day for a month.

Consequences of the hypothesis

The focus of most scientific neurological research has been on drugs that influence the transmission of neural signals. For many pain conditions this approach has been largely unproductive. A focus on schwann cell and nervi nervorum activation involves a paradigm shift in our understanding of a number of neuralgic conditions. Successful utilization of these drugs orally [39] would also offer new perspectives on PHN. Successful use of these drugs topically would emphasize the importance of peripheral sensitization in central sensitization pain syndromes. These approaches might be useful in other pain conditions where "glial" activation has also been implicated, such as CRPS Type I [41]. The potential production of NGF in the keratinocytes and possibly the Schwann cells by vitamin D could mean that a topical vitamin D cream might also have a role in the treatment of diabetic neuropathy.

Conflict of interest statement

The author acknowledges no known conflicts of interest.

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