

22. Neuropathic pain in children

Madeleine Verriotis and Suellen Walker

Abstract

Lesions or disease of the somatosensory nervous system can produce neuropathic pain (NP). Typical features include spontaneous or paroxysmal pain, often described as burning, shooting, like electric shocks, or pins and needles. NP does occur in childhood, but age at the time of injury may influence the risk of NP following traumatic nerve injuries. While conditions commonly associated with NP in adults may be less common in childhood (eg. trigeminal neuralgia) other conditions (e.g. Fabry's disease and erythromelalgia), may present with pain in childhood and present a diagnostic challenge for paediatric practitioners.

Keywords

Neuropathic pain, children, lesion, disease, traumatic, nerve injuries

Summary

Lesions or disease of the somatosensory nervous system can produce neuropathic pain (NP). Typical features include spontaneous or paroxysmal pain, often described as burning, shooting, like electric shocks, or pins and needles. NP does occur in childhood, but age at the time of injury may influence the risk of NP following traumatic nerve injuries. While conditions commonly associated with NP in adults may be less common in childhood (eg. trigeminal neuralgia) other conditions (e.g. Fabry's disease and erythromelalgia), may present with pain in childhood and present a diagnostic challenge for paediatric practitioners.

Introduction

Neuropathic pain (NP) has been defined as pain caused by a lesion or disease of the somatosensory nervous system (Jensen et al., 2011). Chronic pain is reported by up to 6% of children and adolescents (Howard et al., 2014), but the proportion with NP is not clear. However, children with neuropathic pain and Complex Regional Pain Syndrome (CRPS) comprise a significant proportion of cases referred to paediatric chronic pain clinics (Kachko et al., 2014; Rajapakse et al., 2014). Epidemiological studies suggest a prevalence of chronic pain with neuropathic features of 3.3 to 8.2% in the adult population, but conditions associated with NP in children differ from those commonly reported in adults (Howard et al., 2014):

- many conditions associated with NP in adults are rare or not associated with significant pain in children (eg. Parkinson's disease, Alzheimer's disease, post-stroke pain);
- the incidence of post-herpetic neuralgia and trigeminal neuralgia is much lower in children (Hall et al., 2013, 2006);
- painful diabetic neuropathy is a feature of more prolonged disease and is rarely reported before 14 years of age (Hall et al., 2006), but sensory changes have been detected in children prior to onset of pain (Blankenburg et al., 2012);
- some NP conditions are increasingly recognised in children (eg. Complex Regional Pain Syndrome, phantom limb pain, or NP following trauma or surgery);
- NP may be the presenting symptom during childhood of specific genetic conditions (e.g. Fabry's disease or erythromelalgia);
- children may have increased susceptibility to certain types of painful neurological injury (e.g. toxicity following mercury exposure).

NP may be considered as a clinical entity in its own right with a common pattern of symptoms and signs, often with similar management irrespective of the underlying cause. In later sections of this chapter, NP associated with specific conditions in children will be outlined. The classification of CRPS as a neuropathic pain condition is debated, but in this text is included in **Chapter 25 Clinch, Non-inflammatory musculoskeletal pain.**

Pharmacologic management of NP is often extrapolated from adult data (Attal et al., 2010; Dworkin et al., 2010)(see **Chapter 48 Campbell, Drugs for neuropathic pain**). Laboratory data

regarding mechanisms and effects of nerve injury in early life are covered in **Chapter 7, Beggs (Table 22.1)**.

Assessment and diagnostic features

Current guidelines for the assessment and diagnosis of NP are designed for adults, but are often extrapolated to older children or adolescents (Howard et al., 2014).

- Screening questionnaires to identify neuropathic pain include: LANSS, Leeds Assessment of Neuropathic Symptoms and Signs (Bennett, 2001); DN4, Douleur Neuropathique en 4 questions (Bouhassira et al., 2005); NPQ, Neuropathic Pain Questionnaire (Krause and Backonja, 2003); painDETECT (Freyenhagen et al., 2006); ID-Pain, identify Pain (Portenoy, 2006). The sensitivity (66-91%) and specificity (74-94%) of these tools fall within reasonable ranges in adults (Bennett et al., 2007; Haanpää et al., 2009). While the S-LANSS (Chou et al., 2014), painDETECT (Voepel-Lewis et al., 2017), and DN4 (Julien-Marsollier et al., 2017) have been used to identify neuropathic features of persistent postsurgical pain, these tools have not yet been validated in children.
- Pain history including: evaluation of intensity (assessed by numerical rating scale or visual analogue scale); quality (sensory descriptors); temporal aspects of pain (frequency, spontaneous/paroxysmal or continuous, aggravating/relieving factors); and response to treatment. History remains the mainstay of diagnosis, and many children use descriptors that are considered “typical” of neuropathic pain, such as burning, shooting, radiating, electricity-like, pain on contact, stabbing, pricking, tingling, pins and needles, and pinching (Howard et al., 2014). However, young children may be unable to clearly describe their pain in these terms.
- Sensory examination to verify the lesion of the somatosensory system (sensory, motor and autonomic signs; allodynia and hyperalgesia; hypoaesthesia and hypoalgesia). Sensory abnormalities on clinical examination are more difficult to elicit in infants and young children. Quantitative sensory testing evaluates patterns of change in association with NP in adults (Baron et al., 2017), but paediatric use of this technique is often limited to research studies (Sethna et al., 2007; Lebel et al., 2008), although some reference values exist in children (e.g. Blankenburg et al., 2010; van den Bosch et al., 2017)
- Assessment of disability, quality of life, sleep, and mood. In adults, NP is associated with a greater disease burden than other forms of chronic pain, with impacts on quality of life, impaired sleep, higher anxiety/depression scores, and increased use of healthcare and specialist services (Attal et al., 2011; Smith and Torrance, 2012). The impact of chronic pain on quality of life, mood, and disability is covered in many chapters throughout this text, but relatively few paediatric series have evaluated the impact of NP per se on quality of life (Kandula et al., 2016), and disease-specific pain or quality of life scales are often not validated in children (Hopkin et al., 2016).

- Additional tests may be indicated, although many are limited to research settings or specific cases (eg. electroneuromyography, microneurography, functional brain imaging, skin biopsy). Investigations may be required to confirm a specific underlying diagnosis (e.g. Fabry's disease) or to exclude other causes.

Neuropathic pain following trauma and surgery

Laboratory models of traumatic peripheral nerve injury have demonstrated a reduced susceptibility to neuropathic pain if the injury is performed at a younger age (first 3 postnatal weeks in the rodent)(see Chapter 7 Beggs; and Chapter 3 Moriarty and Walker Long-term effects of early pain: animal models). Clinical studies are also suggestive of an increased likelihood of neuropathic pain following trauma or surgery at older ages.

Post-surgical neuropathic pain

Neuropathic pain can occur acutely or as a feature of persistent post-surgical pain in adults (Howard et al., 2014; Schug et al., 2016). Although much data comes from retrospective questionnaires (Aasvang and Kehlet, 2007; Kristensen et al., 2010), prospective evaluations of persistent postoperative pain in children are now emerging.

Determining the prevalence of persistent postsurgical pain (PPSP) in children is further complicated by differing definitions of PPSP (e.g. any pain vs. moderate/severe pain, and pain lasting >2-6 months), inclusion of a range of surgical procedures, and variable durations between time of surgery and pain report (Rabbitts et al., 2017a; Williams et al., 2017). A recent meta-analysis of studies published between 2012 and 2016 reported a median prevalence of PPSP of 20% at 1 year following surgery, based on 4 studies with 628 participants having a range of different surgeries, but many of which had scoliosis or major chest wall surgery during adolescence (Rabbitts et al., 2017a). A more recent study similarly reported a high incidence of persistent pain following scoliosis (Julien-Marsollier et al., 2017). Further research is needed to identify the prevalence of PPSP after specific surgical interventions.

In adults, pre-surgical risk factors for developing PPSP include older age, female sex, greater pre-surgical and post-surgical pain, and higher levels of pre-surgical anxiety and pain catastrophizing (Rabbitts et al., 2017a; Williams et al., 2017). Surveys suggest that older age may also be associated with higher risk for developing PPSP in children, although recall bias in children undergoing surgery at a younger age cannot be ruled out (Williams et al., 2017). A meta-analysis based on 3 studies found no effect of either age or sex on the incidence of PPSP, although the majority of patients were female (Rabbitts et al., 2017a). Pre-operative pain was associated with increased incidence of PPSP in some studies but not others (Walker, 2015; Rabbitts et al., 2017a; Williams et al., 2017; Voepel-Lewis et al., 2017). A small number of studies reported that higher pain intensity within 2 weeks following surgery was associated with increased risk of PPSP or slower recovery and higher pain scores at 4 and 12 months (Williams et al., 2017). Other medical factors including scoliosis severity and

time since scoliosis diagnosis did not predict PPSP (Rabbitts et al., 2017a; Williams et al., 2017).

Non-medical factors, including pre-surgery child anxiety and poorer pain coping efficacy, and parental pain catastrophizing pre-operatively and 2-3 days post-operatively have also been associated with increased pain intensity 6-12 months following surgery (Rabbitts et al., 2017a; Williams et al., 2017). Interestingly, pain unpleasantness 2-3 days post-operatively predicted the transition from high acute post-operative pain to PPSP at 6 months, while anxiety sensitivity predicted the maintenance of PPSP from 6 to 12 months (Pagé et al., 2013). Greater dissatisfaction with body image may also be associated with slower post-surgical pain recovery (Williams et al., 2017). Poorer sleep quality was associated with greater pain intensity the following day in 10-18 year olds followed up longitudinally over 4 months post-surgery, but further research is required to assess whether disruption of sleep post-surgery contributes to the transition to PPSP (Rabbitts et al., 2017b).

While there is limited reporting of the contribution of neuropathic pain to PPSP, both early and delayed onset of pain with neuropathic descriptors has been reported in small series (e.g. Howard et al., 2014; Julien-Marsollier et al., 2017). Using Quantitative Sensorty Testing, persistent mixed patterns of sensory gain and loss have been associated with scars related to inguinal surgery (Kristensen et al., 2012) or thoracotomy (Kristensen et al., 2010) in childhood and following neonatal surgery in extremely preterm-born young adults (Walker et al., 2018).

In summary, neuropathic pain can occur following surgery in children, but additional larger studies are required to evaluate the prevalence and duration of symptoms, associated risk factors, potential for nerve damage associated with different types of surgery, and impact of perioperative analgesic and anaesthetic regimens.

Phantom limb pain

Limb amputation is associated with nerve damage and can lead to altered sensory function that is classified as non-painful phantom sensations or phantom limb pain. The majority of current literature is based on retrospective case series with differing methodology, variable response rates and wide variability in prevalence (Howard et al., 2014; DeMoss et al., 2018).

Characteristics of phantom pain

Pain that is experienced in the region of the missing limb following amputation (i.e. phantom limb pain) has been described by children as sharp, tingling, stabbing, pins & needles, throbbing, piercing, squeezing, tight and uncomfortable (Howard et al., 2014; DeMoss et al., 2018).

Phantom pain is frequently of moderate or severe intensity, with reported mean ratings of 5.29 ± 2.4 (Wilkins et al., 1998) and 6.4 ± 1.8 out of 10 (Wilkins et al., 2004). Typically, pain is episodic, lasts for seconds or minutes, with a frequency varying from daily to monthly, and only a small proportion of children have reported constant pain.

Exercise, objects approaching the stump, cold weather, and 'feeling nervous' have been reported to trigger episodes of phantom pain. Psychosocial triggers were more common in girls, whereas pain was triggered by physical stimuli in a higher proportion of boys (Howard et al., 2014).

Associated phenomena

Non-painful sensations experienced in the region of the missing limb (i.e. phantom sensations) are reported by 50-100% of children following surgical amputation and in 7-20% of children with congenitally deficient limbs (Howard et al., 2014). These have been described as tingling, pins and needles, tickling, 'feels asleep', numb, itching, and prickling (Howard et al., 2014), and appear to have minimal impact on daily activities (Wilkins et al., 2004, 1998).

Stump pain often co-exists with phantom limb pain but may also occur in isolation. A higher incidence has been reported following surgery than in children with a congenitally absent limb (Wilkins et al., 2004, 1998).

Incidence of phantom limb pain

It is now well established that NP can follow amputation in children, but it is difficult to accurately estimate the incidence. Much of the data comes from retrospective questionnaires with response rates below 50% or from medical case notes that may not accurately record all symptoms. Samples are often small, may be derived from the community or clinics, and the duration between surgery and assessment is often variable. Factors that have been associated with an increased incidence in children include (Howard et al., 2014; DeMoss et al., 2018):

- Surgical amputation (49-76%) versus congenitally deficient limbs (3-4%).
- Older age at time of amputation. A negative correlation has been reported between age at amputation and onset of a phantom limb but it is not clear if this relationship holds for phantom pain as well as phantom sensations (Melzack et al., 1997).
- Cancer and Chemotherapy. Phantom pain following amputations for cancer has been reported in 48-90% of children, and was higher than following amputations for trauma (32/67 versus 1/8). Perioperative chemotherapy may also increase the risk of phantom pain (74% incidence) compared to post-operative (44%) or no (12%) chemotherapy. Other causes of cancer-related neuropathic pain are discussed later in the chapter.
- Major burns due to electrical (10/19) versus flame (3/15) injury (Thomas et al., 2003).
- Preoperative pain. The presence of pain prior to amputation was reported in 35-75% of patients who developed phantom pain (Krane and Heller, 1995; Wilkins et al., 1998), and in one series both patients with the most persistent pain had also experienced pain prior to amputation (Burgoyne et al., 2012).

Time course

Pain onset in the early post-operative period is common (53%- 85%) (Krane and Heller, 1995; Wilkins et al., 1998), but may be delayed for weeks to years in some cases (Melzack et al., 1997). Earlier onset is more common in those receiving perioperative chemotherapy (Howard et al., 2014).

There is a perception that phantom limb pain resolves more rapidly in children than in adults, but there is limited supporting evidence. Phantom pain is often poorly documented in medical case notes (Krane and Heller, 1995), and there has been little prospective follow-up. Phantom limb pain can persist for months or years (Krane and Heller, 1995; Burgoyne et al., 2012). More detailed prospective studies are needed to further evaluate prevalence and time course.

Obstetric Brachial Plexus Injury (OBPI)

The brachial plexus innervates the upper limb and is formed from the lower cervical (C5,6,7,8) and the first thoracic (T1) nerve roots. Obstetric complications, such as shoulder dystocia or breech delivery can be associated with traction injuries of the brachial plexus in the newborn. The associated nerve lesions range in degree from neuropraxia to complete root avulsion, and can affect part or all of the plexus. Surgical exploration and repair, where possible, is often performed if there is no spontaneous recovery or elbow flexion by 3-6 months (Malessy and Pondaag, 2011). The incidence of OBPI ranges between 0.38 and 4.6 cases per 1000 births (Smania et al., 2012). Associations between OBPI and pain or sensory function in later life have been assessed in a small number of series, which vary in the outcomes measured and the time since injury. In addition, it is difficult to differentiate neuropathic pain associated with the initial injury from pain related to: re-innervation following early microsurgical repair and nerve grafts; subsequent surgical procedures (e.g. tendon transfers or rotational osteotomies) that may be required throughout childhood to improve function; trophic injuries associated with reduced sensory function; and musculoskeletal pain.

A recent systematic review of 29 articles (mean follow-up: 10.8 years) that assessed sensory function, pain, or proprioception, highlights the large proportion of patients having poor sensory function in the affected vs. unaffected limb (Corkum et al., 2017). In a small number of studies, patients subjectively reported normal tactile sensation (93.7%), whereas the majority of studies using objective measures (Semmes-Weinstein monofilament and two-point discrimination) found a significant proportion (41.2%) of patients with abnormal sensation. In one series, Quantitative Sensory Testing demonstrated reduced thermal sensitivity in 16% of patients (Strömbeck et al., 2007), and altered sensitivity to pinprick has been reported in 30.9% (Corkum et al., 2017). Retrospective surveys that included pain questions showed mixed results, with prevalence ranging from pain of low intensity and minimal impact on patients' lives in 66.2% to significant pain affecting function in 50% of

patients. The severity of the injury may have an impact, as patients with complete BPI were less likely to recover tactile sensation and reported increased pain (Corkum et al., 2017).

There is often limited information on the specific type of pain. Although some studies suggest neuropathic pain is rare following OBPI (Anand and Birch, 2002; Strömbeck et al., 2007), this may be influenced by the severity of the injury or subsequent surgery. Twenty-one of 46 children with OBPI requiring microsurgery (nerve grafting or transfer) before 12 months reported that their affected limb felt different from their unaffected limb, and used words that are suggestive of neuropathic origin, but did not always describe these sensations as pain (Ho et al., 2015). Similarly, self-mutilation behavior, which may reflect sensory loss, and/or painful dysaesthesias in a hypoaesthetic or reinnervated area, was more common following microsurgery involving the plexus (29.1%; 7/24) (McCann et al., 2004).

These studies highlight that altered sensation and pain are relatively common but higher quality studies assessing sensory function, pain, and quality of life using objective measures and validated tools are required (Corkum et al., 2017).

Trauma during childhood

Brachial plexus injury during childhood

Trauma during childhood can result in brachial plexus injury (BPI), but the number of reports and details of associated pain are limited. Ten children aged 3 to 16 yrs had BPI and fractures following motor vehicle accidents. Reconstructive surgery was performed 1 to 8 months later, and there were no reports of deafferentation pain (El-Gammal et al., 2003). In a further 25 cases of traumatic BPI (2mths to 14yrs) related to motor vehicle accidents, 16 required plexus exploration and several subsequent orthopaedic procedures. Two teenagers with root avulsions complained of moderate pain, but there are no further details of the nature or time course of symptoms (Dumontier and Gilbert, 1990). By contrast, BPI in association with proximal humerus fracture in 4 patients (10-14yrs), was associated with neurologic recovery by 5 to 9 months, but all had NP (often described as burning) for at least 6 months (Hwang et al., 2008).

Peripheral nerve injury

Neuropathic symptoms and increased sensitivity to thermal or pinprick stimuli were more common in older children (>5yrs) during average 2-year follow-up of 49 children with distal upper limb nerve injury (Atherton et al., 2008). Pins and needles and painful dysaesthesias were associated with nerve injury in 13.3% of 166 children with supracondylar fracture (Kwok et al., 2016).

Spinal cord injury

Pain after spinal cord injury (SCI) in adults is classified as nociceptive (musculoskeletal, visceral, other) or neuropathic (Bryce et al., 2012), with the latter categorised as:

- “at level SCI pain” occurring in a segmental pattern within 3 dermatomes of the neurological level of the injury, and likely due to injury to the nerve roots and/or cord;
- “below level SCI pain” occurring more than 3 dermatomes below the neurological level of injury, which is a result of damage to the spinal cord, and can occur following either complete (no motor function preserved below the level) or incomplete injuries;
- other co-existent causes of NP not related to the spinal lesion (eg. trigeminal neuralgia).

Only 3-5% of new cases of SCI are in children, but SCI can occur in neonates as a complication of delivery, and tends to have a better recovery than seen at older ages (Pape, 2012). Complete cord lesions are more common in younger age groups, and there is a male predominance at all ages. Follow-up on average of 15 years following SCI (mean age at injury 14 years, n=216) reported an overall incidence of pain at any site of 69%, with younger age at injury associated with orthopaedic complications such as scoliosis and hip subluxation, and older age at injury associated with ankle pain and spasticity (Vogel et al., 2002). Adults with paediatric-onset injury report lower levels of pain and improved function than those injured during adulthood, although values are still worse relative to healthy controls (Ma et al., 2016). In adults with paediatric-onset injury, pain interference is associated with poorer sleep (January et al., 2015) and is predictive of depressive symptoms (January et al., 2014), while factors associated with increased pain intensity, duration, frequency, and/or interference include older age at injury, longer duration of injury, and psychological (depression and anxiety symptoms) factors (Murray et al., 2017). Similarly, neuropathic pain has also been reported to be less common if injury occurs at a younger age: 26% (24/91) before 20 years of age versus 45% (139/311) at older ages (Werhagen et al., 2004). In a series of 31 participants, aged between 5 months and 18 years at the time of SCI, 65% reported chronic pain, and this had neuropathic features in 19%, but was associated with less interference in daily activities than in adults (Jan and Wilson, 2004).

Cancer-related neuropathic pain

Neuropathic pain occurs in 20-40% of adult patients with cancer (Howard et al., 2014). The overall rate of cancer-related neuropathic pain is likely to be lower in children, but as noted above, phantom limb pain is more common in children who require amputations for cancer and perioperative chemotherapy. Significant pain may occur in specific populations:

- *Primary tumours* within the nervous system. Neurofibromatosis type 1 (NF1) and type 2 (NF2) are neurocutaneous disorders associated with tumors affecting the central and peripheral nervous systems (Schulz et al., 2018; Ardern-Holmes et al., 2017). Pain is experienced by 46-71% of children with plexiform neurofibromas (Howard et al., 2014; Lai et al., 2017), and increasing pain and rapid growth of the tumour may indicate development of a malignant nerve sheath tumour (Ardern-Holmes and North, 2011). Pain can also have significant impact on health-related

quality of life in children with NF (Krab et al., 2009; Nutakki et al., 2017; Wolters et al., 2015) and this condition is also discussed in [Chapter 33 Collins and Mherekumombe, Persisting pain in childhood medical illness.](#)

- *Tumour invasion or compression* of neural structures (spinal cord, spinal nerve roots, nerve plexus, peripheral nerves). As the incidence of solid tumours is lower in children, tumour invasion/compression is less common in children than in adults, but can result in severe pain with high analgesic requirements, which may be difficult to control with opioids alone, and in some cases requires regional blockade with local anaesthetic (Howard et al., 2014).
- *Neurovascular compression* (e.g. trigeminal neuralgia; see subsequent section)

Cancer treatment-related neuropathic pain

Treatment-related NP may occur following surgery (e.g. [post amputation pain](#); see ['Phantom limb pain' section](#)) or chemotherapy. Perioperative chemotherapy has also been associated with an increased incidence and earlier onset of post-amputation pain (Smith and Thompson, 1995).

Peripheral neuropathy occurs in 50-90% of those treated with platinum compounds (cisplatin) and almost half of those with vinca alkaloids (vincristine) (Vondracek et al., 2009). In 21 children with solid tumours and 9 with leukaemia aged between 10 and 17 years, neuropathic pain symptoms (paraesthesia, numbness and burning pain in the fingers and toes, hyperalgesia and tactile allodynia) commenced within days of beginning chemotherapy. In addition, pain was severe (mean baseline VAS >75/100) (Vondracek et al., 2009). In a retrospective review, 174/498 patients developed peripheral neurotoxicity with vincristine treatment for acute lymphoblastic leukaemia (Angheliescu et al., 2011). Associated NP occurred in 35%, with recurrent episodes in 16 - 30.6%. Age at diagnosis ranged from 1 to 19 years, but had minimal influence on the rate of NP, which varied from 31% in the 1-5 year group, to 40% in those aged 16-20 years. Pain was described as aching, burning, cramping, tingling, numbness, sharp, or stinging; and was most common in the lower limbs, back and jaw (Angheliescu et al., 2011).

Data from a large US Childhood Cancer Survivor Study (>388,000 from 1975 to 2011; diagnosis 1970-1986) indicates persistent pain of moderate or excruciating severity in 12.3% of childhood cancer survivors, but there is no information about the proportion with neuropathic pain (Lu et al., 2011). Increased risk of back pain was reported in this study (Bowers et al., 2012), consistent with adult research where neuropathy was associated with the number of intrathecal chemotherapy injections (Ness et al., 2017). While survival following childhood cancer is increasing, self-reported health has not significantly improved (Ness et al., 2017). Further studies are required to assess incidence and severity of chemotherapy-induced peripheral neuropathy and neuropathic pain, their impact on quality of life and function, potential risk factors, and management of pain (Kandula et al., 2016; Mohrmann et al., 2017). While somatosensory changes associated with chemotherapy-induced peripheral neuropathy and NP have been reported in adults using

QST (e.g. Velasco et al., 2015; Reddy et al., 2016), no studies have assessed sensory changes in children and adolescents, and screening tools for detecting peripheral neuropathy and NP in this cohort have not been validated.

Treatment of high-risk neuroblastoma with a monoclonal antibody directed against the tumour-associated disialoganglioside GD2 can result in severe acute pain in children (Anghelescu et al., 2015; Mora, 2016). Laboratory studies have confirmed mechanical allodynia as a result of C-fibre activation (Xiao et al., 1997) and complement activation (Sorkin et al., 2010), which is reduced by gabapentin (Gillin and Sorkin, 1998). Current clinical treatment protocols incorporate neuropathic pain management strategies, such as oral gabapentin, and addition of intravenous ketamine or lidocaine if pain is inadequately controlled by intravenous opioid (Wallace et al., 1997)(see also Chapter 48 Rastogi and Campbell, Drugs for neuropathic pain).

Metabolic disorders

Fabry's Disease

Clinical features

Pain is a common presenting symptom in Fabry's disease, and often has an onset during childhood (Howard et al., 2014; Laney et al., 2015; Hopkin et al., 2016). As pain may be the only feature for some years, Fabry's disease should be considered in the differential diagnosis of pain clinic referrals (Pagnini et al., 2011). 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 (Howard et al., 2014; Hopkin et al., 2016) and can be triggered by changes in environmental or body temperature, exercise, or emotional stress. Pain is present in over 70%, with a higher incidence in males (80% vs 65%) (Hoffmann et al., 2007), and has a significant impact on quality of life. Other features of Fabry's disease include hypo- or hyperhidrosis, gastrointestinal disturbances and abdominal pain, angiokeratomas, and ophthalmological abnormalities (cornea verticillata)(Mehta et al., 2010; Laney et al., 2015).

Pathophysiology

Fabry's disease is an X-linked recessive disorder, and females typically have less severe symptoms that develop at a later age (Rodrigues and Kang, 2016). Mutations in the *GLA* gene that encodes the lysosomal enzyme alpha-galactosidase A result in failure to catabolize lipids containing alpha-D-galactosyl moieties. Accumulation of glycolipids, including globotriaosylceramide (Gb3) in cells and tissues results in dysfunction of multiple organ systems including heart, kidney, gastrointestinal tract, and nervous system (Howard et al., 2014; Rodrigues and Kang, 2016). Neuropathic pain symptoms are predominantly related to A δ small fibre loss in peripheral tissues identified with QST in adults (Üçeyler et al., 2014; Hopkin et al., 2016), and may also be related to glycolipid accumulation in peripheral nerves or altered channel kinetics in dorsal root ganglia neurons (Borsook, 2012; Choi et al., 2015).

Age

Reported ages at diagnosis range from 5 to 77 years (Pagnini et al., 2011). However, acroparesthesia/neuropathic pain has been reported from 2 years of age (Laney et al., 2015). Overall, neuropathic pain was reported in 59% of boys (median 7yrs) and 41% of girls (median 9 yrs) (Hopkin et al., 2008).

Diagnosis and management

The diagnosis is based on measurement of plasma alpha-galactosidase A activity (although levels may be normal in carrier females), and of plasma or urinary Gb3 or lyso-Gb3; and is confirmed by genetic analysis of *GLA* gene (Mehta et al., 2010).

Enzyme replacement therapy with alpha-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 (Howard et al., 2014), with reductions in neuropathic “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 neuropathic treatment with anti-convulsants (Howard et al., 2014). In others, the overall prevalence of pain was not altered by enzyme replacement therapy, but those with pain at the onset of therapy did show a decrease in severity (Ramaswami et al., 2012).

Neurological disorders

Neuropathic pain is a feature of several neurological conditions. Pain associated with neurofibromatosis, Guillain Barre syndrome, neuromuscular disorders and pain associated with HIV are covered in **Chapter 33 Collins and Mherekumombe, Persisting pain in childhood medical illness.**

Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease producing demyelination and axonal damage in the brain and spinal cord (Mariotti et al., 2010). Pain is common in adults with a prevalence from 57 to 65%, and 43-54% have pain at the time of diagnosis. Patients with MS may experience multiple types of pain (including tonic spasms, back pain, and headache) but additionally may experience central neuropathic pains.

- Dysaesthetic extremity pain occurs in up to 23% of patients. Pain is burning, typically bilateral, often in the legs and feet, worse at night, and is exacerbated by exercise.
- Trigeminal neuralgia is more common than in the general population with a higher rate of bilateral symptoms.
- Brief electric shock sensations in the back of the neck, lower back, or other parts of body, are brought on by neck flexion (Lhermitte’s sign).

An estimated 2 to 5% of patients experience their first symptoms of MS before 16 years of age, with onset usually between 8 and 14 years, and a higher incidence in females (ranging from 1.3 to 3 times). Cohorts of paediatric MS patients report sensory symptoms in 13-69%, but there is little information about the proportion with neuropathic pain (Ness et

al., 2007). Headache is more frequent in paediatric than in adult patients with MS (Mariotti et al., 2010). The course of the disease may be slower in children, but can have a significant impact on schooling and psychosocial function (Ness et al., 2007); further reductions in quality of life have been associated with increasing age and duration of illness. The impact of disease modifying therapies, such as interferon, on pain symptoms are not clear (O'Connor et al., 2008).

Postherpetic neuralgia

Reactivation of varicella zoster virus infection, which has been dormant within sensory neurons, results in painful eruptions along the distribution of the nerve (also known as shingles), and approximately 14% of adults develop persistent neuropathic pain (i.e. postherpetic neuralgia, PHN) (Delaney et al., 2009). Overall, zoster infection and PHN are less common in children, and incidence increases with age (Hall et al., 2013), but children who are immuno-compromised (Gershon et al., 2015), particularly in association with cancer treatment, are at higher risk. In a series of 226 children with acute lymphoblastic leukaemia, zoster eruptions occurred 90 times, with recurrent episodes in 14 children. All experienced pain with the acute eruption and were treated with acyclovir, and 5 developed postherpetic neuralgia, which persisted for more than 2 months in 2 patients (Sørensen et al., 2011).

Trigeminal neuralgia

Clinical features

Clinical features of trigeminal neuralgia include (Bender et al., 2011; Howard et al., 2014):

- Unilateral pain in the distribution of the trigeminal nerve. The trigeminal innervation is divided into 3 zones: V1 ophthalmic (scalp, forehead, upper eyelid, eye); V2 maxillary (lower eyelid, cheek, nose, upper teeth and gums); and V3 mandibular (lower teeth and gums, jaw, parts of external ear). Pain may be experienced in one or more zones; most commonly V2 followed by V2/3 combined.
- Pain is described as sharp, lancinating or shooting, electric-shock like, and occasionally burning.
- Pain is intermittent and paroxysmal.
- 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 spasm of the facial muscles, or *tic doloureux*.

Incidence

The incidence of trigeminal neuralgia is much lower in children (Hall et al., 2013), and less than 1.5% of patients with trigeminal neuralgia report an onset of symptoms before 18 years of age (Bender et al., 2011). Case series report trigeminal neuralgia in children aged from 3 to 18 years, with median ages of 11 to 13 years (Howard et al., 2014).

Pathophysiology

Trigeminal neuralgia may be classified as idiopathic or result from either vascular compression within the intracranial course of the nerve or by tumour (Howard et al., 2014). As idiopathic trigeminal neuralgia and glossopharyngeal neuralgia (pain in the posterior tongue, pharynx, beneath angle of lower jaw and/or in ear) are rare in children, appropriate imaging and investigations are required to exclude underlying causes (Arruda et al., 2011; Grande-Martín et al., 2015). (da Silva et al., 2006).

Neuropathic Pain and Genetic Disorders

Erythromelalgia

Clinical features

Erythromelalgia (EM) is characterised by severe episodic pain and redness affecting the hands and feet, and may include the ears (Dib-Hajj et al., 2013; Waxman et al., 2014; Yang et al., 2018). Pain is aggravated by warmth, prolonged standing and exercise, and relieved by cooling and submersion in iced water, but is often poorly responsive to analgesia (Howard et al., 2014).

Pathophysiology

Primary or inherited erythromelalgia has recently been associated with a genetic mutation, which may occur spontaneously, or in association with a positive family history. Nine subtypes of voltage gated sodium channels have been identified (Na_v1.1 to Na_v1.9). Na_v1.7 is of particular importance for pain as it is selectively expressed within nociceptive dorsal root ganglion and sympathetic ganglion neurons (Dib-Hajj et al., 2009, 2013). Mutations in the SCN9A gene, which encodes the Na_v1.7 channel, can result in either:

1. loss of function and congenital insensitivity to pain (Cox et al., 2006; Staud et al., 2011), or;
2. gain of function and increased pain (Howard et al., 2014; Waxman et al., 2014; Yang et al., 2018). Point mutations at different sites result in two distinct phenotypes: Paroxysmal Extreme Pain Disorder (PEPD) or Primary Erythromelalgia. Mutations associated with erythromelalgia alter channel activation, reduce threshold and increase firing frequency, and increase excitability (Dib-Hajj et al., 2013).

Erythromelalgia has also been reported in association with myeloproliferative or autoimmune disorders, and in such cases may be termed secondary erythromelalgia (Howard et al., 2014).

Age-dependent effects

The degree of change in channel kinetics varies with the site of the mutation, and larger depolarising shifts have been associated with onset of symptoms at younger ages. However, variable expression of neonatal and adult isoforms of the channel may also influence the age at which symptoms first appear (Howard et al., 2014).

Management

Diverse views of the pathophysiology of EM have resulted in a range of treatments directed at vascular (vaso-active drugs such as topical GTN, sodium nitroprusside infusion, clonidine)(Cohen, 2000), anti-inflammatory, and neuropathic etiologies (amitriptyline, gabapentin, lidocaine patches)(Natkunarahaj et al., 2009; Cook-Norris et al., 2012). With awareness of the potential involvement of $Na_v1.7$ in EM, there has been increased use of drugs with sodium channel blocking activity. Different EM-related mutations may be more responsive to either mexiletine or carbamazepine (Howard et al., 2014). Specific $Nav1.7$ antagonists are also being developed for neuropathic pain (Zakrzewska et al., 2017; Yang et al., 2018).

Paroxysmal Extreme Pain Disorder

PEPD can present soon after birth with episodic pain in association with redness over the buttocks, legs and feet. Through infancy and childhood, the condition progresses to include episodes of (Fertleman et al., 2006; Choi et al., 2011):

- rectal pain, often induced by a bowel movement, and burning pain and redness in the lower limbs
- brief episodes of intense burning ocular pain associated with redness around the eyes and runny nose and eyes
- bilateral mandibular pain and redness, which may be triggered by cold, eating, or emotional state.

Mutations at different points on SCN9A result in altered channel kinetics (impaired inactivation, prolonged action potential and repetitive firing) and a phenotype that differs from erythromelalgia (Estacion et al., 2008). PEPD has been reported to be differentially sensitive to carbamazepine (Fertleman et al., 2006).

Conclusion

Neuropathic pain is a frequent reason for referral to a paediatric chronic pain clinic, and diagnosis is predominantly based on the pain history and descriptors. NP following trauma is more common when the initial injury occurs later in childhood (e.g. following amputation at >6 years). However, NP can occur at younger ages, particularly in higher risk populations (e.g. cancer, chemotherapy and immunosuppression) or in association with specific conditions (e.g. Fabry's disease). Pharmacological management of NP is largely extrapolated from adult studies (see Chapter 48 Rastogi and Campbell). However, pain is often severe and only partially responsive to pharmacological interventions, and multidisciplinary care is required. As discussed in other chapters throughout this text, assessment and management of chronic pain (including NP) must also encompass non-pharmacological and psychological interventions, include family or caregivers, and address issues related to poor sleep and school attendance.

Perspective

My 14 year old daughter had routine appendicectomy last year. Although the pain from her surgery resolved within several days, she now has abdominal pain that began 3 months following her surgery. This has been difficult to understand because there is no visible injury, and the area around her surgical scar is not swollen or red. In addition, her symptoms are unusual; she describes her pain as burning, shooting, and stabbing, and her abdomen is sensitive to touch. Her pain has become more severe in the last 6 months, and she experiences pain more frequently, and often without any apparent trigger. She has now stopped wearing tight-fitting trousers, no longer participates in physical exercise at school, and is increasingly avoiding stairs. She has become very anxious about taking part in any activity that could provoke pain and is beginning to spend less time with her friends. She is now sleeping poorly as a result of her pain and is missing school more frequently.

Recently, my daughter was referred to a specialist Chronic Pain Service, where she was seen by a multidisciplinary team of clinicians, who explained that she has neuropathic pain and requires different types of treatment. The physiotherapist who assessed her found that she was weak in her core and lower limb muscles as a result of her reduced activity. The psychologist spoke to her about her poor sleep and her anxiety and low mood. We now have a better plan for managing her pain.

References

- Aasvang, E.K., Kehlet, H., 2007. Chronic pain after childhood groin hernia repair. *J. Pediatr. Surg.* 42, 1403–1408. <https://doi.org/10.1016/j.jpedsurg.2007.03.042>
- Anand, P., Birch, R., 2002. Restoration of sensory function and lack of long-term chronic pain syndromes after brachial plexus injury in human neonates. *Brain J. Neurol.* 125, 113–122.
- Anghelescu, D.L., Faughnan, L.G., Jeha, S., Relling, M.V., Hinds, P.S., Sandlund, J.T., Cheng, C., Pei, D., Hankins, G., Pauley, J.L., Pui, C.-H., 2011. Neuropathic pain during treatment for childhood acute lymphoblastic leukemia. *Pediatr. Blood Cancer* 57, 1147–1153. <https://doi.org/10.1002/pbc.23039>
- Anghelescu, D.L., Goldberg, J.L., Faughnan, L.G., Wu, J., Mao, S., Furman, W.L., Santana, V.M., Navid, F., 2015. Comparison of pain outcomes between two anti-GD2 antibodies in patients with neuroblastoma. *Pediatr. Blood Cancer* 62, 224–228. <https://doi.org/10.1002/pbc.25280>
- Ardern-Holmes, S., Fisher, G., North, K., 2017. Neurofibromatosis Type 2. *J. Child Neurol.* 32, 9–22. <https://doi.org/10.1177/0883073816666736>
- Arruda, M.A., Albuquerque, R.C.A.P., Bigal, M.E., 2011. Uncommon headache syndromes in the pediatric population. *Curr. Pain Headache Rep.* 15, 280–288. <https://doi.org/10.1007/s11916-011-0192-4>
- Atherton, D.D., Taherzadeh, O., Elliot, D., Anand, P., 2008. Age-dependent development of chronic neuropathic pain, allodynia and sensory recovery after upper limb nerve injury in children. *J. Hand Surg. Eur. Vol.* 33, 186–191. <https://doi.org/10.1177/1753193408087029>

- Attal, N., Cruccu, G., Baron, R., Haanpää, M., Hansson, P., Jensen, T.S., Nurmikko, T., European Federation of Neurological Societies, 2010. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur. J. Neurol.* 17, 1113-e88. <https://doi.org/10.1111/j.1468-1331.2010.02999.x>
- Attal, N., Lanteri-Minet, M., Laurent, B., Fermanian, J., Bouhassira, D., 2011. The specific disease burden of neuropathic pain: results of a French nationwide survey. *Pain* 152, 2836–2843. <https://doi.org/10.1016/j.pain.2011.09.014>
- Baron, R., Maier, C., Attal, N., Binder, A., Bouhassira, D., Cruccu, G., Finnerup, N.B., Haanpää, M., Hansson, P., Hüllemann, P., Jensen, T.S., Freynhagen, R., Kennedy, J.D., Magerl, W., Mainka, T., Reimer, M., Rice, A.S.C., Segerdahl, M., Serra, J., Sindrup, S., Sommer, C., Tölle, T., Vollert, J., Treede, R.-D., 2017. Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. *Pain* 158, 261–272. <https://doi.org/10.1097/j.pain.0000000000000753>
- Bender, M.T., Pradilla, G., James, C., Raza, S., Lim, M., Carson, B.S., 2011. Surgical treatment of pediatric trigeminal neuralgia: case series and review of the literature. *Childs Nerv. Syst. ChNS Off. J. Int. Soc. Pediatr. Neurosurg.* 27, 2123–2129. <https://doi.org/10.1007/s00381-011-1593-8>
- Bennett, M., 2001. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain* 92, 147–157.
- Bennett, M.I., Attal, N., Backonja, M.M., Baron, R., Bouhassira, D., Freynhagen, R., Scholz, J., Tölle, T.R., Wittchen, H.-U., Jensen, T.S., 2007. Using screening tools to identify neuropathic pain. *Pain* 127, 199–203. <https://doi.org/10.1016/j.pain.2006.10.034>
- Blankenburg, M., Boekens, H., Hechler, T., Maier, C., Krumova, E., Scherens, A., Magerl, W., Aksu, F., Zernikow, B., 2010. Reference values for quantitative sensory testing in children and adolescents: developmental and gender differences of somatosensory perception. *Pain* 149, 76–88. <https://doi.org/10.1016/j.pain.2010.01.011>
- Blankenburg, M., Kraemer, N., Hirschfeld, G., Krumova, E.K., Maier, C., Hechler, T., Aksu, F., Magerl, W., Reinehr, T., Wiesel, T., Zernikow, B., 2012. Childhood diabetic neuropathy: functional impairment and non-invasive screening assessment. *Diabet. Med. J. Br. Diabet. Assoc.* 29, 1425–1432. <https://doi.org/10.1111/j.1464-5491.2012.03685.x>
- Borsook, D., 2012. Neurological diseases and pain. *Brain J. Neurol.* 135, 320–344. <https://doi.org/10.1093/brain/awr271>
- Bouhassira, D., Attal, N., Alchaar, H., Boureau, F., Brochet, B., Bruxelle, J., Cunin, G., Fermanian, J., Ginies, P., Grun-Overdyking, A., Jafari-Schluep, H., Lantéri-Minet, M., Laurent, B., Mick, G., Serrie, A., Valade, D., Vicaut, E., 2005. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 114, 29–36. <https://doi.org/10.1016/j.pain.2004.12.010>
- Bowers, D.C., Griffith, T., Gargan, L., Cochran, C.J., Kleiber, B., Foxwell, A., Farrow-Gillespie, A., Orino, A., Germann, J.N., 2012. Back pain among long-term survivors of

- childhood leukemia. *J. Pediatr. Hematol. Oncol.* 34, 624–629.
<https://doi.org/10.1097/MPH.0b013e31827080de>
- Bryce, T.N., Biering-Sørensen, F., Finnerup, N.B., Cardenas, D.D., Defrin, R., Lundeborg, T., Norrbrink, C., Richards, J.S., Siddall, P., Stripling, T., Treede, R.-D., Waxman, S.G., Widerström-Noga, E., Yezierski, R.P., Dijkers, M., 2012. International spinal cord injury pain classification: part I. Background and description. March 6-7, 2009. *Spinal Cord* 50, 413–417. <https://doi.org/10.1038/sc.2011.156>
- Burgoyne, L.L., Billups, C.A., Jirón, J.L., Kaddoum, R.N., Wright, B.B., Bikhazi, G.B., Parish, M.E., Pereiras, L.A., 2012. Phantom limb pain in young cancer-related amputees: recent experience at St Jude children’s research hospital. *Clin. J. Pain* 28, 222–225. <https://doi.org/10.1097/AJP.0b013e318227ce7a>
- Choi, J.-S., Boralevi, F., Brissaud, O., Sánchez-Martín, J., Morsche, R.H.M. te, Dib-Hajj, S.D., Drenth, J.P.H., Waxman, S.G., 2011. Paroxysmal extreme pain disorder: a molecular lesion of peripheral neurons. *Nat. Rev. Neurol.* 7, 51–55.
<https://doi.org/10.1038/nrneurol.2010.162>
- Choi, L., Vernon, J., Kopach, O., Minett, M.S., Mills, K., Clayton, P.T., Meert, T., Wood, J.N., 2015. The Fabry disease-associated lipid Lyso-Gb3 enhances voltage-gated calcium currents in sensory neurons and causes pain. *Neurosci. Lett.* 594, 163–168.
<https://doi.org/10.1016/j.neulet.2015.01.084>
- Chou, J., Chan, C., Chalkiadis, G.A., 2014. Post-thoracotomy pain in children and adolescence: a retrospective cross-sectional study. *Pain Med. Malden Mass* 15, 452–459.
- Cohen, J.S., 2000. Erythromelalgia: new theories and new therapies. *J. Am. Acad. Dermatol.* 43, 841–847. <https://doi.org/10.1067/mjd.2000.109301>
- Cook-Norris, R.H., Tollefson, M.M., Cruz-Inigo, A.E., Sandroni, P., Davis, M.D.P., Davis, D.M.R., 2012. Pediatric erythromelalgia: a retrospective review of 32 cases evaluated at Mayo Clinic over a 37-year period. *J. Am. Acad. Dermatol.* 66, 416–423. <https://doi.org/10.1016/j.jaad.2011.01.010>
- Corkum, J.P., Kuta, V., Tang, D.T., Bezuhly, M., 2017. Sensory outcomes following brachial plexus birth palsy: A systematic review. *J. Plast. Reconstr. Aesthetic Surg. JPRAS* 70, 987–995. <https://doi.org/10.1016/j.bjps.2017.05.007>
- Cox, J.J., Reimann, F., Nicholas, A.K., Thornton, G., Roberts, E., Springell, K., Karbani, G., Jafri, H., Mannan, J., Raashid, Y., Al-Gazali, L., Hamamy, H., Valente, E.M., Gorman, S., Williams, R., McHale, D.P., Wood, J.N., Gribble, F.M., Woods, C.G., 2006. An SCN9A channelopathy causes congenital inability to experience pain. *Nature* 444, 894–898. <https://doi.org/10.1038/nature05413>
- Delaney, A., Colvin, L.A., Fallon, M.T., Dalziel, R.G., Mitchell, R., Fleetwood-Walker, S.M., 2009. Postherpetic neuralgia: from preclinical models to the clinic. *Neurother. J. Am. Soc. Exp. Neurother.* 6, 630–637. <https://doi.org/10.1016/j.nurt.2009.07.005>
- DeMoss, P., Ramsey, L.H., Karlson, C.W., 2018. Phantom Limb Pain in Pediatric Oncology. *Front. Neurol.* 9, 219. <https://doi.org/10.3389/fneur.2018.00219>

- Dib-Hajj, S.D., Binshtok, A.M., Cummins, T.R., Jarvis, M.F., Samad, T., Zimmermann, K., 2009. Voltage-gated sodium channels in pain states: role in pathophysiology and targets for treatment. *Brain Res. Rev.* 60, 65–83.
<https://doi.org/10.1016/j.brainresrev.2008.12.005>
- Dib-Hajj, S.D., Yang, Y., Black, J.A., Waxman, S.G., 2013. The Na(V)1.7 sodium channel: from molecule to man. *Nat. Rev. Neurosci.* 14, 49–62. <https://doi.org/10.1038/nrn3404>
- Dumontier, C., Gilbert, A., 1990. Traumatic brachial plexus palsy in children. *Ann. Chir. Main Memb. Superieur Organe Off. Soc. Chir. Main Ann. Hand Up. Limb Surg.* 9, 351–357.
- Dworkin, R.H., O'Connor, A.B., Audette, J., Baron, R., Gourlay, G.K., Haanpää, M.L., Kent, J.L., Krane, E.J., Lebel, A.A., Levy, R.M., Mackey, S.C., Mayer, J., Miaskowski, C., Raja, S.N., Rice, A.S.C., Schmader, K.E., Stacey, B., Stanos, S., Treede, R.-D., Turk, D.C., Walco, G.A., Wells, C.D., 2010. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin. Proc.* 85, S3-14.
<https://doi.org/10.4065/mcp.2009.0649>
- El-Gammal, T.A., El-Sayed, A., Kotb, M.M., 2003. Surgical treatment of brachial plexus traction injuries in children, excluding obstetric palsy. *Microsurgery* 23, 14–17.
<https://doi.org/10.1002/micr.10084>
- Estacion, M., Dib-Hajj, S.D., Benke, P.J., Te Morsche, R.H.M., Eastman, E.M., Macala, L.J., Drenth, J.P.H., Waxman, S.G., 2008. NaV1.7 gain-of-function mutations as a continuum: A1632E displays physiological changes associated with erythromelalgia and paroxysmal extreme pain disorder mutations and produces symptoms of both disorders. *J. Neurosci. Off. J. Soc. Neurosci.* 28, 11079–11088.
<https://doi.org/10.1523/JNEUROSCI.3443-08.2008>
- Fertleman, C.R., Baker, M.D., Parker, K.A., Moffatt, S., Elmslie, F.V., Abrahamsen, B., Ostman, J., Klugbauer, N., Wood, J.N., Gardiner, R.M., Rees, M., 2006. SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. *Neuron* 52, 767–774.
<https://doi.org/10.1016/j.neuron.2006.10.006>
- Freyhagen, R., Baron, R., Gockel, U., Tölle, T.R., 2006. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr. Med. Res. Opin.* 22, 1911–1920. <https://doi.org/10.1185/030079906X132488>
- Gershon, A.A., Breuer, J., Cohen, J.I., Cohrs, R.J., Gershon, M.D., Gilden, D., Grose, C., Hambleton, S., Kennedy, P.G.E., Oxman, M.N., Seward, J.F., Yamanishi, K., 2015. Varicella zoster virus infection. *Nat. Rev. Dis. Primer* 1, 15016.
<https://doi.org/10.1038/nrdp.2015.16>
- Gillin, S., Sorkin, L.S., 1998. Gabapentin reverses the allodynia produced by the administration of anti-GD2 ganglioside, an immunotherapeutic drug. *Anesth. Analg.* 86, 111–116.
- Grande-Martín, A., Díaz-Conejo, R., Verdú-Pérez, A., Hernández-Moneo, J.-L., 2015. Trigeminal Neuralgia in a Child With a Cerebellopontine Angle Arachnoid Cyst. *Pediatr. Neurol.* 53, 178–179. <https://doi.org/10.1016/j.pediatrneurol.2015.03.010>

- Haanpää, M.L., Backonja, M.-M., Bennett, M.I., Bouhassira, D., Cruccu, G., Hansson, P.T., Jensen, T.S., Kauppila, T., Rice, A.S.C., Smith, B.H., Treede, R.-D., Baron, R., 2009. Assessment of neuropathic pain in primary care. *Am. J. Med.* 122, S13-21. <https://doi.org/10.1016/j.amjmed.2009.04.006>
- Hall, G.C., Carroll, D., Parry, D., McQuay, H.J., 2006. Epidemiology and treatment of neuropathic pain: the UK primary care perspective. *Pain* 122, 156–162. <https://doi.org/10.1016/j.pain.2006.01.030>
- Hall, G.C., Morant, S.V., Carroll, D., Gabriel, Z.L., McQuay, H.J., 2013. An observational descriptive study of the epidemiology and treatment of neuropathic pain in a UK general population. *BMC Fam. Pract.* 14, 28. <https://doi.org/10.1186/1471-2296-14-28>
- Ho, E.S., Curtis, C.G., Clarke, H.M., 2015. Pain in children following microsurgical reconstruction for obstetrical brachial plexus palsy. *J. Hand Surg.* 40, 1177–1183. <https://doi.org/10.1016/j.jhsa.2015.02.003>
- Hopkin, R.J., Bissler, J., Banikazemi, M., Clarke, L., Eng, C.M., Germain, D.P., Lemay, R., Tylki-Szymanska, A., Wilcox, W.R., 2008. Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry. *Pediatr. Res.* 64, 550–555. <https://doi.org/10.1203/PDR.0b013e318183f132>
- Hopkin, R.J., Jefferies, J.L., Laney, D.A., Lawson, V.H., Mauer, M., Taylor, M.R., Wilcox, W.R., Fabry Pediatric Expert Panel, 2016. The management and treatment of children with Fabry disease: A United States-based perspective. *Mol. Genet. Metab.* 117, 104–113. <https://doi.org/10.1016/j.ymgme.2015.10.007>
- Howard, R.F., Wiener, S., Walker, S.M., 2014. Neuropathic pain in children. *Arch. Dis. Child.* 99, 84–89. <https://doi.org/10.1136/archdischild-2013-304208>
- Hwang, R.W., Bae, D.S., Waters, P.M., 2008. Brachial plexus palsy following proximal humerus fracture in patients who are skeletally immature. *J. Orthop. Trauma* 22, 286–290. <https://doi.org/10.1097/BOT.0b013e31816b7898>
- Jan, F.K., Wilson, P.E., 2004. A survey of chronic pain in the pediatric spinal cord injury population. *J. Spinal Cord Med.* 27 Suppl 1, S50-53.
- January, A.M., Zebracki, K., Chlan, K.M., Vogel, L.C., 2015. Sleep, well-being, and psychological symptoms in adults with pediatric-onset spinal cord injury. *Rehabil. Psychol.* 60, 328–334. <https://doi.org/10.1037/rep0000061>
- January, A.M., Zebracki, K., Chlan, K.M., Vogel, L.C., 2014. Symptoms of depression over time in adults with pediatric-onset spinal cord injury. *Arch. Phys. Med. Rehabil.* 95, 447–454. <https://doi.org/10.1016/j.apmr.2013.11.011>
- Jensen, T.S., Baron, R., Haanpää, M., Kalso, E., Loeser, J.D., Rice, A.S.C., Treede, R.-D., 2011. A new definition of neuropathic pain. *Pain* 152, 2204–2205. <https://doi.org/10.1016/j.pain.2011.06.017>
- Julien-Marsollier, F., David, R., Hilly, J., Brasher, C., Michelet, D., Dahmani, S., 2017. Predictors of chronic neuropathic pain after scoliosis surgery in children. *Scand. J. Pain* 17, 339–344. <https://doi.org/10.1016/j.sjpain.2017.09.002>

- Kachko, L., Ben Ami, S., Lieberman, A., Shor, R., Tzeitlin, E., Efrat, R., 2014. Neuropathic pain other than CRPS in children and adolescents: incidence, referral, clinical characteristics, management, and clinical outcomes. *Paediatr. Anaesth.* 24, 608–613. <https://doi.org/10.1111/pan.12375>
- Kandula, T., Park, S.B., Cohn, R.J., Krishnan, A.V., Farrar, M.A., 2016. Pediatric chemotherapy induced peripheral neuropathy: A systematic review of current knowledge. *Cancer Treat. Rev.* 50, 118–128. <https://doi.org/10.1016/j.ctrv.2016.09.005>
- Krab, L.C., Oostenbrink, R., de Goede-Bolder, A., Aarsen, F.K., Elgersma, Y., Moll, H.A., 2009. Health-related quality of life in children with neurofibromatosis type 1: contribution of demographic factors, disease-related factors, and behavior. *J. Pediatr.* 154, 420–425, 425.e1. <https://doi.org/10.1016/j.jpeds.2008.08.045>
- Krane, E.J., Heller, L.B., 1995. The prevalence of phantom sensation and pain in pediatric amputees. *J. Pain Symptom Manage.* 10, 21–29. [https://doi.org/10.1016/0885-3924\(94\)00062-P](https://doi.org/10.1016/0885-3924(94)00062-P)
- Krause, S.J., Backonja, M.-M., 2003. Development of a neuropathic pain questionnaire. *Clin. J. Pain* 19, 306–314.
- Kristensen, A.D., Ahlburg, P., Lauridsen, M.C., Jensen, T.S., Nikolajsen, L., 2012. Chronic pain after inguinal hernia repair in children. *Br. J. Anaesth.* 109, 603–608. <https://doi.org/10.1093/bja/aes250>
- Kristensen, A.D., Pedersen, T. a. L., Hjortdal, V.E., Jensen, T.S., Nikolajsen, L., 2010. Chronic pain in adults after thoracotomy in childhood or youth. *Br. J. Anaesth.* 104, 75–79. <https://doi.org/10.1093/bja/aep317>
- Kwok, I.H.Y., Silk, Z.M., Quick, T.J., Sinisi, M., MacQuillan, A., Fox, M., 2016. Nerve injuries associated with supracondylar fractures of the humerus in children: our experience in a specialist peripheral nerve injury unit. *Bone Jt. J.* 98–B, 851–856. <https://doi.org/10.1302/0301-620X.98B6.35686>
- Lai, J.-S., Jensen, S.E., Patel, Z.S., Listernick, R., Charrow, J., 2017. Using a qualitative approach to conceptualize concerns of patients with neurofibromatosis type 1 associated plexiform neurofibromas (pNF) across the lifespan. *Am. J. Med. Genet. A.* 173, 79–87. <https://doi.org/10.1002/ajmg.a.37987>
- Laney, D.A., Peck, D.S., Atherton, A.M., Manwaring, L.P., Christensen, K.M., Shankar, S.P., Grange, D.K., Wilcox, W.R., Hopkin, R.J., 2015. Fabry disease in infancy and early childhood: a systematic literature review. *Genet. Med. Off. J. Am. Coll. Med. Genet.* 17, 323–330. <https://doi.org/10.1038/gim.2014.120>
- Lebel, A., Becerra, L., Wallin, D., Moulton, E.A., Morris, S., Pendse, G., Jasciewicz, J., Stein, M., Aiello-Lammens, M., Grant, E., Berde, C., Borsook, D., 2008. fMRI reveals distinct CNS processing during symptomatic and recovered complex regional pain syndrome in children. *Brain J. Neurol.* 131, 1854–1879. <https://doi.org/10.1093/brain/awn123>
- Lu, Q., Krull, K.R., Leisenring, W., Owen, J.E., Kawashima, T., Tsao, J.C.I., Zebrack, B., Mertens, A., Armstrong, G.T., Stovall, M., Robison, L.L., Zeltzer, L.K., 2011. Pain in long-term adult survivors of childhood cancers and their siblings: a report from the

- Childhood Cancer Survivor Study. *Pain* 152, 2616–2624.
<https://doi.org/10.1016/j.pain.2011.08.006>
- Ma, J.K., Post, M.W.M., Gorter, J.W., Martin Ginis, K.A., 2016. Differences in health, participation and life satisfaction outcomes in adults following paediatric- versus adult-sustained spinal cord injury. *Spinal Cord* 54, 1197–1202.
<https://doi.org/10.1038/sc.2016.45>
- Malessy, M.J.A., Pondaag, W., 2011. Nerve surgery for neonatal brachial plexus palsy. *J. Pediatr. Rehabil. Med.* 4, 141–148. <https://doi.org/10.3233/PRM-2011-0166>
- Mariotti, P., Nociti, V., Cianfoni, A., Stefanini, C., De Rose, P., Martinelli, D., Dittoni, S., Vollono, C., Batocchi, A.P., Della Marca, G., 2010. Migraine-like headache and status migrainosus as attacks of multiple sclerosis in a child. *Pediatrics* 126, e459-464.
<https://doi.org/10.1542/peds.2009-2098>
- McCann, M.E., Waters, P., Goumnerova, L.C., Berde, C., 2004. Self-mutilation in young children following brachial plexus birth injury. *Pain* 110, 123–129.
<https://doi.org/10.1016/j.pain.2004.03.020>
- Mehta, A., Beck, M., Eyskens, F., Feliciani, C., Kantola, I., Ramaswami, U., Rolfs, A., Rivera, A., Waldek, S., Germain, D.P., 2010. Fabry disease: a review of current management strategies. *QJM Mon. J. Assoc. Physicians* 103, 641–659.
<https://doi.org/10.1093/qjmed/hcq117>
- Melzack, R., Israel, R., Lacroix, R., Schultz, G., 1997. Phantom limbs in people with congenital limb deficiency or amputation in early childhood. *Brain J. Neurol.* 120 (Pt 9), 1603–1620.
- Mohrmann, C., Armer, J., Hayashi, R.J., 2017. Challenges Evaluating Chemotherapy-Induced Peripheral Neuropathy in Childhood Cancer Survivors. *J. Pediatr. Oncol. Nurs. Off. J. Assoc. Pediatr. Oncol. Nurses* 34, 106–114.
<https://doi.org/10.1177/1043454216651016>
- Mora, J., 2016. Dinutuximab for the treatment of pediatric patients with high-risk neuroblastoma. *Expert Rev. Clin. Pharmacol.* 9, 647–653.
<https://doi.org/10.1586/17512433.2016.1160775>
- Murray, C.B., Zebracki, K., Chlan, K.M., Moss, A.C., Vogel, L.C., 2017. Medical and psychological factors related to pain in adults with pediatric-onset spinal cord injury: a biopsychosocial model. *Spinal Cord* 55, 405–410.
<https://doi.org/10.1038/sc.2016.137>
- Natkunarah, J., Atherton, D., Elmslie, F., Mansour, S., Mortimer, P., 2009. Treatment with carbamazepine and gabapentin of a patient with primary erythralgia (erythromelalgia) identified to have a mutation in the SCN9A gene, encoding a voltage-gated sodium channel. *Clin. Exp. Dermatol.* 34, e640-642.
<https://doi.org/10.1111/j.1365-2230.2009.03355.x>
- Ness, J.M., Chabas, D., Sadovnick, A.D., Pohl, D., Banwell, B., Weinstock-Guttman, B., International Pediatric MS Study Group, 2007. Clinical features of children and

- adolescents with multiple sclerosis. *Neurology* 68, S37-45.
<https://doi.org/10.1212/01.wnl.0000259447.77476.a9>
- Ness, K.K., Hudson, M.M., Jones, K.E., Leisenring, W., Yasui, Y., Chen, Y., Stovall, M., Gibson, T.M., Green, D.M., Neglia, J.P., Henderson, T.O., Casillas, J., Ford, J.S., Effinger, K.E., Krull, K.R., Armstrong, G.T., Robison, L.L., Oeffinger, K.C., Nathan, P.C., 2017. Effect of Temporal Changes in Therapeutic Exposure on Self-reported Health Status in Childhood Cancer Survivors. *Ann. Intern. Med.* 166, 89–98.
<https://doi.org/10.7326/M16-0742>
- Nutakki, K., Varni, J.W., Steinbrenner, S., Draucker, C.B., Swigonski, N.L., 2017. Development of the pediatric quality of life inventory neurofibromatosis type 1 module items for children, adolescents and young adults: qualitative methods. *J. Neurooncol.* 132, 135–143. <https://doi.org/10.1007/s11060-016-2351-2>
- O'Connor, A.B., Schwid, S.R., Herrmann, D.N., Markman, J.D., Dworkin, R.H., 2008. Pain associated with multiple sclerosis: systematic review and proposed classification. *Pain* 137, 96–111. <https://doi.org/10.1016/j.pain.2007.08.024>
- Pagé, M.G., Stinson, J., Campbell, F., Isaac, L., Katz, J., 2013. Identification of pain-related psychological risk factors for the development and maintenance of pediatric chronic postsurgical pain. *J. Pain Res.* 6, 167–180. <https://doi.org/10.2147/JPR.S40846>
- Pagnini, I., Borsini, W., Cecchi, F., Sgalambro, A., Olivotto, I., Frullini, A., Cimaz, R., 2011. Distal extremity pain as a presenting feature of Fabry's disease. *Arthritis Care Res.* 63, 390–395. <https://doi.org/10.1002/acr.20385>
- Pape, K.E., 2012. Developmental and maladaptive plasticity in neonatal SCI. *Clin. Neurol. Neurosurg.* 114, 475–482. <https://doi.org/10.1016/j.clineuro.2012.01.002>
- Portenoy, R., 2006. Development and testing of a neuropathic pain screening questionnaire: ID Pain. *Curr. Med. Res. Opin.* 22, 1555–1565.
<https://doi.org/10.1185/030079906X115702>
- Rabbitts, J.A., Fisher, E., Rosenbloom, B.N., Palermo, T.M., 2017a. Prevalence and Predictors of Chronic Postsurgical Pain in Children: A Systematic Review and Meta-Analysis. *J. Pain Off. J. Am. Pain Soc.* 18, 605–614. <https://doi.org/10.1016/j.jpain.2017.03.007>
- Rabbitts, J.A., Zhou, C., Narayanan, A., Palermo, T.M., 2017b. Longitudinal and Temporal Associations Between Daily Pain and Sleep Patterns After Major Pediatric Surgery. *J. Pain Off. J. Am. Pain Soc.* 18, 656–663. <https://doi.org/10.1016/j.jpain.2017.01.004>
- Rajapakse, D., Lioffi, C., Howard, R.F., 2014. Presentation and management of chronic pain. *Arch. Dis. Child.* 99, 474–480. <https://doi.org/10.1136/archdischild-2013-304207>
- Ramaswami, U., Parini, R., Pintos-Morell, G., Kalkum, G., Kampmann, C., Beck, M., FOS Investigators, 2012. Fabry disease in children and response to enzyme replacement therapy: results from the Fabry Outcome Survey. *Clin. Genet.* 81, 485–490.
<https://doi.org/10.1111/j.1399-0004.2011.01671.x>
- Reddy, S.M., Vergo, M.T., Paice, J.A., Kwon, N., Helenowski, I.B., Benson, A.B., Mulcahy, M.F., Nimeiri, H.S., Harden, R.N., 2016. Quantitative Sensory Testing at Baseline and During Cycle 1 Oxaliplatin Infusion Detects Subclinical Peripheral Neuropathy and

- Predicts Clinically Overt Chronic Neuropathy in Gastrointestinal Malignancies. *Clin. Colorectal Cancer* 15, 37–46. <https://doi.org/10.1016/j.clcc.2015.07.001>
- Rodrigues, A.C., Kang, P.B., 2016. Neuropathic and Myopathic Pain. *Semin. Pediatr. Neurol.* 23, 242–247. <https://doi.org/10.1016/j.spen.2016.10.008>
- Schug, S.A., Palmer, G.M., Scott, D.A., Halliwell, R., Trinca, J., 2016. Acute pain management: scientific evidence, fourth edition, 2015. *Med. J. Aust.* 204, 315–317.
- Schulz, A., Grafe, P., Hagel, C., Bäumer, P., Morrison, H., Mautner, V.-F., Farschtschi, S., 2018. Neuropathies in the setting of Neurofibromatosis tumor syndromes: Complexities and opportunities. *Exp. Neurol.* 299, 334–344. <https://doi.org/10.1016/j.expneurol.2017.06.006>
- Sethna, N.F., Meier, P.M., Zurakowski, D., Berde, C.B., 2007. Cutaneous sensory abnormalities in children and adolescents with complex regional pain syndromes. *Pain* 131, 153–161. <https://doi.org/10.1016/j.pain.2006.12.028>
- Smania, N., Berto, G., La Marchina, E., Melotti, C., Midiri, A., Roncari, L., Zenorini, A., Ianes, P., Picelli, A., Waldner, A., Faccioli, S., Gandolfi, M., 2012. Rehabilitation of brachial plexus injuries in adults and children. *Eur. J. Phys. Rehabil. Med.* 48, 483–506.
- Smith, B.H., Torrance, N., 2012. Epidemiology of neuropathic pain and its impact on quality of life. *Curr. Pain Headache Rep.* 16, 191–198. <https://doi.org/10.1007/s11916-012-0256-0>
- Smith, J., Thompson, J.M., 1995. Phantom limb pain and chemotherapy in pediatric amputees. *Mayo Clin. Proc.* 70, 357–364. [https://doi.org/10.1016/S0025-6196\(11\)63416-2](https://doi.org/10.1016/S0025-6196(11)63416-2)
- Sørensen, G.V., Rosthøj, S., Würtz, M., Danielsen, T.K., Schrøder, H., 2011. The epidemiology of herpes zoster in 226 children with acute lymphoblastic leukemia. *Pediatr. Blood Cancer* 57, 993–997. <https://doi.org/10.1002/pbc.22969>
- Sorkin, L.S., Otto, M., Baldwin, W.M., Vail, E., Gillies, S.D., Handgretinger, R., Barfield, R.C., Ming Yu, H., Yu, A.L., 2010. Anti-GD(2) with an FC point mutation reduces complement fixation and decreases antibody-induced allodynia. *Pain* 149, 135–142. <https://doi.org/10.1016/j.pain.2010.01.024>
- Staud, R., Price, D.D., Janicke, D., Andrade, E., Hadjipanayis, A.G., Eaton, W.T., Kaplan, L., Wallace, M.R., 2011. Two novel mutations of SCN9A (Nav1.7) are associated with partial congenital insensitivity to pain. *Eur. J. Pain Lond. Engl.* 15, 223–230. <https://doi.org/10.1016/j.ejpain.2010.07.003>
- Strömbeck, C., Remahl, S., Krumlinde-Sundholm, L., Sejersen, T., 2007. Long-term follow-up of children with obstetric brachial plexus palsy II: neurophysiological aspects. *Dev. Med. Child Neurol.* 49, 204–209. <https://doi.org/10.1111/j.1469-8749.2007.00204.x>
- Thomas, C.R., Brazeal, B.A., Rosenberg, L., Robert, R.S., Blakeney, P.E., Meyer, W.J., 2003. Phantom limb pain in pediatric burn survivors. *Burns J. Int. Soc. Burn Inj.* 29, 139–142.
- Üçeyler, N., Ganendiran, S., Kramer, D., Sommer, C., 2014. Characterization of pain in fabry disease. *Clin. J. Pain* 30, 915–920. <https://doi.org/10.1097/AJP.000000000000041>

- van den Bosch, G.E., van Dijk, M., Tibboel, D., Valkenburg, A.J., 2017. Thermal quantitative sensory testing in healthy Dutch children and adolescents standardized test paradigm and Dutch reference values. *BMC Pediatr.* 17, 77. <https://doi.org/10.1186/s12887-017-0827-7>
- Velasco, R., Videla, S., Villoria, J., Ortiz, E., Navarro, X., Bruna, J., 2015. Reliability and accuracy of quantitative sensory testing for oxaliplatin-induced neurotoxicity. *Acta Neurol. Scand.* 131, 282–289. <https://doi.org/10.1111/ane.12331>
- Voepel-Lewis, T., Caird, M.S., Tait, A.R., Malviya, S., Farley, F.A., Li, Y., Abbott, M.D., van Veen, T., Hassett, A.L., Clauw, D.J., 2017. A High Preoperative Pain and Symptom Profile Predicts Worse Pain Outcomes for Children After Spine Fusion Surgery. *Anesth. Analg.* 124, 1594–1602. <https://doi.org/10.1213/ANE.0000000000001963>
- Vogel, L.C., Krajci, K.A., Anderson, C.J., 2002. Adults with pediatric-onset spinal cord injuries: part 3: impact of medical complications. *J. Spinal Cord Med.* 25, 297–305.
- Vondracek, P., Oslejskova, H., Kepak, T., Mazanek, P., Sterba, J., Rysava, M., Gal, P., 2009. Efficacy of pregabalin in neuropathic pain in paediatric oncological patients. *Eur. J. Paediatr. Neurol. EJPN Off. J. Eur. Paediatr. Neurol. Soc.* 13, 332–336. <https://doi.org/10.1016/j.ejpn.2008.06.011>
- Walker, S.M., 2015. Pain after surgery in children: clinical recommendations. *Curr. Opin. Anaesthesiol.* 28, 570–576. <https://doi.org/10.1097/ACO.0000000000000227>
- Walker, S.M., Melbourne, A., O'Reilly, H., Beckmann, J., Eaton-Rosen, Z., Ourselin, S., Marlow, N., 2018. Somatosensory function and pain in extremely preterm young adults from the UK EPICure cohort: sex-dependent differences and impact of neonatal surgery. *Br. J. Anaesth.* 121, 623–635. <https://doi.org/10.1016/j.bja.2018.03.035>
- Wallace, M.S., Lee, J., Sorkin, L., Dunn, J.S., Yaksh, T., Yu, A., 1997. Intravenous lidocaine: effects on controlling pain after anti-GD2 antibody therapy in children with neuroblastoma--a report of a series. *Anesth. Analg.* 85, 794–796.
- Waxman, S.G., Merkies, I.S.J., Gerrits, M.M., Dib-Hajj, S.D., Lauria, G., Cox, J.J., Wood, J.N., Woods, C.G., Drenth, J.P.H., Faber, C.G., 2014. Sodium channel genes in pain-related disorders: phenotype-genotype associations and recommendations for clinical use. *Lancet Neurol.* 13, 1152–1160. [https://doi.org/10.1016/S1474-4422\(14\)70150-4](https://doi.org/10.1016/S1474-4422(14)70150-4)
- Werhagen, L., Budh, C.N., Hultling, C., Molander, C., 2004. Neuropathic pain after traumatic spinal cord injury--relations to gender, spinal level, completeness, and age at the time of injury. *Spinal Cord* 42, 665–673. <https://doi.org/10.1038/sj.sc.3101641>
- Wilkins, K.L., McGrath, P.J., Finley, G.A., Katz, J., 2004. Prospective diary study of nonpainful and painful phantom sensations in a preselected sample of child and adolescent amputees reporting phantom limbs. *Clin. J. Pain* 20, 293–301.
- Wilkins, K.L., McGrath, P.J., Finley, G.A., Katz, J., 1998. Phantom limb sensations and phantom limb pain in child and adolescent amputees. *Pain* 78, 7–12.

- Williams, G., Howard, R.F., Liossi, C., 2017. Persistent postsurgical pain in children and young people: prediction, prevention, and management. *Pain Rep.* 2, e616.
<https://doi.org/10.1097/PR9.0000000000000616>
- Wolters, P.L., Burns, K.M., Martin, S., Baldwin, A., Dombi, E., Toledo-Tamula, M.A., Dudley, W.N., Gillespie, A., Widemann, B.C., 2015. Pain interference in youth with neurofibromatosis type 1 and plexiform neurofibromas and relation to disease severity, social-emotional functioning, and quality of life. *Am. J. Med. Genet. A.* 167A, 2103–2113. <https://doi.org/10.1002/ajmg.a.37123>
- Xiao, W.H., Yu, A.L., Sorkin, L.S., 1997. Electrophysiological characteristics of primary afferent fibers after systemic administration of anti-GD2 ganglioside antibody. *Pain* 69, 145–151.
- Yang, Y., Mis, M.A., Estacion, M., Dib-Hajj, S.D., Waxman, S.G., 2018. Nav1.7 as a Pharmacogenomic Target for Pain: Moving Toward Precision Medicine. *Trends Pharmacol. Sci.* 39, 258–275. <https://doi.org/10.1016/j.tips.2017.11.010>
- Zakrzewska, J.M., Palmer, J., Morisset, V., Giblin, G.M., Obermann, M., Ettlin, D.A., Cruccu, G., Bendtsen, L., Estacion, M., Derjean, D., Waxman, S.G., Layton, G., Gunn, K., Tate, S., study investigators, 2017. Safety and efficacy of a Nav1.7 selective sodium channel blocker in patients with trigeminal neuralgia: a double-blind, placebo-controlled, randomised withdrawal phase 2a trial. *Lancet Neurol.* 16, 291–300. [https://doi.org/10.1016/S1474-4422\(17\)30005-4](https://doi.org/10.1016/S1474-4422(17)30005-4)

Table 22.1: Neuropathic pain conditions in children

Classification	Examples
Trauma	<ul style="list-style-type: none"> • post surgery • phantom limb pain • brachial plexus injury • peripheral nerve injury • spinal cord injury
Complex Regional Pain Syndrome	<ul style="list-style-type: none"> • following trauma / fracture • no precipitating cause
Neurological and neuromuscular disease	<ul style="list-style-type: none"> • Guillain-Barre disease • trigeminal neuralgia • multiple sclerosis
Metabolic disease	<ul style="list-style-type: none"> • Fabry's disease
Neuropathy following infection	<ul style="list-style-type: none"> • HIV/AIDS • post-herpetic neuralgia
Tumour	<ul style="list-style-type: none"> • nervous system tumour (neurofibromatosis) • invasion / compression by tumour • effect of treatment (eg. post-surgery; chemotherapy)
Genetic	<ul style="list-style-type: none"> • erythromelalgia

	<ul style="list-style-type: none">• paroxysmal extreme pain disorder
--	--