Neuropathic pain in hereditary peripheral neuropathy

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INTRODUCTION

Charcot-Marie-Tooth (CMT) disease is known as hereditary motor and sensory neuropathy and one of the most common hereditary neuromuscular diseases, with worldwide prevalence 1/2,500 (Emery, 1991). CMT is a genetically heterogeneous group of disorders and is induced by mutations of genes, leading to a length-dependent axonal degeneration. CMT1 (demyelinating form) and CMT2 (neuronal form) are major subdivision of CMT. CMT disease is characterized by loss of touch sensation across various parts of the body and progressive muscle atrophy in the extremities. Neuropathic pain is often a symptom of CMT referred by CMT patients (Carter et al., 1998; Pazzaglia et al., 2010; Ribiere et al., 2012). Severe pain is also frequently complained by CMT patients and it interferes with quality of life. Thus, understanding this relationship may provide a novel view in identifying the main mechanism causing neuropathic pain in CMT as well as useful strategy for the treatment of neuropathic pain in peripheral neuropathies.

CHARCOT-MARIE-TOOTH DISEASE

CMT is inherited neuropathies without known metabolic un-

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Received: August 13, 2013 / Revised: August 14, 2013 / Accepted: August 14, 2013

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and CMTX refer to Déjerine-Sottas disease, autosomal recessive forms and X-linked varieties, respectively.

**NEUROPATHIC PAIN**

Pain is the unpleasant sensory consequence of neuronal activity in specific nociceptive pathways. Infection, nerve injury, diabetes and so on influencing peripheral nerves occasionally results in the development of chronic pain, clinically important 'neuropathic pain' (Baron, 2006). May patients with neuropathic pain show persistent and paroxysmal pain that is independent on a stimuli. This stimulus-independent pain ought to be shooting and lancinating or burning. Spontaneous activity in nociceptive C fibers may respond to persistent burning sensation. Spontaneous activity in myelinated A fibers is also thought to be responsible for paraesthesia and dysesthesia. Two key features of stimulus-evoked pain is hyperalgesia and allodynia. Hyperalgesia and allodynia are and increased pains response to a suprathreshold noxious stimulus and non-noxious stimulus. Many recent studies indicate that the abnormal excitability of dorsal horn neurons and the activation of spinal microglia by peripheral sensory input affect the induction of neuropathic pain (Costigan et al., 2009; Tsuda et al., 2003; Tsuda et al., 2005; Woolf and Salter, 2000). A variety of pathological processes affecting peripheral nerves, dorsal root ganglion neurons, spinal roots and central nervous system can induce neuropathic pain. The common denominator of these pathologies is segmental dysmyelination/demyelination and axonopathy. Interestingly, the prominent involvement of neuroglia in the pathophysiological alterations following peripheral nerve injury offers new treatment approach for intractable neuropathic pain (Dworkin et al., 2003). To date, pharmacotherapy for neuropathic pain has been disappointing. Non-steroidal anti-inflammatory drugs and resistance can not affect patient with neuropathic pain. In addition, resistance and insensitivity of opiates to neuropathic pain is also common (Kingery, 1997). Thus, there is necessary to develop more effective treatment and to understand exact etiology, mechanisms and symptoms of neuropathic pain.

**NEUROPATHIC PAIN IN CHARCOT-MARIE- TOOTH DISEASE**

In neuromuscular diseases, 62% of the case shows chronic pain and the mean intensity of this pain is moderate (Tiffreau et al., 2006). Few researches focused on pain in CMT and its frequency ranges from 56 to 96% (Abresch et al., 2002; Cater et al., 1998; Gemignani et al., 2004; Jensen et al., 1998; Padua et al., 2006; Padua et al., 2008; Tiffreau et al., 2006; Truini et al., 2010). Pain of CMT is usually moderate, symmetric and predominantly occurs in lower limbs. The most of pain is often neuropathic with cramps, paresthesia and restlessness. Especially, neuropathic pain in CMTA1, most the common type, is related to damages in Aδ-type nerve fibers (Pazzaglia et al., 2010). In 1998, Carter et al. reported the frequency and extent to which subject with CMT show pain and comparison of qualities of pain in CMT to other painful neuropathic disorder (Cater et al., 1998). In the study, of all CMT subjects, 71% subjects reported pain with the most severe pain sites noted as low back (70%), knee (53%) and ankles (50%), toes (46%) and feet (44%). In addition, of all CMT subjects, 39% reported interruption of activities of daily living by pain. In 2008, Paudua et al performed a multi-dimensional assessment in CMT patients and reported that pain is a relevant symptom related to gender, CMT subtypes and clinical pictures, focusing on quality of life and disability (Padua et al., 2008). However, the derangement whether neuropathic pain in CMT patients is primarily due to the neuropathy or to other causes is still unsolved.

The pharmacological care management of neuropathic pain in CMT is symptomatic. Neuropathic pain is poorly relived by common analgesics and tricyclic or serotonin and norepinephrine uptake inhibitors, antidepressants, and anticonvulsants have all limited efficacy and undesirable side-effects (Kingery, 1997). This is why physical therapy via exercise and rehabilitation is important for this disease.

**CONCLUSIONS**

In summary, to date, a lot of studies showed an association between the subjective pain perception and the nociceptive system function in patients with CMT. Neuropathic pain being quite common in CMT disease must be rescued from its adverse events. The treatment of neuropathic pain in CMT is symptomatic. Because neuropathic pain is poorly relived by common pharmacological treatment, physical therapy via exercise and rehabilitation is essential for managing this symptom. More research is needed to identify and develop effective treatments for neuropathic pain in CMT. Thus, in order to treat neuropathic pain correctly, it is expected that this highlight can help to discovery of a useful strategy for the treatment of neuropathic pain in peripheral neuropathies.
CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

This work was supported by the Dong-A University research fund.

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