Neuropathic Pain in Children: Special Considerations

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Neuropathic pain is relatively uncommon in children. Although some syndromes closely resemble those found in adults, the incidence and course of the condition can vary substantially in children, depending on developmental status and contextual factors. There are some neuropathic pain syndromes that are rare and relatively unique to the pediatric population. This article discusses the array of neuropathic pain conditions in children and available treatment strategies. Data are limited by small numbers and few randomized controlled trials. Research and clinical implications are discussed.

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CNS = central nervous system; CRPS = complex regional pain syndrome; TENS = transcutaneous electronic nerve stimulation

Neuropathic pain is rarely studied systematically in infants, children, and adolescents. Perhaps a central reason for this is the fact that many of the most common neuropathic pain conditions seen in adults are rare in children. For example, among children with diabetes, complications do not progress to the point that neuropathy would be of concern. Likewise, conditions such as postherpetic neuralgia, trigeminal neuralgia, radiculopathies, and complications of stroke are of extremely low incidence in young patients. However, some neuropathic conditions are becoming increasingly recognized in children and adolescents, including complex regional pain syndromes (CRPSs) (principally type 1), phantom limb pain, spinal cord injury, trauma and postoperative neuropathic pain, autoimmune and degenerative neuropathies (eg, Guillain-Barré syndrome, Charcot-Marie-Tooth disease), and the effects of cancer disease processes and treatment. Finally, some neuropathic pain syndromes that are rare are relatively unique to the pediatric population, including toxic and metabolic neuropathies (eg, lead, mercury, alcohol, infection), hereditary neurodegenerative disorders (eg, Fabry disease), mitochondrial disorders, and primary erythromelalgia.

Neuropathic pain affects only a subgroup of adults with the same underlying lesion or disease, with incidences ranging from a small percentage with cortical stroke to more than half with spinal cord injury. This variability is attributed to individual differences in processes of degeneration and regeneration initiated by neural damage, often involving a reversal of cellular programs from the adult to an embryonic state. Throughout early development, and especially at the youngest ages, both the central nervous system (CNS) and peripheral nervous system are far more plastic than among adults. For example, after peripheral nerve injury, changes are likely in the CNS, reflecting neuronal plasticity and neuronal reorganization, all within the context of development. Thus, in comparing neuropathic pain in children vs adults, one can expect substantial differences in prevalence, presenting symptoms, course of disease or pain, especially with regard to chronicity, duration, and recurrences, and potential effect of different treatments.

Because of the relatively low incidence of this problem, data on the assessment and treatment of neuropathic pain in children are limited. Although recognition of neuropathic pain in children has increased during the past 20 years, good epidemiological studies are lacking to truly ascertain the incidence and correlates of neuropathic pain syndromes. Cases can be heterogeneous, making it difficult to articulate inclusion and exclusion criteria for research. In addition, the circumstances and context of the neuropathic pain may be of greater focus than the pain problem (ie, rarely is neuropathic pain the primary issue of concern in young patients). Longitudinal data for disease trajectories are extremely limited, including the course of neuropathic

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pain. Taking all these factors together, conducting epidemiological or well-controlled clinical trials of treatments in the pediatric population is exceptionally challenging.

A literature search was conducted using MEDLINE in June 2008, first entering the terms *neuropathic pain* and *neuralgia* with an age limitation of birth to 18 years. Subsequent analyses included terms for specific syndromes that may be considered neuropathic pain, including *complex regional pain syndrome, reflex sympathetic dystrophy,* and *phantom limb* and combining the term *pain* with other elements, such as *Fabry disease, Charcot-Marie-Tooth disease,* or *Guillain-Barré syndrome,* all with the same age limiters. Case reports, clinical series, and clinical trials were included in this review.

The Oxford Centre for Evidence-Based Medicine[1] defined levels of evidence for evaluating outcomes. Ideally, the first level of evidence, randomized controlled clinical trials, should guide practice when possible. Because of the aforementioned limitations, most studies of neuropathic pain in children are principally descriptive, limited to case studies or clinical series (levels 4 and 5). It is hoped that, as awareness of these syndromes increases, there will be more collaborative endeavors among various sites so that studies of etiology and treatment can be powered to yield reliable results.

COMPLEX REGIONAL PAIN SYNDROMES

Formerly known as reflex sympathetic dystrophy, CRPS type 1 has been well described in the pediatric population. Formerly referred to as causalgia, CRPS type 2 is less common, with only sparse reports in the literature. Although causal factors for CRPS type 1 in both children and adults remain elusive,[2] a handful of case studies and clinical series purport to identify coincident or correlational effects. Included among these are case studies of a 15-year-old girl whose symptoms were attributed to posttraumatic stress disorder,[3] a 15-year-old girl whose symptoms were deemed to have arisen from Munchausen syndrome,[4] an 11-year-old girl who developed symptoms after receiving a rubella vaccine,[5] and a 10-year-old boy with evidence of a sympathetically maintained pain syndrome.[6] An early report describing a clinical series of 18 patients aged 9 to 19 years described a number of features seen in the syndrome and specifically warns about attributing cause to psychiatric disorders, such as conversion disorder or malingering.[7]

A bit more helpful to understanding correlates is the handful of studies reporting on the prevalence of CRPS in children and adolescents. Wilder et al[8] described a series of 70 patients evaluated at the Children's Hospital Boston, Boston, MA, during a 41-month period. Data showed a high female-to-male ratio (approximately 6:1) and that occurrences were more common in the lower extremities than upper extremities. Low et al,[9] reporting on 20 patients, found an incidence in girls of 90%, that lower limbs were affected in 85% of patients, and that 80% of the time onset was precipitated by minor trauma. Murray et al[10] found a history of trauma only 54% of the time among 46 patients.

Sethna et al[11] performed standardized neurologic examinations and quantitative sensory testing on 42 patients aged 7 to 17 years with unilateral lower-extremity CRPS. Compared with a healthy control sample, most quantitative sensory testing parameters were unchanged except for cold and heat pain detection thresholds. Specifically, cold allodynia was observed, and a number of participants showed a combination of dynamic mechanical allodynia and hyperalgesia to pinprick. Tan et al[12] conducted a medical record review of 78 children (≤16 years) and 951 adults with CRPS. The pediatric population was predominantly girls, with a median age of 13 years, consistent with the female predominance in adults. Compared with the adult sample, among children the skin temperature of the involved extremity at onset was cooler, the lower extremity was involved more frequently, and the neurologic and sympathetic symptoms were less pronounced.

Using functional magnetic resonance imaging, LeBel et al[13] studied CNS activation in 12 patients, aged 9 to 18 years, with CRPS in the lower extremity. Participants underwent 2 functional magnetic resonance imaging sessions, once during an active period of pain and once after symptomatic recovery. Mechanical (brush) and thermal (cold) stimuli were applied to the affected region of the involved limb and the corresponding mirror region of the unaffected limb. Results showed that in the children with CRPS, stimuli that evoked mechanical or cold allodynia produced patterns of CNS activation similar to those reported in adults with CRPS because there were significant decreases in BOLD (blood oxygen level dependent) signal, suggesting pain-induced activation of endogenous pain modulatory systems. Cold- or brush-induced activations in regions such as the basal ganglia and parietal lobe may explain some CNS-related symptoms in CRPS, including movement disorders, hemineglect, and inattention. After resolution of CRPS, significant activation differences persisted despite nearly complete elimination of evoked pain. Although nonnoxious stimuli to the unaffected limb were perceived as equivalent in children during and after CRPS, the same stimulus produced different patterns of activation in the 2 states, suggesting that the CRPS brain responds differently to normal stimuli applied to unaffected regions and that significant changes occur in CNS circuitry in patients with CRPS.

Given the relative dearth of data on the causes of CRPS, it is not surprising that approaches to treatment have varied. In 1977, a case report described successful treatment with transcutaneous electronic nerve stimulation (TENS) in a

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6-year-old girl with CRPS.[14] This was followed by similar reports in a 3½-year-old boy[15] and a clinical series of 9 girls and 1 boy between the ages of 8 and 18 years.[16] In 1987, thermal biofeedback was reported to be helpful for a 12-year-old boy.[17] In the aforementioned follow-up study by Wilder et al,[8] 57% of patients improved with conservative treatment alone, consisting of physical therapy, TENS, cognitive behavioral therapy, and tricyclic antidepressants, whereas 28 of 37 patients benefited from interventional sympathetic blocks. Unfortunately, 38 children continued to have pain or functional problems after treatment. Of importance, the treatment of CRPS in this population was not standardized by protocol, and therapies were not determined by strict criteria. Therefore, it is difficult to extrapolate any recommendations regarding the use of interventional or noninterventional treatment modalities or conclude which of many pharmacological agents is most effective in children.

Subsequent studies have shown the value of aggressive physical therapy without use of pharmacological agents or interventional nerve blocks. One of the first studies was an extended clinical series by Sherry et al[18] that focused on 103 patients treated in a "reflex neurovascular clinic" during a nearly 13-year period. Standard diagnostic criteria were used, and treatment specifically eliminated the use of any medications. Exercise therapy that focused on aerobic exercise weight-bearing, functional activities, and hydrotherapy was at the core of intervention, administered 5 to 6 hours daily, in addition to evening and weekend regimens that ranged from 45 minutes to 3 hours. Although initially much of the work was performed in an inpatient setting, over time the focus was more on an outpatient basis. Complete resolution of pain and full function were restored in 92% of patients, and long-term data for 49 patients indicated lasting benefit for most patients. Recurrent episodes occurred 31% of the time but generally resolved with reinitiation of rehabilitative strategies. Although these data are impressive, more information is needed about how specific patients were selected or self-selected for completion of this treatment protocol before generalizability can be assessed.

Lee et al[19] conducted a prospective, randomized, single-blind trial of 28 children aged 8 to 17 years who were diagnosed as having CRPS. Participants were randomly assigned to either (1) physical therapy once per week for 6 weeks or (2) physical therapy 3 times per week for 6 weeks; both groups received 6 sessions of cognitive-behavioral treatment. All 5 measures of pain and function improved significantly in both groups, and sustained benefits were evident in most patients at long-term follow-up. The number of participants in each group was too small to detect differences in treatment, and because there was no wait list or control group, one cannot determine whether these benefits of treatment were a result of placebo effects, the passage of time, or both. Recurrent episodes were reported in 50% of patients, with 10 patients eventually receiving sympathetic blockade.

A clinical series of 23 children used a multidisciplinary outpatient or inpatient approach that emphasized physical therapy (range of motion, function of affected limb, muscle strength, desensitization, balance, and proprioception) and counseling with reasonably good outcomes.[20] Meier et al[21] showed that aggressive physical therapy and cognitive behavioral interventions were effective in treating 20 children and adolescents for both pain and regional and systemic autonomic responses. Low et al[9] described outcomes among 20 children diagnosed as having CRPS during a 4-year period. Treatment consisted of intensive physiotherapy and psychological therapy, although 70% received adjuvant medications (amitriptyline and/or gabapentin) for analgesia and to facilitate participation in physiotherapy. Although most children had complete resolution of symptoms with this treatment regimen (mean, 15.4 weeks; range, 3 days to 64 weeks), 40% required treatment as inpatients, and 20% had a relapse episode.

Strategies for using topical and regional anesthetic techniques have also been described. In 1994, EMLA was reported to have helped a 15-year-old boy.[22] Intravenous regional anesthesia blocks (Bier blocks) with guanethidine and prilocaine paired with physical therapy were used in girls 10 and 13 years of age.[23] In 2005, continuous peripheral nerve blocks provided at home were used in 13 children between 9 and 16 years of age who had intractable CRPS with substantial short-term benefit.[24] A computed tomography–guided lumbar sympathetic block likewise was reported to be successful in a 13-year-old girl.[25]

A double-blind, placebo-controlled crossover trial was conducted with 23 patients 10 to 18 years of age who had unilateral lower limb CRPS.[26] A catheter was placed along the lumbar sympathetic chain, and patients received intravenous lidocaine and lumbar sympathetic saline or lumbar sympathetic lidocaine and intravenous saline. Immediate short-term differences were noted as mean pain intensity of allodynia to brush, and pinprick temporal summation was reduced in the latter group, as well as reduction in pain intensity from pretreatment for allodynia to brush, pinprick, pinprick temporal summation, and verbal pain scores. Findings led the authors to assert that a component of pain in CRPS may be mediated by abnormal sympathetic activity.

The diagnostic intravenous phentolamine test has been used as a predictor for therapeutic Bier block with guanethidine in adolescents,[27] similar to its use for predicting sympathetic block efficacy in adults.[28] Although attractive from a pharmacological perspective, the phentolamine test has not gained wide acceptance because of the cost of the drug, its commercial unavailability (in the United States), and

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TABLE 1. **Comparison of Neuropathic Pain in Children and Adults**

Diagnosis	Clinical phenotype	Therapeutic approaches
CRPS type 1	Similar in adolescents and adults	Same spectrum as in adults (medications, physical therapy, blocks, cognitive-behavioral therapy, TENS) but lower level of evidence
Plexus avulsion	Infants rarely develop neuropathic pain due to plexus lesions during birth	Surgical repair, if possible, symptomatic treatment may be unnecessary
Amputation	Phantom limb pain occurs in children; differences in incidence vs adults unclear	No data
Nerve trauma	Less severe symptoms at young age, similar to adults at later age	Spectrum as in adults (TCAs, AEDs, TENS) but lower level evidence
Guillain-Barré syndrome	Neuropathic pain affects 75% of cases, often as the earliest symptom	Disease-modifying treatment plus antineuropathic pain agents as above
Fabry disease	Isolated small fiber neuropathy with intact large fiber function as an early sign (adolescents or young adults), frequently painful	Disease-modifying treatment, AEDs, capsaicin cream

AED = antiepileptic drug; CRPS = complex regional pain syndrome; TCA = tricyclic antidepressant; TENS = transcutaneous electronic nerve stimulation.

the relatively low rate of sympathetically maintained pain in most cases of CRPS.

Pharmacological interventions have included gabapentin, first reported in 2 case studies of 9-year-old girls,[29] dronabinol in a 15-year-old girl and a 14-year-old boy,[30] and oxcarbazepine administered to a 12-year-old boy.[31] Intravenous ketorolac and lidocaine were given to 11- and 15-year-old girls,[32] pamidronate was infused into a 15-year-old girl and a 14-year-old boy,[33] and anesthetic ketamine and midazolam were administered to a 17-year-old girl,[34] all with reported success. Intrathecal preparations have also been reported, including high-dose ziconotide for a 17-year-old girl[35] and a combination of ropivacaine and fentanyl for an 8-year-old girl.[36] A combination of iloprost, physiotherapy, and psychological counseling was provided to 7 girls aged 6 to 11 years, with reported success.[37] More invasive strategies have been reported, including a thorascopic sympathectomy performed on an 11-year-old girl[38] and spinal stimulation for 7 girls between the ages of 11 and 14 years.[39]

After reviewing the available literature on treatments of CRPS in children and adolescents, Wilder[40] concluded that, although an array of treatments may have some benefit, the mainstay of treatment appears to be physical therapy involving desensitization, strengthening, and functional improvement. In summary, treatment of CRPS type 1 in children has been extrapolated from the treatment of CRPS type 1 in adults, with some low-level evidence for efficacy of physical therapy, TENS, cognitive-behavioral therapy, nerve blocks, tricyclic antidepressants, gabapentin, and some other drugs (Table 1).

PLEXUS AVULSION AND PHANTOM LIMB PAIN

On the basis of clinical anecdote, phantom limb pain is not unusual in children who have undergone amputations related to either neoplasm or trauma. Krane and Heller[41] conducted a retrospective survey of 5- to 19-year-olds who had undergone limb amputation in the preceding 10 years because of congenital deformity, trauma or infection, or cancer. Phantom sensations were experienced in all patients, and most stated that they experienced phantom pain as well; 35% continued to have phantom pain at the time of data collection. Melzack et al[42] reported that phantom limbs were experienced by 20% of those with congenital limb deficiencies and 50% of those who underwent amputation before the age of 6 years. Phantom pain was reported in 20% and 42% of these groups, respectively. Finally, Wilkins et al[43] relied on diary data and noted recurrent episodes of phantom pain due to congenital limb deficiencies, surgery, and trauma, with an average intensity of 6.43 (on a 0- to 10-point scale).

Of interest, although brachial plexus injuries in adults frequently result in chronic pain, perinatal brachial plexus injuries usually do not produce chronic limb pain in children; at least it does not seem to produce pain at a later age at which children are able to report such pain. Using a range of noninvasive quantitative measures validated in adults, including mechanical, thermal, and vibration perception thresholds, Anand and Birch[44] assessed sensory and cholinergic sympathetic function (sweating) in 24 patients between 3 and 23 years of age who had severe brachial plexus injury at birth. Recovery of function after spinal root avulsion was related to surgery, but differences from adults were striking, including excellent restoration of sensory function and evidence of exquisite CNS plasticity, even to the point of perfect localization of restored sensation in avulsed spinal root dermatomes, presumably routed via nerves that had been transferred from a distant spinal region. Sensory recovery exceeded motor or cholinergic sympathetic recovery; however, some pa-

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tients who require surgical dissection of the plexus after obstetrical trauma may exhibit self-mutilation behavior in infancy.[45]

As sparse as reports on the epidemiology and etiology of phantom pain in the young may be, data on interventions are even more anecdotal and underwhelming. In 1995, intravenous ketamine was administered to a 17-year-old boy who had undergone amputation of the lower leg because of osteosarcoma of the tibia.[46] Gabapentin was reported to be beneficial in a case series of 7 children and young adults with phantom pain.[47]

In summary, brachial plexus avulsions during birth have a lower risk of neuropathic pain than similar damage at a later age. Phantom limb pain after amputations occurs in children, but the incidence, prevention, and treatment efficacy are unclear (Table 1).

TRAUMA AND SURGERY

Trauma is a general category and may actually reflect an array of insults with implications for neuropathic pain. Atherton et al[48] followed up 49 children who presented with distal upper limb nerve injury resulting from fracture, knife wounds, crush, or lacerations from broken glass at an average of 2.25 years after their injury. Patients younger than 5 years (n=15) did not report chronic neuropathic pain or allodynia. Patients with allodynia on sensory testing but no chronic neuropathic pain symptoms (n=8) were all older than 5 years. Chronic neuropathic pain (CRPS type 2) was found in 5 children, all of whom were older than 12 years at the time of injury. These authors reasonably concluded that "young children show better sensory recovery and are less likely to develop long-term chronic neuropathic pain than adults following nerve injury." Indeed, this may partially or wholly explain why preadolescents with neuropathic pain are infrequent visitors to most pediatric pain clinics and why virtually all reported cases of CRPS in children are in those older than 8 years.

Additional case reports have highlighted some unusual bases for traumatic neuropathic pain, including a case of a 14-year-old boy who had been struck by a car and developed CRPS type 2 of the lower limb and who was treated with gabapentin and intensive physical therapy[49] and an atypical trigeminal neuralgia related to tongue piercing in an 18-year-old woman.[50] Lauder and White[51] reported on a clinical series of 6 patients (11-17 years of age) with cerebral palsy who developed neuropathic pain after multilevel orthopedic surgery. Five of these patients improved markedly with interventions that included amitriptyline, gabapentin, and TENS as first-line treatments. One patient received additional mental health services, and one patient underwent a caudal epidural with bupivacaine and low-dose ketamine. Finally, a case report described use of ketamine to assist with pain and allodynia associated with an appendectomy wound in a 17-year-old girl.[52]

In conclusion, some evidence exists for a better prognosis of nerve injury–related neuropathic pain in young children than in older populations. Treatment approaches have been extrapolated with some success from adults (Table 1).

AUTOIMMUNE DISORDERS

Guillain-Barré syndrome is thought to occur when the body's immune system attacks native proteins in the peripheral nervous system. Korinthenberg et al[53] prospectively followed up 95 children (median age, 6.2 years) with Guillain-Barré syndrome. Most often the first symptom was disturbance of gait or neuropathic pain, which progressed for a median of 7 days. Of note, 79% experienced neuropathic pain that was often severe. All but 8 children were treated with intravenous immunoglobulin, and improvement began approximately 2 weeks after the first symptom with a span of approximately 4 months for children to be symptom free; however, the role of intravenous immunoglobulin in healing of neuropathic pain is speculative, at best. At the end of the observation period (288 days), 75% of patients were free of symptoms, and 21% had residual symptoms that had no effect on daily functioning. Clearly, severe neuropathic pain should be recognized and treated in this patient group.

METABOLIC DISEASES

Fabry disease is an X-linked lysosomal disease caused by deficiency of α-galactosidase A. Hopkin et al[54] evaluated signs and symptoms occurring during childhood and adolescence in 352 Fabry registry patients. At enrollment, 77% of male patients and 51% of female patients reported symptoms, with a median age of symptom onset of 6 and 9 years, respectively. Neuropathic pain was the most frequent symptom (59% of male patients; median age, 7 years; 41% of female patients; median age, 9 years). Using quantitative sensory testing in male patients with Fabry disease, Maag et al[55] demonstrated a small-fiber sensory neuropathy that selectively affects C- and A-δ fibers. A comparison with somatosensory profiles of painful sensory neuropathies related to other causes showed that the Fabry disease profile is characterized by more severe impairment of thermal and preserved vibratory and mechanical discrimination. Laaksonen et al[56] reported similar sensory profiles in heterozygous women. Treatment includes enzyme replacement as disease-modifying treatment (Table 1) and neuropathic pain medications, such as gabapentin,[57,58] although the success of antineuro-

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TABLE 2. **Case Reports or Series Describing Interventions for Neuropathic Pain in Children and Adolescents**

Report	Reference and date
Gabapentin for bilateral foot pain due to erythromelalgia (9-year-old girl)	1997[61]
Intrathecal low-dose ketamine for sciatic nerve injury (13-year-old boy)	1998[62]
Neurovascular compression of cranial nerves as cause of trigeminal neuralgia (9-year-old boy, 12-year-old boy); glossopharyngeal neuralgia (13-year-old girl)	2000[63]
Long-term ketamine for pain due to spinal cord tumor (12-year-old girl)	2001[64]
Gabapentin for pain related to contractures and extended neck (3-week-old boy)	2001[65]
Intravenous adenosine for neuropathic pain associated with degenerative metabolic disorder (15-year-old boy)	2001[66]
Peripheral glycerol injection for trigeminal neuralgia (clinical series, 11 boys and 7 girls; 10-14 years of age)	2004[67]
Gabapentin for pain related to Ewing sarcoma at L4-L5 (12-year-old boy)	2004[68]
Gabapentin for cancer-related neuropathic pain (18-year-old woman, 17-year-old girl, 14-year-old girl, 15-year-old boy) and neck pain at C3 (9-year-old girl)	2006[69]
Stellate ganglion block, multiple medications, TENS, hypnosis; followed by acupuncture (13-year-old girl with postherpetic neuralgia)	2007[70]
Infraorbital nerve resection for neuropathic pain related to trauma to the orbit (14-year-old boy)	2007[71]
Microvascular decompression for trigeminal neuralgia related to severe Epstein-Barr virus with mild meningoencephalitis (11-year-old boy)	2008[72]

TENS = transcutaneous electronic nerve stimulation.

pathic pain drugs in small-fiber neuropathies has not been impressive.

ADDITIONAL TREATMENT REPORTS

As previously mentioned, few controlled studies have been performed on interventions for neuropathic pain in children. Even the most commonly used first-line interventions,[59] certain types of antidepressants and antiepileptic drugs, are almost exclusively prescribed on the basis of data from adults. In 2006, Golden et al[60] published a review of nonepileptic uses of antiepileptic drugs in the pediatric population and found no published trials evaluating the safety or efficacy of antiepileptic drugs in children. During the past decade, reports on an array of presumed neuropathic pain problems in the young have been published, along with some relatively innovative approaches to management. These interventions, presented in chronological order, are outlined in Table 2.

CLINICAL IMPLICATIONS

The paucity of research on neuropathic pain in children leaves us with many important and unanswered questions regarding clinical practice. Assessment of pain and sensory testing in children may be challenging, but appropriate tools have been developed and validated for pain other than that of neuropathic origin: recurrent or chronic musculoskeletal, abdominal, or headache pain.[73-75] Validated indices of neuropathic pain in adults[76-78] may be useful in children as well, but the developmental factors that are central to pain experience and expression in the young need to be considered.[79,80]

Many of the published studies on interventions for neuropathic pain in children are case reports or clinical series with few or no systematic controls. Thus, good evidence of efficacy is lacking, perhaps because placebo effects or merely passing of time may have led to similar outcomes. This may be of greater concern in children because clearly developmental processes strongly pull in the direction of normalcy.

In a parallel fashion, downward generalization of interventions used for neuropathic pain in adults may or may not be appropriate for children. Keeping in mind that medications with indications for the treatment of neuropathic pain were not studied in children or for pediatric problems as part of the review process for the Food and Drug Administration, data are lacking on the safety and efficacy of these drugs in children. Well-conducted pharmacological trials are needed to determine pharmacokinetic and pharmacodynamic properties of antiepileptic drugs and antidepressants in children. Clinical experience makes clear that children have different metabolic profiles than adults and demonstrate different adverse effects and manifestations of toxicity; thus, efficacy may be different as well.

RESEARCH IMPLICATIONS

In pursuing research of pharmacological and interventional strategies in children, a number of ethical and practical factors must be considered. For example, as previously discussed, many of these syndromes are rare in children and often present with heterogeneous symptom clusters. As a result, sufficiently powering a study with clear and meaningful inclusion criteria is difficult. Without sufficient power, the study lacks validity and is therefore unethical to pursue.

In addition, many analgesic trials are placebo-controlled studies. Federal law allows for placebo-controlled trials in children with strict limitations. Denying a child pain relief when alternatives are available presents greater than minimal risk with no direct benefit to the patient; this strategy can be considered ethically only if the test drug is presumed to have true equipoise with placebo.[81] Thus, studies must be designed to meaningfully demonstrate the safety and efficacy of analgesic medications while still providing additional analgesia to ensure comfort to the degree pos-

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sible. The need for different study designs than in adults is not specific for neuropathic pain in children but is shared with many other areas of pediatrics. Therefore, we hope that refinement of clinical research tools in pediatrics in general will also benefit this patient group.

Through more systematic study of the natural history and physiology of pain resolution in children, valuable clues can be obtained about the mechanisms related to poor recovery in adults. This is related to the fact that neural damage often reverts cellular programs to an immature state, and therefore mechanisms of regeneration are partly similar to those of normal maturation (Figure, top). An example is illustrated in the Figure (bottom): in immature or damaged neurons, chloride uptake via the cotransporter NKCC1 shifts the chloride equilibrium potential to depolarized values, and hence the opening of chloride channels by γ-aminobutyric acid (GABA) may have excitatory effects.[82] In contrast, healthy mature neurons express a potassium chloride cotransporter (KCC2) that helps maintain a low intracellular chloride concentration; in these neurons, GABA may produce its inhibitory effect via a chloride influx that hyperpolarizes the neurons.

Finally, this review did not focus on the potential contribution of neuropathic mechanisms in common pain problems, such as chronic abdominal pain or headache. These syndromes may be associated with hyperalgesia and hence with central (or peripheral) sensitization and changes in descending control. Certainly these mechanisms will be important to address in treating such patients. Some medications that are efficacious in treating neuropathic pain may be active against chronic headache or recurrent abdominal pain if their mechanisms of action address those CNS mechanisms. If we maintain that neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system,[83] then central mechanisms that may underlie chronic headache and abdominal pain would not be included.

However, we recognize that this is an emerging field and that definitions of neuropathic pain certainly have not achieved universal consensus. The International Association for the Study of Pain[84] defines neuropathic pain as "pain initiated or caused by a primary lesion or dysfunction in the nervous system." If the focus is on dysfunction and not only identified lesions or diseases, our definitions may broaden. Although a comprehensive review of this debate is well beyond the scope of this article, a brief discussion of recent neuroimaging studies pertaining to headache will highlight some of the provocative issues.

The trigeminal brainstem nuclear complex, a rostral correlate of the dorsal horn of the spinal cord, shows neuronal excitation, best demonstrated in patients who have undergone noninvasive neuroimaging techniques, such as functional magnetic resonance imaging and cerebral near-infrared spectroscopy.[85] Resulting cortical activity ultimately determines and modulates pain perception. In adult studies, a dynamic neural network is activated during the chronic pain state, including the thalamus, primary and secondary somatosensory cortices, anterior cingulate cortex, insula, nucleus accumbens, amygdala, ventral striatum, hippocampus, and cerebellum.[86] Such a chronic pain signature has been noted in adults with interictal migraines,[87] and magnetic resonance imaging spectroscopy shows biochemical differences in similar brain regions in patients with interictal migraine.[88] There is also evidence of gray matter and cortical thickness changes with chronic symptoms.[89,90] Investigation of chronic pain from both a developmental and a neuroplastic perspective may be possible because noninvasive neuroimaging methods are used in pediatric patients. In the pediatric population, the brain is undergoing rapid changes, is more plastic, and may have an increased ability to recover after injury, possibly leading to enhanced understanding of neuropathic treatment modalities.

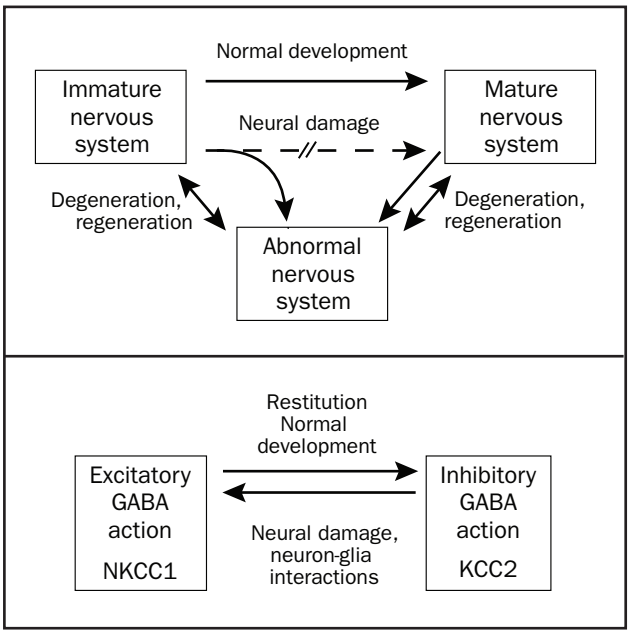

FIGURE. Top, Possible interactions of cellular mechanisms in neural damage and normal development. Bottom, Chloride equilibrium and γ-aminobutyric acid (GABA) actions in immature, damaged, and mature nervous system. KCC2 = potassium chloride cotransporter.

CONCLUSION

Neuropathic pain conditions are relatively uncommon in children. In conditions typically associated with neuropathic pain in adults, such as diabetic neuropathy and postherpetic neuralgia, this may be due to a disease duration that

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is too short for the development of late complications; nevertheless, preventive measures would be indicated to lower the incidence of neuropathic pain persisting to adulthood. In conditions such as plexus avulsion and nerve trauma, some evidence shows that the higher plasticity of the young nervous system leads to a better restitution of function and lower incidence of pain than in adults. In other conditions, such as CRPS type 1, clinical phenotype and treatment efficacy in adolescents have been found to be similar to those in adults. Finally, some conditions lead to neuropathic pain syndromes specifically in pediatric and young adult populations; for Fabry disease, an efficacious disease-modifying treatment is available (enzyme replacement).

As with most pediatric disorders, few systematic studies have been performed on the nature, etiology, diagnosis, prognosis, and treatment of these conditions. Most of the literature consists of case reports or small clinical series with no controls and extremely limited follow-up. Because of developmental concerns, downward extension of assessment and intervention strategies used in adults with neuropathic pain are questionable and possibly dangerous. Through collaborative and carefully designed research studies, greater insights and more efficacious treatments may be identified for children with neuropathic pain. Multicenter randomized controlled trials based on research designs that address the major issues unique to pediatric patients are needed. This includes the fact that chronic pain is relatively rare in children, that there are major concerns with placebo controls, and that all these factors take place within the highly rich and variable context of synaptogenesis and growth of the central and peripheral nervous systems. Thus, suggested research designs may need to include crossover trials, multiple studies with sample sizes of one, enriched placebo study designs, and high- vs low-dosage studies.

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