



## Review

# Neuropathic pain in children: Steps towards improved recognition and management

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## ABSTRACT

Neuropathic pain in children can be severe and persistent, difficult to recognise and manage, and associated with significant pain-related disability. Recognition based on clinical history and sensory descriptors is challenging in young children, and screening tools require further validation at older ages. Confirmatory tests can identify the disease or lesion of the somatosensory nervous system resulting in neuropathic pain, but feasibility and interpretation may be influenced by age- and sex-dependent changes throughout development. Quantitative sensory testing identifies specific mechanism-related sensory profiles; brain imaging is a potential biomarker of alterations in central processing and modulation of both sensory and affective components of pain; and genetic analysis can reveal known and new causes of neuropathic pain. Alongside existing patient- and parent-reported outcome measures, somatosensory system research methodologies and validation of mechanism-based standardised end-points may inform individualised therapy and stratification for clinical trials that will improve evidence-based management of neuropathic pain in children.

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## 1. Introduction

Neuropathic pain is defined as pain caused by a disease or lesion of the somatosensory nervous system, which underlies perception of touch, pressure, pain, temperature, position and vibration [1]. A range of different diseases, injuries or drugs may affect the peripheral and/or central nervous system [2,3], resulting in acute or more persistent pain that is maintained by ongoing pathology and/or alterations in nociceptive signalling and modulation. Peripheral injury can alter the function of sensory nerves and increase excitatory input into the spinal cord, where alterations in the balance of local and descending excitatory and inhibitory modulation and neuroimmune interactions can result in enhanced sensitivity and pain. Ascending pathways project to brain regions involved in sensory, affective and autonomic responses to pain, and descending pathways can have facilitatory or inhibitory effects on spinal transmission. Shifts to increased excitability and reduced inhibition at multiple sites from the periphery to the brain can contribute to neuropathic pain (see recent review for further details [1]). As a result, patients can experience hyperalgesia (increased pain in response to a normally noxious stimulus), allodynia (pain caused by a normally non-noxious stimulus), or pain in

areas of reduced sensitivity or sensory loss. Designation as neuropathic pain requires a relevant neurological disease or lesion and a neuroanatomically plausible distribution of pain [4], whereas altered nociception and sensitisation without clear evidence of peripheral nociceptor activation or somatosensory nerve disease/lesion is classified as nociplastic pain [5].

Chronic neuropathic pain can be difficult to manage as current pharmacological treatments are extrapolated from adult data [6] and often have limited efficacy and/or significant side-effects. Pain is often severe and prolonged, and associated impairments of physical, emotional and social function can be marked and require interdisciplinary management [3,7,8]. In adults, chronic pain prevalence is estimated at 30–50%, and neuropathic pain at 6–11% [9]. In children, chronic recurrent pains are common (overall 40–50%; including headache 8–83%, abdominal pain 4–53%, musculoskeletal pain 4–40%, multiple pains 4–49%), and prevalence increases throughout adolescence particularly in girls [10,11]. Chronic pain that interferes with function occurs in 5–6% [12], but the specific prevalence of neuropathic pain in children is unknown [3]. While neuropathic pain can account for 10–30% of patients attending paediatric pain clinics [13–15], these data are influenced by variation in diagnostic criteria, referral patterns and access to specialist services.

Chronic neuropathic pain is subdivided into peripheral and central causes in the recent International Classification of Diseases by the World Health Organisation (ICD-11) [2]. Neuropathic pain is also

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**Table 1**  
Classification and causes of neuropathic pain.

ICD-11 classification	Mechanisms/generators of pain	Examples/differences in children and adolescents
<i>Chronic peripheral neuropathic pain:</i> [2]		
Peripheral [2] nerve injury	surgery [17] surgery / trauma [17] cancer-related [16] compression/infiltration	persistent post-surgical pain [26] phantom limb pain less common if amputation <6 years age [3] solid tumour [27] neurofibromatosis [20] chemotherapy induced peripheral neuropathy [27,28,35] Guillain-Barre syndrome: less common in children but neuropathic pain in >70% and can be presenting symptom [73] Erythromelalgia: rare but severe and significant comorbidity [34] Fabry disease: neuropathic pain presenting symptom [72] much less common in children unless immunocompromised
Painful polyneuropathy	neurotoxic drug auto-immune	onset before 18yrs in <2% cases [3] surgery (eg. scoliosis) [26] neuroblastoma [27]
Postherpetic neuralgia	genetic / channelopathy genetic / metabolic infection	
Trigeminal neuralgia	compression/idiopathic	
Painful radiculopathy	nerve root trauma tumour	
<i>Chronic central neuropathic pain:</i> [2]		
Spinal cord injury	trauma / tumour	pain less common than in adults [3] supra- and infratentorial tumours
Brain injury	tumour	
Post-stroke	cerebrovascular lesion, infarct or haemorrhage	less common in children; potentially secondary to diseases such as congenital cardiac or sickle cell disease [25] onset before 16yrs in 2–5% [3]
Multiple sclerosis		

included within other 'parent' categories, such as cancer-related pain [16] and chronic postsurgical or posttraumatic pain [17]. Complex regional pain syndrome in the absence of a recognised nerve injury (i.e. CRPS Type 1) is grouped with chronic primary pain [18]. These classifications are applicable to children (Table 1), but additional age-related factors can influence the presentation of peripheral neuropathic pain in children. A recent Lancet Child Adolescent Health Commission calls on clinicians, researchers, funding bodies, healthcare providers and policy makers to achieve 4 transformative goals for paediatric pain: 'make pain matter'; 'make pain visible'; 'make pain understood'; and 'make pain better' [19]. The Commission document encompasses broader issues such as the need for additional teaching and training of healthcare providers, patient-advocacy, funding and changes in policy. The current review will focus on evaluations of sensory symptoms and signs that make neuropathic pain 'visible', and the use of research methodologies that help make neuropathic pain 'understood'. These are important steps towards controlled trials with more homogeneous recruitment and sensitive outcomes that will ultimately improve evidence-based management.

## 2. Assessment

### 2.1. Sensory descriptors

Neuropathic pain in children is intense and associated with significant pain-related disability (Fig. 1a (i)). Recognising neuropathic pain can be challenging, and a grading system evaluates the level of certainty (possible, probably, definite) in adults [4]. In addition to history of a relevant neurological disease/lesion and related distribution of pain, reporting specific descriptors (e.g. burning or hot, electric shocks or shooting, pricking or pins and needles) suggest possible neuropathic pain [4]. Similar sensations have been reported by children 6 years and older, including burning, tingling, numbness, itching, pins and needles [20–22], but the reporting and validity of different descriptors is also dependent on each individual's verbal repertoire [23]. The McGill Short-Form questionnaire, which includes sensory and affective adjectives, has identified group differences in adults with neuropathic and non-neuropathic pain [9], and tender, sharp, burning, stabbing and shooting were frequently reported by 10–17 year old adolescents with neuropathic pain (Fig. 1a (ii)).

Altered sensitivity will not be clearly described by young or pre-verbal children, but behavioural observations may give indications of sensory loss (e.g. lack of awareness of noxious stimuli or unrecognised injury) or sensory gain (e.g. withdrawal or distress on touching

an affected area). Observer-based tools for healthcare providers and/or parents have been validated for assessment of the intensity of acute or chronic pain in preverbal, young and cognitively impaired children [24]. However, differentiation of neuropathic from other types of pain in young children will rely to a greater extent on additional aspects of the history, alongside a clinical suspicion or confirmation of pain in a distribution consistent with a disease/lesion involving somatosensory nerves [4]. In adults, a close temporal relationship between the neurological injury and the onset of pain strengthens the clinical likelihood of possible neuropathic pain, but delayed presentations of neuropathic pain have been reported following injury in early childhood.

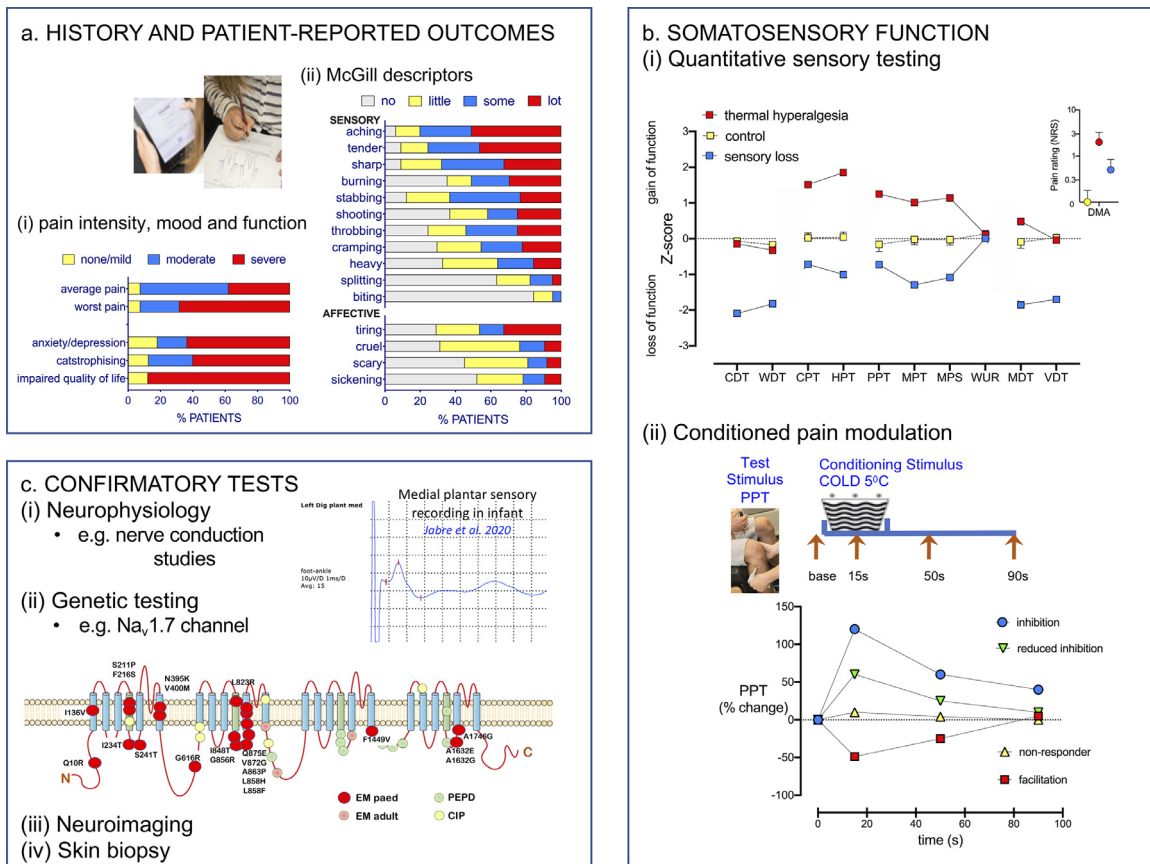
### 2.2. Neuropathic pain screening tools

Neuropathic pain screening tools (e.g. Douleur Neuropathique, DN-4; painDETECT; self-report version of Leeds Assessment of Neuropathic Symptoms and Signs, S-LANSS; Neuropathic Pain Questionnaire) that incorporate specific symptoms, and may include examination items, have cut-off scores associated with high sensitivity and specificity for differentiating neuropathic pain in adults (e.g. DN4  $\geq 4$  out of 10, sensitivity 78–83% and specificity 81–90%) [9]. While also used to describe neuropathic features in adolescents with chronic pain [25,26], further investigation of the sensitivity and specificity, and appropriate cut-off scores, for identifying neuropathic pain in children and adolescents is required.

Neuropathy assessment tools identify signs of chemotherapy toxicity and neuropathic pain in children with cancer [27]. The paediatric modified version of the Total Neuropathy Scale (Ped-mTNS) has been validated in children aged 5–18 years and assesses symptoms (sensory, motor, autonomic) and signs (light touch, pin sensation, vibration, strength, tendon reflexes). The paediatric Neuropathic Pain Scale©-Five (PNPS©-5) incorporates a Faces pain intensity score that can be used by children over 5–6 years of age to report pain intensity [28].

### 2.3. Examination and evaluation of somatosensory function

In addition to age-appropriate neurological examination, evaluation of somatosensory function can identify the mixed patterns of sensory gain or loss often associated with neuropathic pain. Bedside sensory tests with brush, cotton wool and pinprick stimuli [29] have identified altered sensitivity adjacent to surgical scars in children [30], and both the degree and distribution of allodynia can be



**Fig. 1.** Phenotyping neuropathic pain in older children and adolescents. **a.** History and Patient-reported Outcome Measures. (i) The majority of adolescents with neuropathic pain report average and worst pain in the last week at moderate-severe intensity (0–10 cm visual analogue scale: 0–3 mild, 4–7 moderate, >7/10 severe). These adolescents also report significant mood disturbance with moderate-severe levels of anxiety and depression (paediatric Index of Emotional Distress Scale: 0–10 mild, 11–14 moderate, 15–21 severe); high levels of catastrophising about pain (Pain Catastrophizing Scale – Child version: PCS-C 0–14 low, 15–25 moderate, >26 high/severe), and impaired quality of life (Pediatric Quality of Life Core Domains – Child Report (PedsQL-C): >84 normal range, 78–84 mild disease, <70 severe disease). (ii) Adolescents selected the degree to which different sensory and affective descriptors from the short-form McGill Pain Questionnaire were relevant to their current pain, ranging from no my pain does not feel like this, to my pain feels like this a lot or often. Figures are redrawn as summary representations from the author’s data [8] for 66 adolescents (10–17yrs) with peripheral neuropathic pain. **b.** Somatosensory function. (i) Schematic of quantitative sensory testing profiles, with Z-score comparisons to control values. Positive scores indicate gain of function (increased sensitivity and hyperalgesia) and negative scores indicate loss of function (decreased sensitivity and sensory loss). Testing encompasses multiple modalities: CDT, cold detection threshold; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; MDT, mechanical detection threshold; VDT, vibration detection threshold; DMA, dynamic mechanical allodynia with intensity rated on 0–10 numerical rating scale. (ii) Conditioned pain modulation (CPM) assessed with a variable test stimulus (pressure pain threshold, PPT on lateral knee) and cold conditioning stimulus (immersion of contralateral hand in 5 °C water bath). Schematic of potential responses: different degrees of inhibition (increase in PPT during and after immersion); facilitation (decrease in PPT produced by conditioning); and non-responder (degree of change less than standard error of PPT measurement). **c.** Confirmatory tests. A range of confirmatory tests for diseases or lesions of somatosensory nerves include: (i) neurophysiology assessments. For example, nerve conduction studies with a representative medial plantar sensory recording in an infant [48] (from Jabre et al. *Clin Neurophysiol* 2020, reproduced with permission from Elsevier); (ii) genetic testing. As an example, *SCN9A* mutations and resultant amino-acid substitutions in the voltage-gated sodium channel  $Na_v1.7$  associated with phenotypes of erythromelalgia (EM; sites associated with onset of erythromelalgia in childhood (EM paed) identified from a systematic review [34]), paroxysmal extreme pain disorder (PEPD), or congenital insensitivity to pain (CIP). Schematic of  $Na_v1.7$  (modified from Dib-Hajj et al. *Trends Neurosci* 2007, reproduced with permission from Elsevier); (iii) neuroimaging, and (iv) skin biopsy.

mapped with dynamic mechanical (brush) or thermal stimuli (cool and warm rollers) [8,30,31].

Standardised quantitative sensory testing protocols (QST) for assessment of neuropathic pain in adults [32] are also feasible in children from 6 to 8 years of age [33]. While QST is well-tolerated in children and adolescents, this psychophysical testing requires age-appropriate instructions, and an ability of the child to understand and maintain co-operation with testing, particularly with prolonged protocols or testing at multiple sites. QST includes evaluation of small and large fibre function, with a range of stimulus modalities applied at varying intensities to assess detection and pain/discomfort thresholds. Expressing different modalities as Z-score differences from control measures allows group [31] or individual [34] profiles to be plotted independent of the measurement parameter (Fig. 1b (i)). In brief, thermal thresholds assessing C- and A-delta function can be determined with a computer-controlled thermode delivering an increasing stimulus at a standardised rate, and the child presses a

button when a specific sensation is perceived (cool/cold or warm detection, cold or heat pain). Mechanical detection threshold with up-down application of von Frey hairs assesses A-beta function, and mechanical pain threshold with punctate probes of increasing weight evaluates A-delta function. Response relationships with repeated mechanical stimuli quantify mechanical pain sensitivity, and trains of punctate stimuli can be applied to quantify change in reported pain (wind-up ratio or temporal summation) [32].

Altered somatosensory function has been identified in a range of paediatric conditions associated with peripheral nerve injury, including chemotherapy-induced neuropathy in cancer survivors [35], erythromelalgia [34], prior surgery [31], and subclinical signs of diabetic neuropathy [36]. In adults with peripheral neuropathic pain, three distinct sensory profiles that may predict mechanism and improved treatment efficacy for subclasses of anti-neuropathic medication have been identified: sensory loss (denervation and spontaneous pain due to ectopic action potentials proximal to injured

nociceptors; greater response to anti-depressants); thermal hyperalgesia (peripheral sensitisation with low threshold and spontaneous activity in 'irritable nociceptors'; predicted efficacy with sodium channel blocker and moderate response to anti-depressant or gabapentinoid); and mechanical hyperalgesia (sensitisation and spontaneous activity in peripheral and/or central nervous system; predicted efficacy with gabapentinoid) [37,38]. These profiles have high specificity for separating clinical from healthy populations, and can also be identified in adolescents [8]. While clearly improving the recognition of neuropathic pain and quantification of altered somatosensory function, the ability of QST to improve prediction and monitoring of treatment response in children requires further investigation.

Conditioned pain modulation (CPM) evaluates descending endogenous pain modulatory mechanisms by determining the degree to which sensitivity to a test stimulus is inhibited or facilitated by a conditioning stimulus at a distant body site [39,40] (Fig. 1b (ii)). Conditioning reduces pain sensitivity (i.e. evokes descending inhibition) but impaired CPM (reduced degree of inhibition and/or facilitation) is common in patients with chronic pain [41]. CPM was impaired in adolescents with scoliosis, many of whom also reported neuropathic pain descriptors [42] and in adolescents with peripheral neuropathic pain [8]. As CPM has predicted persistent pain in children [43], and treatment response in adults with diabetic neuropathy [44], this methodology provides an additional outcome for clinical evaluation and controlled trials. As CPM may also be influenced by age (degree of inhibition increases throughout adolescence [45]), sex, and psychological factors [46,47] these potential contributing factors also need to be considered, and use of standardised methodology and reporting will improve comparison across different studies [39,40].

#### 2.4. Confirmatory tests

A number of objective diagnostic tests are suggested to confirm a lesion or disease of the somatosensory nervous system in adults (e.g. neuroimaging; skin biopsy; neurophysiological tests such as nerve conduction studies, heat and laser evoked potentials, microneurography; genetic tests) [1,4]. The use of specialised techniques in children with neuropathic pain is more limited, and the feasibility, sensitivity and clinical utility of these confirmatory tests in paediatric practice requires further assessment.

Sensory and motor nerve conduction studies for investigation of peripheral neuropathies are feasible with stick-on rather than needle electrodes in young children. These have the advantage of being independent of patient report, but require specialist expertise and age-matched normative data (Fig. 1c (i)) [48].

Skin biopsy identified reduced intraepidermal nerve fibre density (IENFD) suggestive of small fibre neuropathy in 50% of 7 to 20 year olds with chronic pain, many of whom reported descriptors or triggers suggestive of neuropathic pain [49]. However, specific relationships with pain were not evaluated. IENFD showed a negative correlation with age [49] as children have 3–4 times more neurites that are pruned throughout adolescence [50], and normative age-matched measures from a standardised site are required. While skin biopsy may improve early recognition of conditions with treatment implications [49,50], recent laboratory work documenting chemotherapy-induced allodynia and upregulation of Na<sub>v</sub>1.6 receptors in the absence of changes in IENFD [51], reinforce the need for multimodal evaluation as mechanisms contributing to neuropathic pain can vary with the type, degree, and duration of insult.

Identifying genetic variants associated with altered pain sensitivity and/or specific neuropathic pain conditions has played a significant role in mechanism-based understanding. For example, molecular genetic studies have linked alterations in the function of voltage-gated sodium channels, such as Na<sub>v</sub>1.7 (Fig. 1c (ii)) to neuropathic pain associated with inherited conditions and small fibre neuropathy, and identified new treatment targets [52]. Advances in

genetic analysis [53], and inclusion of patients with neuropathic pain in large rare-disease cohorts integrating clinical and research testing [54] will further enhance discovery of genetic variants and diagnosis of conditions associated with neuropathic pain.

Neuroimaging can play a confirmatory role by identifying lesions/diseases of the peripheral or central nervous system. In addition, alterations in brain structure, function and/or connectivity identified with MRI have improved understanding of changes in pain processing and endogenous modulatory mechanisms with chronic pain states, and provide potential biomarkers and standardised end-points for clinical trials [55]. In adolescents with chronic pain, alterations in brain circuitry and/or activation have identified: brain regions associated with altered somatosensory function and pain modulation; interactions with psychological factors (eg. amygdala and pain-related fear [56], frontolimbic circuitry and pain-related distress [57]); and changes following treatment [13,58]. Ongoing studies in adolescents with neuropathic pain will provide further insights [59,60].

### 3. Causes with specific paediatric or emerging implications

Common causes of neuropathic pain in children differ from adults (Table 1). Central lesions such as post-stroke, and peripheral causes such as postherpetic neuralgia and diabetic neuropathy are much more common in adults, and prevalence increases in the elderly. Pain after traumatic nerve injury during early childhood (e.g. neonatal brachial plexopathy, amputation) is less apparent than when the same injury occurs at older ages, but inability to report and/or delayed onset of symptoms may be contributing factors [3].

#### 3.1. Persistent post-surgical pain

Persistent post-surgical pain (PPSP) is increasingly recognised in children, with rates as high as 20–40% following major surgery in adolescents [61]. Neuropathic features (based on DN4 score  $\geq 4$ ) have been reported in a high proportion of adolescents with PPSP following scoliosis surgery [26]. In clinical cohorts, alterations in somatosensory function adjacent to scars can persist for many years following paediatric surgery, but relationships between self-reported sensory abnormalities and pain intensity vary [31,62]. However, PPSP accounted for a large proportion of adolescents in a neuropathic pain cohort from our tertiary paediatric pain service, and QST identified distinct somatosensory profiles and dynamic allodynia in the region of pain and prior surgical scars, and impaired CPM in a higher proportion than healthy controls [8,46]. Pre-operative alterations in temporal summation, pressure pain threshold and CPM have been associated with PPSP in adults [63], and the ability of sensory changes to predict PPSP risk or guide preventive interventions warrants investigation in adolescents.

#### 3.2. Cancer treatment-related neuropathic pain

Acute and chronic neuropathic pain in children with cancer is often related to treatment, although solid tumours may cause compression of peripheral nerves (e.g. neuroblastoma), or directly involve peripheral nerves (e.g. neurofibromatosis [20]) or the brain. Novel immunotherapy treatments can improve survival with paediatric solid tumours, but may have significant adverse effects, such as acute neuropathic pain with anti-disialoganglioside GD2 monoclonal antibodies for high-risk neuroblastoma [3,64]. Neuropathic pain can commence within days of chemotherapy, occurring in 50–90% of children treated with platinum compounds (e.g. cisplatin for solid and germ-cell tumours) [28] and 35–45% following vincristine for acute lymphoblastic leukaemia [65]. Pain and chemotherapy-induced peripheral neuropathy (CIPN) following vincristine can be persistent and severe, and is worse in older children [28]. Within 3 years of ALL

treatment, CIPN was identified by clinical examination in 14% and by nerve conduction studies in 34% [66], and by altered sensitivity with different QST modalities in 26–73% [35]. At older ages, survivors of childhood cancer continue to be at increased risk of sensory loss and pain relative to healthy siblings [67].

### 3.3. Preclinical studies: postnatal age and nerve injury

Pre-clinical studies utilising different types of nerve injury demonstrate behavioural responses and mechanisms that can differ when the same insult occurs in juvenile versus adult rodents. Following traumatic nerve injury, age-dependent changes in spinal neuro-immune signalling result in a subsequent shift from anti- to pro-inflammatory responses at older ages, that then increases sensitivity of spinal circuits and produces delayed onset allodynia [68]. Similarly, following administration of the chemotherapeutic agents vincristine [69] or cisplatin [70] in juvenile rodents, persistent hypersensitivity emerges only at older ages. Surgical incision in neonatal rodents alters long-term sensitivity of spinal circuits, spinal neuroimmune signalling, and activity in ascending and descending pathways, that contributes to altered baseline thresholds and an enhanced response to surgical injury in later life [71]. Therefore, both pre-clinical and clinical data identify age-dependent changes in mechanisms and/or presentation that support the potential for, and need to recognise, delayed onset neuropathic pain following traumatic nerve injury, cancer treatment, and surgery in children.

### 3.4. Neuropathic pain presentations and rare diseases

Diseases associated with neuropathic pain in childhood that are rare, but have specific implications for treatment and genetic counselling need to be recognised or excluded.

Sodium (Na) channelopathies can produce severe symptoms with specific distributions and triggers of pain. Erythromelalgia related to gain of function mutations of *SCN9A* and enhanced  $\text{Na}_v1.7$  channel activation results in severe episodic pain and redness in children, typically in the feet, hands and in some cases the ears. Pain is exacerbated by environmental temperature and relieved by cooling, to the extent that prolonged immersion in ice water to gain relief can result in local tissue injury or hypothermia. The genotype and specific amino acid substitution influences the degree of hyperpolarising shift of the  $\text{Na}_v1.7$  channel, severity of symptoms, age of onset, and in some cases can predict relative response to non-specific sodium channel agents (mexiletine or carbamazepine) [34,52]. Paroxysmal extreme pain disorder, related to different *SCN9A* mutations and patterns of altered  $\text{Na}_v1.7$  kinetics, is associated with pain and erythema in the buttocks and legs in early infancy and mandibular pain at older ages, can be triggered by mechanical stimuli, and may respond to carbamazepine [52].

Fabry disease is a multisystem disorder due to variants in the *GLA* gene [72]. Deficiency of lysosomal alpha-galactosidase A (AGAL-A) results in accumulation of globotriaosylceramide ( $\text{Gb}_3$ ) and globotriaosylsphingosine ( $\text{LysoGb}_3$ ) in lysosomes in virtually all cell types, including the nervous system. Neuropathic pain in the feet and hands (most commonly soles, palms and fingertips) of children may be the first presentation of Fabry disease, with onset at younger ages (median 7 years) and more severe symptoms in boys due to X-linked inheritance. Typical descriptors include burning and tingling, with episodic pain initially, that is triggered by exercise, heat and fever. Liaison with metabolic physicians for ongoing monitoring of effects on other organ systems (e.g. renal, cardiac gastrointestinal) and consideration of enzyme replacement therapy is essential to optimise management and improve outcome [72].

## 4. Management/treatment

Neuropathic pain in children can be severe, persist for many years, and be difficult to manage. Detailed discussion of management is beyond the scope of this review, but some general principles are outlined. As with other presentations of chronic pain in children, a biopsychosocial assessment and formulation is required [7]. Significant pain-related disability, emotional distress, fear of movement and catastrophising about pain (Fig. 1a (i)) requires interdisciplinary management with physical and psychological interventions to minimise adverse effects on educational attainment, social and family function. Pain education for the patient and family, with explanation about the unusual symptoms and mechanisms of spontaneous pain, is particularly relevant for neuropathic pain. Pharmacological management is extrapolated from evidence-based guidelines for adults with neuropathic pain [6] as very few controlled trials have been performed in children [74]. Gabapentinoid anti-convulsants and tricyclic anti-depressant medications tend to be first-line therapy, but benefit can be limited. An initial therapeutic trial allows gradual titration to minimise sedation, and dose adjustments or cessation based on clinical response [3]. Behavioural disturbances or suicide risk should be considered at initial assessment, and monitored during therapy with gabapentinoids and serotonin-selective reuptake inhibitor anti-depressants in adolescents. Tricyclic anti-depressants given once daily in the evening can improve sleep as well as pain, with a baseline ECG recommended to avoid potential cardiac conduction abnormalities in patients with prolonged QT-interval [27]. For children with localised neuropathic pain, case series report benefit with lidocaine patches [27,75]. Additional agents that are second line or have as yet inconclusive evidence in adults [6] also require further benefit-risk evaluation in children.

There is a clear need for additional controlled trials in children with neuropathic pain; ideally with larger and more homogeneous samples. Improved phenotyping with a range of patient-reported outcome measures, QST and neuroimaging is proposed to improve individualised therapy and stratification for clinical trials in adults [37,38]. Alongside existing validated questionnaires that assess different domains of pain, function, adverse effects, and economic factors [24], QST and neuroimaging are feasible in children and adolescents with neuropathic pain [59], and may provide additional standardised end-points for research trials.

## 5. Outstanding questions

Neuropathic screening tools have the potential to improve recognition by a range of healthcare providers. The sensitivity, specificity and clinical utility of existing neuropathic screening tools need further validation in older children and adolescents, and novel tools that can aid assessment of potential neuropathic pain in younger children require development.

Controlled trials are required to enhance evidence-based management of neuropathic pain in children. Comparative efficacy and side-effect data is needed to guide the choice and dose of pharmacological interventions. Additional data related to the degree and duration of benefit with different components and methods of delivery of interdisciplinary chronic pain management may be generalisable to children with neuropathic pain.

Cross-sectional cohort studies demonstrate the feasibility of detailed phenotyping and somatosensory research methodologies, but the utility and sensitivity as outcome measures for detecting clinically meaningful change in clinical trials requires evaluation.

Longitudinal studies assessing pain, somatosensory function, physical and psychosocial functioning in larger and more homogeneous samples of children with neuropathic pain are needed to evaluate the impact of age, sex, and underlying condition on natural history and treatment response.

Further preclinical studies in developmental models of diseases or injuries associated with neuropathic pain will improve understanding of age- and sex-dependent differences throughout childhood, and allow evaluation of the relative efficacy and safety of mechanism-based interventions.

## 6. Conclusions

Paediatric practice encompasses a wide range of developmental stages, from preterm neonates through to late adolescence, that influences the underlying causes, mechanisms and presentation of neuropathic pain. Improved recognition and phenotyping in children with different diseases or lesions of the somatosensory nervous system producing neuropathic pain are important first steps. Increased expertise and resources for detailed assessments of somatosensory function, age-matched data for confirmatory tests that are feasible and acceptable in children of different ages, and advances in genetic analysis will improve mechanism-based understanding and inform the design of clinical trials that will advance evidence-based management of neuropathic pain in children.

## 7. Search strategy and selection criteria

Data for this review were identified by a systematic search of PubMed using the term “neuropathic” AND “pain” AND “children”, “neuropathic pain questionnaire AND children” or were manually sought from relevant articles. Only articles published in English were included. Preference was given to: peer-reviewed clinical articles in paediatric series; relevant systematic reviews; comparative adult clinical recommendations, guidelines and evidence published by the International Association for the Study of Pain (IASP) Neuropathic Pain Special Interest Group (NeuPSIG); and publications from the last 5 years.

## Contributors

Suellen Walker compiled the figure and table, and wrote and revised the manuscript.

## Declaration of Interests

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