Neuropathic pain in children
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ABSTRACT
Neuropathic pain (NP), due to a lesion or disease of the somatosensory nervous system, is not well documented or researched in children. NP is a clinical diagnosis that can be difficult, especially in younger children. Nevertheless, it is important to recognise NP, as pain mechanisms and consequently management and prognosis differ from other types of long-term pain. NP is common in adult pain clinics but many of the underlying disease states in which it occurs are infrequently or never encountered in paediatric practice. However, NP in childhood has been reported, even in the very young in certain clinical situations. Causes of NP include traumatic injury, complex regional pain syndrome type II, cancer and chemotherapy, chronic infection, neurological and metabolic disease, and inherited sensory nerve dysfunction. The clinical and laboratory study of traumatic peripheral nerve injury has revealed important age-related differences in clinical presentation and prognosis. It is clear that mechanisms operating during development can profoundly modify the consequences of nerve damage and NP. Clinically, diagnosis, assessment and treatment of NP are based on methods and evidence derived from data in adults. Improvements in the understanding and management of NP are likely to come from developmentally appropriate improvements in the clarity and consistency of diagnosis and systematic, well-researched approaches to treatment.

INTRODUCTION
Neuropathic pain (NP) is caused by a lesion or disease of the somatosensory nervous system.1 NP is due to pathological changes in the functioning of nociceptors and nociceptive pathways causing abnormal pain signalling leading to persistent and characteristic symptoms and signs. NP may be a component of chronic pain states, but NP and chronic pain are not synonymous as pain can also persist with a normal and intact somatosensory nervous system.

NP is complex. Many different types of damage to neural tissue can cause NP, not all patients with the same injury experience NP, and the intensity of pain and degree of pain-related functional impairment vary considerably between individuals. Distressingly frequent characteristics of NP are its poor response to currently available treatments and potentially prolonged duration. In adults, the prognosis for recovery from NP is frequently poor, depending somewhat on the source and nature of the underlying nervous tissue injury or abnormality. However, there is growing evidence that the incidence and prognosis of NP in childhood differs from that seen when neural injury occurs later in life.

NP can be localised to the area of a single nerve or nerves or be more extensive depending on the type of damage that has occurred and whether peripheral and central neural structures are involved. Clinical diagnosis of NP can be difficult; however, typical features include spontaneous or paroxysmal pain, often described as burning, shooting, electric shock-like, or ‘pins and needles’. Allodynia (painful touch) and hyperalgesia (increased pain from a stimulus that normally provokes pain) can occur, sometimes accompanied by adjacent areas of reduced sensation or anaesthesia. Allodynia and hyperalgesia also occur in nociceptive pain but in contrast to NP they are usually accompanied by obvious signs of tissue injury and inflammation.

Prevalence and underlying causes of NP
Chronic pain, that is, pain that persists for more than 3 months or beyond the expected time for healing to occur after an injury, is thought to occur in about 6% of children and adolescents.2 The proportion of these children who have NP is not known. Epidemiological studies in adults suggest a prevalence of chronic pain with neuropathic features of 3.3%–8.2%.3 4 Current evidence suggests that although NP is seen in a significant proportion of referrals to paediatric chronic pain clinics,5 6 the prevalence is much lower, and the conditions with which it is associated differ from those commonly reported in adults.7 In fact, it is well known that many causes of NP in adults are either rare in childhood or less frequently associated with significant pain, for example, Parkinson’s disease, Alzheimer’s disease, cerebro-vascular accidents, postherpetic and trigeminal neuralgia, Guillain–Barré syndrome and painful diabetic neuropathy.8

Established causes of NP in children (table 1) include genetic conditions affecting sensory nerve function such as Fabry’s disease and erythromelalgia (EM)9 10 and situations where nerve damage has occurred, for example, post-traumatic, phantom limb pain, postchemotherapy, and in some chronic conditions or infections such as HIV/AIDS.11 Complex regional pain syndrome (CRPS) is an important idiopathic condition that occurs in both children and adults that is generally thought to be characterised by NP. CRPS type II occurs as after known nerve injury, whereas the more frequent CRPS type I has similar clinical features, yet often has little or no obvious precipitating cause.12 Both CRPSs and NP after nerve damage seem to occur at a lower frequency in children, and to have a better long-term prognosis. This difference and contrasting observations such as children’s apparent increased susceptibility to certain types of painful neurological injury, for example, toxicity following mercury exposure,13 have raised some important questions about the ontology of NP.
NP after injury or surgery

The study of the effects of different types of nerve injury at different developmental ages and of NP conditions that are seen across the age spectrum have helped us to begin to understand how mechanisms operating in childhood NP may differ from that in the adult. Laboratory models of traumatic peripheral nerve injury have demonstrated a reduced susceptibility to NP if the injury is performed at a younger age (first three postnatal weeks in the rodent), and are being used to improve understanding of age-related changes in the pathophysiology of NP.\(^{14-15}\)

Traumatic severe traction nerve injury at birth can cause brachial plexus palsy that is sometimes repaired surgically. This type of injury might be expected to result in sensory changes including NP, but long-term follow-up studies have mostly shown that recovery of sensory function is relatively better than motor function, whether surgically repaired or not, with little or no evidence of NP.\(^{16-17}\)

Pain in the affected limb can occur, but the incidence of NP, rather than musculo-skeletal nociceptive pain or temporary re-innervation pain, appears to be extremely low.\(^{16-18}\) Traumatic brachial plexus injury occurs in older children but the number of reports and pain details are limited, but again, they do not appear to show consistent reports of NP.\(^{19}\)

However, there have been reports of more distal nerve injury due to fractured humerus leading to NP in children older than 5 years, with an apparent increase in severity in teenagers.\(^{20}\)

More extensive neurological damage in spinal cord injury is rare in children, but can occur in neonates as a complication of delivery; again, it seems to have a better recovery in younger patients than similar lesions experienced at older ages, although pain, including NP, does occur.\(^{24-27}\)

Nerve damage can also result from surgery. Persistent postsurgical pain (PPP) with features of NP has been well described in adults presumably due to inadvertent operative trauma to nervous tissue.\(^{28-29}\) PPP has been reported in children, but the overall incidence, role of NP or relevance of age at the time of surgery is not known.\(^{30-31}\)

In adults who had inguinal hernia repair before 5 years of age, persistent pain was reported in 13.5% in one study.\(^{32}\)

Neuropathic descriptors were used by 53% of those with pain. Similarly, in patients who underwent thoracotomy between 0 and 25 years of age who were assessed 39.3±7.7 years following surgery, a greater proportion of older patients reported chronic pain and three patients who had initial surgery between 7 and 25 years still reported at NP the surgery site.\(^{33}\) NP was reported in six of 40 children with cerebral palsy who underwent multilevel orthopaedic surgery to reduce contractures.\(^{34}\)

Phantom limb pain

Limb amputation and consequent nerve damage are known to lead to altered sensory function that can be classified as non-painful phantom sensations or phantom limb pain. Non-painful sensations experienced in the region of the missing limb are reported by 50%–100% of children following surgical amputation compared with 7%–20% of children with congenitally deficient limbs. These low intensity non-painful sensations have minimal impact on daily activities and have been described as tingling, pins and needles, tickling, ‘feels asleep’, numb, itching, and prickling.\(^{35-38}\) Phantom limb pain is more problematic, typically exhibiting features of NP, that is, episodic, sharp, stabbing, pins and needles, throbbing, piercing, squeezing, tight and uncomfortable, frequently leading to pain-associated disability and impacting on daily functioning.\(^{35-37}\) Phantom limb pain can be spontaneous but reported precipitants include exercise, objects approaching the stump, cold weather and ‘feeling nervous’; psychosocial triggers were reported as more common in girls, whereas pain was triggered by physical stimuli in a higher proportion of boys.\(^{36-37}\)

Factors that are thought to predispose to phantom limb pain are surgical amputation (pain prevalence 49%–76% in contrast to 3%–4% in congenitally deficient limbs), older age at time of amputation, preoperative pain and amputation for cancer.\(^{35-39}\)

Chemotherapy may also increase the risk of phantom pain (see below). There is a perception that phantom limb pain resolves more rapidly in children than in adults. However, phantom limb pain can persist for months or years, and again, older age at amputation seems to be a negative prognostic indicator for recovery.\(^{35-38}\)

NP in cancer and chemotherapy

NP occurs in 20%–40% of adult patients with cancer.\(^{41}\) In children, the overall rate of cancer-related NP is unknown. However, pain is frequent in those with primary tumours within the nervous system, for example, up to 46% of children with plexiform neurofibromas.\(^{42}\)

Tumour invasion or compression of neural structures including spinal cord, spinal nerve roots, nerve plexus, or peripheral nerves can occur, but as the incidence of solid tumours is lower in children, these sources of NP are also less common. Nevertheless, cases of probable NP with high analgesic requirements, resistance to opioid therapy and response to local anaesthetic blockade have been described.\(^{43-45}\)

Treatment-related NP may occur following surgery, for example, postamputation pain or chemotherapy. In addition, perioperative chemotherapy has also been associated with an increased incidence and earlier onset of postamputation pain.\(^{39}\)

Peripheral neuropathy occurs in 50%–90% of those treated with platinum compounds and almost half with vinca alkaloids.\(^{46}\) In 21 children with solid tumours and nine with leukaemia aged between 10 and 17 years, symptoms of severe NP started within days of beginning chemotherapy.\(^{46}\) In a retrospective review, 174/498 patients developed peripheral neurotoxicity with vincristine treatment for acute lymphoblastic leukaemia. Associated NP occurred in 35%, with recurrent episodes in 16%–30%. Age had minimal influence on the rate of NP which varied from 31% in the 1–5-year group to 40% in

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<th>Table 1 Causes of neuropathic pain in children</th>
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<td>Classification</td>
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<tr>
<td>Traumatic</td>
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<td>Complex regional pain syndrome type II</td>
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<td>Neurological and neuromuscular disease</td>
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<td>Metabolic disease</td>
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those aged 16–20 years.47 Treatment of high-risk neuroblastoma with monoclonal antibody directed against the tumour-associated disialoganglioside GD2 can result in severe acute NP in children.48 49 Laboratory studies have confirmed mechanical allodynia as a result of C-fibre and complement activation,49 50 which is reduced by gabapentin.51 Current clinical treatment protocols therefore incorporate specific analgesia for NP, such as oral gabapentin, intravenous ketamine or lidocaine.48

NP in chronic illnesses
Neuropathy and sensory nerve dysfunction are characteristic of a number of neurological diseases and chronic illnesses. As before, symptoms of NP in childhood are generally less frequent and their severity relates to the underlying cause, age at onset or duration of disease.

Trigeminal neuralgia
is unilateral (rarely bilateral) NP in the distribution of the trigeminal nerve.52–54 Intermittent paroxysms of pain can be triggered by light touch in the trigeminal region (cutaneous trigger zones), chewing, brushing the teeth, cold wind or exercise. Pain may also be associated with spasms of the facial muscles, or tic douloureux. Trigeminal neuralgia may be idiopathic or result from vascular compression within the intracranial course of the nerve or tumour.52 54–56 The incidence of trigeminal neuralgia is low in children, and fewer than 1.5% of patients report symptoms before the age of 18 (range 3–18, median 11–13).59 52 53 55 Although NP is uncommon in infants, a schwannoma in the trigeminal nerve presented with episodic crying and allodynia over the ear in a 1-year-old child.56

Peripheral neuropathy in diabetes
is a common underlying cause of NP in the adult population. The true rate of nerve dysfunction in children with diabetes has probably been underestimated as pain and other symptoms are very infrequent.57 However, sensory changes including subtle differences in nociceptive thresholds can be detected in children in the absence of NP symptoms.58

Fabry’s disease
is an X linked recessive disorder due to mutations in the GLA gene that encodes the lysosomal enzyme α-galactosidase. Accumulation of glycolipids, including globotriaosylceramide (Gb3) in cells and tissues, results in dysfunction of multiple organ systems including the CNS.59 Pain is a common presenting symptom.59–61 As pain may be the only feature for some years, Fabry’s disease should be considered in the differential diagnosis of pain clinic referrals.62 Episodic burning pain and pins and needles may initially be restricted to the hands and feet, but pain becomes more persistent and generalised with time and can be triggered by changes in environmental or body temperature, exercise or emotional stress.59 60 Pain is present in 70%, with a higher incidence in males (80% vs 65%), with a significant impact on quality of life.59 60 63 Age at diagnosis ranges from childhood to 77 years.62 However, NP has been reported from 3 years of age in boys and 6 years in girls, at a mean age of 7.8±3.2 years.60 64 Small fibre (nociceptor) loss in peripheral tissues and glycolipid accumulation in the dorsal root ganglia of sensory nerves may underlie NP. Enzyme replacement therapy with α-galactosidase A reduces glycolipid storage in tissues, but effects on pain take time. Improvement in all dimensions of pain perception after 24 months has been reported, with reductions in ‘pain at its worst’ scores in both boys and girls (2.8 to 1.5) and ‘average pain’ from 2.2 to 0.9, and a reduced requirement for treatment with anticonvulsants.59 61 The overall prevalence of pain was not altered by enzyme replacement therapy in another study, but those with pain at the onset of therapy did show a decrease in severity.61

Erythromelalgia (EM) is characterised by severe episodic pain and redness affecting the hands and feet that has been attributed to vascular, inflammatory and neuropathic causes.66 Bilateral pain and redness of the ears may also represent a variant of EM.67 68 Pain is aggravated by warmth, prolonged standing and exercise. Cooling with fans and submersion in iced water relieve pain, although the latter is discouraged as prolonged exposure to iced water has been associated with ischaemic injuries. EM has also been associated with myeloproliferative or autoimmune disorders, and in such cases may be termed secondary EM.69 Primary EM has been related to genetic mutations in the SCN9A gene, which encodes the Na,1.7 voltage gated sodium channel expressed on nociceptive and sympathetic nerve fibres.66 70 Resultant alterations in channel kinetics reduce threshold and increase excitability, thereby enhancing pain transmission. Onset of symptoms at younger ages has been associated with mutations that produce larger depolarising shifts71 72 and with changes in expression of neonatal or adult isoforms of the channel.73

Paroxysmal extreme pain disorder (PEPD) has also been associated with point mutations at different sites on the SCN9A gene, producing a different pattern of channel kinetics (impaired inactivation and repetitive firing) and a distinct phenotype.74–76 A red flush over the buttocks and legs may be apparent soon after birth, and symptoms progress through infancy and childhood: initially, rectal pain induced by bowel opening and associated with burning pain and redness in the legs; burning pain and redness around the eyes lasting for a few minutes and associated with runny nose and eyes; and at older ages, episodes of bilateral mandibular pain and redness that may triggered by cold, eating or stress.76

EM and PEPD are often poorly responsive to analgesia. Awareness of involvement of Na,1.7 channels has increased the use of sodium channel blocking drugs such as carbamazepine or mexiletine for these specific neuropathic conditions.77–80

Multiple sclerosis (MS) is a chronic inflammatory disease producing demyelination and axonal damage in the brain and spinal cord.81 Pain is common in adults with a prevalence from 57% to 65%. Patients with MS may experience multiple types of pain including tonic spasms, back pain, headache and central NP. Trigeminal neuralgia is more common with a higher rate of bilateral symptoms. In all, 29%–55% of patients experience their first symptoms of MS before 16 years of age, with onset usually between 8 and 14 years; incidence is higher in girls. Sensory symptoms were reported in 13%–69% of children with MS, but the proportion with NP82 Headache is more frequent than in adult patients with MS.81 The course of the disease may be slower in children, with higher rates of spontaneous recovery but it can still have a significant impact on schooling and quality of life.82

HIV/AIDS. Indicators of peripheral neuropathy have been reported in children with HIV although symptoms are said to be mild compared with adults.83–85 Nevertheless, pain has been reported in a higher proportion of HIV infected children than normal controls, although NP was not selectively identified and the overall incidence of pain appears to be lower than in adults.86 87 Peripheral neuropathy is a known toxic effect of antiretroviral therapy but again the incidence appears to be lower in children. Longitudinal studies indicate that with increasing survival of HIV infected children, rates of non-infectious complications such as peripheral neuropathy are increasing.88–89

Postherpetic neuralgia. Reactivation of dormant varicella zoster virus infection results in painful eruptions along the
distribution of the nerve; approximately 14% of adults develop NP. Overall, zoster infection and postherpetic neuralgia PHN are less common in children. Children who are immunocompromised, for example, cancer treatment, are at higher risk. Of 226 children with Acute Lymphoblastic Leukaemia (ALL), zoster eruptions occurred 90 times, and five developed PHN which persisted for greater than 2 months in two patients.

**Diagnosis and assessment**

Current guidelines for the assessment and diagnosis of NP are designed for adults but are often extrapolated to older children or adolescents (see below). As there are no specific laboratory tests for NP the diagnosis is made on the basis of clinical indicators. This is subject to the well-described problems of pain assessment in young children. History remains the mainstay of diagnosis; children may use qualitative descriptors that are considered indicative of NP, such as burning, shooting, radiating, burning, electricity-shock, stabbing, pricking, tingling, pins and needles, and pinching. Young children may be unable to clearly describe their pain using these terms but nevertheless pain history should include: evaluation of intensity; quality (sensory descriptors); temporal aspects of pain (frequency, spontaneous/paroxysmal or continuous, aggravating and relieving factors); and response to treatment. Pain intensity should be evaluated using a validated scale; unfortunately, observational scales have mostly been designed for use in acute pain settings and may not be reliable. Self-reporting of pain intensity using visual analogue or numerical rating scales where possible is therefore preferred. Screening questionnaires have been developed to identify NP such as Leeds Assessment of Neuropathic Symptoms and Signs (LANSN). Douleur Neuropathique en 4 questions (DN4); Neuropathic Pain Questionnaire (NPQ); painDETECT; and identify Pain (ID-Pain) but they have not yet been validated in children.

Physical examination should attempt to verify and locate the lesion of the somatosensory system and document associated neurological signs. Sensory abnormalities are more difficult to elicit in infants and young children; newer techniques such as quantitative sensory testing (QST) evaluate patterns of change in association with NP in adults. QST requires cooperation and a level of cognitive functioning that currently limits its use to research studies in restricted populations of children. Electroneurography, microneurography, functional brain imaging and skin biopsy may be indicated although again their use is mostly confined to research.

Assessment of pain-associated disability is important. Quality of life, sleep, mood and role functioning should be standard assessment for all long-term pain including NP. In adults, chronic pain with NP is associated with a greater disease burden, impacting on quality of life, sleep, anxiety/depression, and use of healthcare and specialist services.

**Management**

Long-term pain, from any cause, rarely responds to a single analgesic medication or pain management strategy. All pain is modulated by activity in higher brain centres, which are in turn influenced by cognitive and situational factors and therefore a multi-modal approach based on a biopsychosocial pain model should always be employed. Management should include specific analgesics preferably chosen on the basis of the pain mechanisms that are thought to be involved, and a range of pain management strategies appropriate to the clinical assessment of pain and any associated functional impairment. Although NP can persist even when the underlying disease process is identified and controlled, optimal management, which might include limitation of tumour growth or suppression of infection, may improve symptoms and limit ongoing nerve damage. In contrast, better treatment of some conditions leading to longer survival may paradoxically increase the incidence of NP.

Drug therapy in NP is often empirical and unsatisfactory as the specific underlying mechanism is rarely well understood. Guidelines devised for the treatment of NP in adults, and therefore based on studies of commoner conditions encountered in the adult population, may not be appropriate for children. Nevertheless, a general approach based on an assessment of likely benefit balanced against side-effects is reasonable. The majority of medications available for NP have a variety of mechanisms of action and so they should be introduced on a therapeutic trial basis and dose adjustments or withdrawal based on clinical response. The analgesics used most frequently for NP in children include the tricyclic antidepressants amitryptiline and nortryptiline and the gabapentinoids gabapentin and pregabalin. Localised NP may respond to topical 5% lidocaine plasters although efficacy has mostly been demonstrated in adult diabetic neuropathy and PHN. Many other drug treatments are available, mostly with significant side-effects or low therapeutic indices, and so in the absence of good clinical data their use should be confined to the framework of expert management or clinical trials in order to validate their efficacy.

**Conclusions**

Evidence of NP has been detected in very young children, but it is clear from our current knowledge of prevalence and prognosis that there are important differences in the sensory response to nerve injury and CNS damage that appear to strongly relate to developmental age. Although NP in children often appears to be less severe when direct comparisons are made with adult patients, evaluations and criteria for diagnosis and assessment may be less valid in children. Severe and debilitating NP does occur in childhood and it is often as refractory to treatment. Improvements in the management of NP are likely to come from a better understanding of the diverse mechanisms that are involved at different stages of development, improvements in the accuracy of clinical diagnosis and a much more systematic and carefully documented approach to therapy.

**Contributors** SW and SMW conducted literature searches. All authors were involved in the interpretation of data. RFH and SMW were involved in drafting the manuscript; externally peer reviewed.

**Provenance and peer review** Commissioned; externally peer reviewed.

**REFERENCES**