Investigating the role of genetics in the development of neuropathic pain

Neuropathic pain is relatively common, with prevalence estimates ranging from 1–2% up to 6–8% of the general population, and is associated with significant burden to both patients and society. Efficacy of currently available treatment options is variable, with not all patients receiving adequate pain relief. Much of the medical research in the past decade has focused on the correlation between disease and genetic markers and phenotypic variance. Indeed, since 2000, there has been a rapid surge in the number of pain-relevant candidate gene association studies in humans. For neuropathic pain specifically, a number of candidate genes have been identified. While still an emerging field of research, developing a greater understanding of the role of genetics in the pathogenesis of neuropathic pain may lead to improved targeted therapies for these painful conditions.

Pain responses and reporting of pain in clinical practice vary between individuals, which is believed to be due to the complex interaction between environmental and other factors. Multiple causative factors, including an inciting event or insult, environment, genotype and pathophysiology, interact to result in neuropathic pain syndromes (see Figure). While different individuals may experience the same disorder or injury, not all develop chronic pain. The genotype-environment interaction plays an important role, i.e., the initial insult combined with inherited susceptibility and other factors results in chronic neuropathic pain. For instance, not every patient who suffers from acute herpes zoster infection (shingles) will go on to develop postherpetic neuralgia.

Heritability studies show familial pattern for some pain syndromes

Occipital neuralgia is characterized by paroxysmal stabbing pain in the distribution of the greater and/or lesser occipital nerves. A report in a Chinese family revealed five cases spanning three generations, with some family members also suffering from nervus intermedius neuralgia. Familial trigeminal neuralgia has also been reported, and is believed to be due to autosomal dominant transmission. Furthermore, the musculoskeletal disorder of concurrent low back and neck-shoulder pain demonstrated high heritability in a cross-sectional study of twins in Sweden.
Possible role of sodium channel mutation in neuropathic pain

Voltage-gated sodium channels (Nav) are located throughout the nervous system and are believed to play a significant role in the pathogenesis of neuropathic pain. The sodium channels Navα1.7, Navα1.8 and Navα1.9 are expressed in dorsal root ganglia and trigeminal ganglia neurons. The SCN9A gene codes for the Navα1.7 channel; in humans, point mutations within this gene have been associated with the inherited pain syndromes: erythromelalgia and paroxysmal extreme pain disorder. Another mutation within this gene that causes loss of function of the Navα1.7 sodium channel results in congenital pain insensitivity. Hence, sodium channels provide a potential target for pharmacotherapeutic targets in of neuropathic pain.

Gene therapy for neuropathic pain

Gene therapy aims to target biomolecules that are directly involved in the pathophysiology of neuropathic pain; hence, in theory, treatment would be localized and adverse effects minimized. Studies on gene therapy for neuropathic pain have been conducted in animal models, and a few trials in humans are currently ongoing. Targets for gene therapy in the animal studies have included:

- opioid pathways;
- interplay between inflammatory cytokines;
- γ-amino butyric acid (GABA) pathways;
- norepinephrine pathways; and
- ion channels.

The first human trial of gene therapy for chronic pain has recently been published. Research in animal models of pain has shown that pain-related behaviour can be reduced following gene transfer to the dorsal root ganglion using replication-defective herpes simplex virus (HSV)-based vectors. This multicentre, dose-escalation Phase I clinical trial was conducted in patients with moderate to severe intractable focal pain caused by cancer. Ten subjects received NP2, a replication-defective HSV-based vector expressing human preproenkephalin, injected intradermally into the dermal fat tissue(s) that corresponded to the radicular distribution of pain. Pain was relieved in the patient cohorts that received the medium and high doses of NP2, but not the low dose. Treatment was well tolerated, with no serious adverse events reported.

While initial research shows promise, gene therapy is not without limitations. Most of the data on efficacy and safety at this stage are from animal models, with trials in humans only just commencing. Human clinical trials of gene therapy for non-pain conditions have raised concerns, but randomized, controlled trials in larger patient populations will be required to demonstrate efficacy and address any safety concerns.

Conclusion

The rapid expansion of research into the role of genotype in development of disease is continuing. A complex interplay of factors are involved in the development of neuropathic pain, including genetics. Heritability studies show a familial pattern for some neuropathic pain conditions, and genes involved in neuropathic pain development have been identified. Early trials of gene therapy in humans show potential for novel, targeted treatments, but randomized, controlled trials in larger patient populations will be required to demonstrate efficacy and address any safety concerns.

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Multidisciplinary treatment for neuropathic pain: Role of anaesthesiologists and orthopaedic surgeons

In the previous issue of Challenges in Neuropathic Pain, we featured the first in a series of interviews with Multidisciplinary Panel on Neuropathic Pain (MPNP) members by specialty. Multidisciplinary management of neuropathic pain is often necessary for effective treatment of neuropathic pain, and can involve a range of specialist physicians and allied health professionals. In this issue, we hear from Dr Phoon Ping Chen and Dr Steven Wong, anaesthesiologists specialized in pain medicine, and Dr Josephine Ip Wing Yuk, an orthopaedic surgeon.

All three members practice in public hospitals that have multidisciplinary pain clinics. Healthcare professionals involved in these pain clinics include pain medicine specialists, anaesthesiologists, orthopaedic surgeons, pain nurses, physiotherapists, occupational therapists, clinical psychologists, podiatrists and orthotists. Dr Wong commented that the role of the pain clinic is to manage the patient through a biopsychosocial approach. The members receive most referrals from general practitioners (GPs) and other specialists, such as neurologists, neurosurgeons, oral and maxillofacial surgeons, and accident and emergency physicians.

At the pain clinic, Dr Chen and Dr Wong commonly treat patients with a wide variety of neuropathic pain conditions, including postherpetic neuralgia, trigeminal neuralgia and facial pain, complex regional pain syndrome, post-nerve injury pain, postsurgical pain and entrapment neuropathies. Most of the referred patients are difficult to treat and already

INTERVIEW

Dr Chen

Dr Wong

Dr Ip
neuropathic pain and peripheral nerve injury who are refractory to first-line treatment, and provides pharmacological management and assessment of whether surgical treatment is required. She most frequently prescribes \( \alpha_2-\delta \) ligands and performs nerve decompression and nerve grafting procedures.

When asked about advances in the management of neuropathic pain in their field over the past decade, Dr Wong cited the introduction of new pharmacological agents and pulsed radiofrequency treatment; Dr Chen mentioned advances in neuropharmacology and greater understanding of the genetics of pain, and the use of functional MRI (fMRI) in pain research and management; and Dr Ip commented on the advances made in neuroectomy surgery.

All members commented that international guidelines may be useful in determining suitable treatment for patients with neuropathic pain. This includes guidelines from the European Federation of Neurological Societies (EFNS), the International Association for the Study of Pain (IASP) and the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom. For instance, the EFNS guideline on pharmacological management of neuropathic pain provides evidence-based recommendations by neuropathic pain condition.1

For patients with chronic neuropathic pain, Dr Chen stated that important factors to consider are early treatment, trial of a drug regimen to achieve therapeutic response, and clarification of a patient’s expectations of outcome. Dr Wong added that chronic neuropathic pain is a disease of its own. Nerve recovery usually takes a long time and successful management depends on adherence to treatment and effective coping strategies.

References

INTERVENTIONAL THERAPIES FOR NEUROPATHIC PAIN

Part 2: Neurectomy and radiofrequency procedures

In part 2 of this series on interventional therapies for neuropathic pain, we explore neurectomy and radiofrequency procedures. Neurectomy involves excision of the inciting nerve or nerves, while radiofrequency procedures deliver radio waves to create thermal energy to destroy fibres in the nerves that are causing the painful condition.

A guideline from the American Academy of Neurology and European Federation of Neurological Societies recommends early surgical treatment for patients with trigeminal neuralgia (TN) who are refractory to pharmacological therapy.1 A nationwide review of invasive procedures for TN conducted in the Netherlands from 2002 to 2004 found 672 patients had percutaneous radiofrequency thermoacoagulation (RFT), 39 underwent partial sensory rhizotomy and 87 received microvascular decompression (MVD).2 Percutaneous RFT was associated with a higher risk of repeat procedure, but fewer complications requiring hospital readmission.

A recently published cost-effectiveness analysis of surgical treatments for TN revealed that all treatments relieved pain and long-term results were comparable (>25% recurrence rate between 5 and 10 years postoperatively).3 However, percutaneous techniques (including radiofrequency rhizotomy) were more cost-effective than MVD and gamma knife rhizotomy.

Neurectomy for TN has been mostly superseded by these newer surgical techniques. Indeed, a study by Cericovic and colleagues demonstrated that while peripheral neurectomy and avulsion provided pain relief in the short-term, pain recurrence following the first neurectomy occurred after about 15 months; following subsequent neurectomies, the pain-free period was progressively shorter.4 Nevertheless, this technique may be useful in elderly patients with TN after failure of other interventional procedures.

Other neuropathic pain conditions in which these procedures can be used include inguinal nerve entrapment, occipital neuralgia and lumbar radicular pain. Inguinal nerve entrapment may occur following inguinal hernia repair. Iliouinguinal neurectomy is an effective treatment for this condition, with one study reporting total pain relief in 72% of patients.5 In another study, at least partial pain relief was achieved by 67% of patients; however, a high proportion of patients reported some return of pain in the long-term.6 Several studies have observed that pulsed radiofrequency of the greater and/or lesser occipital nerve is an effective treatment for occipital neuralgia, with few complications reported.7,8 In one retrospective study (n=102), 51% of patients reported ≥50% pain relief and satisfaction with treatment lasting at least 3 months,9 while in a prospective trial (n=17), 53% of patients reported that their pain had improved substantially after 6 months.10

A number of studies have investigated the effect of continuous radiofrequency lesioning of the dorsal root ganglion for chronic lumbar sacral radicular pain, with mixed results.10,11 Another study observed that pulsed radiofrequency applied to the lumbar dorsal root ganglion in patients with pain arising from different aetiologies was more effective in those with herniated disc and spinal stenosis than those with failed back surgery syndrome.12 Repeat procedures in patients with initial success after radiofrequency lesioning of the dorsal root ganglion for lumbar radicular pain show potential for effective longer-term treatment in some patients.13

References
Postmastectomy pain

Presentation
A 46-year-old lady complained of persistent right upper chest and medial upper arm pain since her right mastectomy 3 months previously. The pain was described as burning and stabbing. The painful area was also associated with hyperalgesia (increased pain sensation due to painful stimulus) and allodynia (pain due to a stimulus that does not normally provoke pain). There was no evidence of infection or localized scar tenderness.

Management strategy
The patient was initially treated with ibuprofen, tramadol and gabapentin 300 mg tds, but without satisfactory response. The pain affected her sleep, mood and right arm function. Her gabapentin dose was increased to 900 mg tds and nortriptyline 25 mg nocte was added over 3 weeks. She complained of some somnolence initially, but which subsequently improved, and her pain decreased to an acceptable level. At the same time, she received physiotherapy and was referred to the clinical psychologist for sleep and mood management.

Discussion
Postmastectomy pain is a well-known example of postoperative pain syndromes. The prevalence of this painful condition has been reported to range from 20–68%.1,2 Postmastectomy pain may present in the arm, axilla, shoulder or the upper anterior or lateral chest wall, with pain that is often described as burning, sharp, shooting, stabbing, pressure sensation or numbness, with associated hyperalgesia and allodynia.3 Although the mechanisms are not entirely clear, it is likely that postmastectomy pain is a type of neuropathic pain that may be caused by nerve injury during surgery, neumora or phantom pain. Young age, nerve trauma or section, axillary dissection, tumour located in the upper lateral quarter and those who have undergone breast surgery previously are more likely to develop postmastectomy pain.1,4 Techniques such as paravertebral block for perioperative analgesia, and perioperative use of some antidepressants and anticonvulsants have been found to decrease the incidence and severity of postmastectomy pain.4,5 Good postoperative pain control is important. Like other neuropathic pain conditions, treatments for postmastectomy pain include antidepressants and anticonvulsants or combined therapy, topical capsaicin and lignocaine,6 as well as patient education, physical and psychological management.

Source: MPNP members

References