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Neuropathic and Myopathic Pain

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The evaluation and management of childhood pain syndromes of neuromuscular origin have distinct challenges, as the patterns of disease presentation and the ability of a child to describe symptoms may differ from that of an adult. Advances in scientific and clinical knowledge are leading to significant progress in the care of affected children. The genetic origins of Fabry disease and the inherited form of erythromelalgia are better understood. The increasing interest in neuroimmunology among pediatric neurologists has led to more sophisticated diagnostic and therapeutic approaches. Treatment protocols for complex regional pain syndrome have become more standardized. In addition, investigations continue into potential new interventions for metabolic muscle diseases such as McArdle disease and carnitine palmitoyl transferase deficiency type II. In the years to come, children with pain of neuromuscular origin will have access to more precise diagnostic tools and novel therapies that would alleviate this particularly distressing category of disease.
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Introduction

Pain is an uncomfortable physical sensation that serves to signal injury or impending injury to the body and accompanies many diseases and disorders. Pain in children can be very difficult for physicians to diagnose and treat owing to the subjective nature of the symptom and limitations on some children's abilities to describe abnormalities in sensation. The quality and severity of the sensation can vary even among the same types of injuries. It can be described as dull, throbbing, stabbing, aching, pinching, shooting, steady, lancinating, and electric. This article gives a broad overview of the different types of neuropathic and myopathic disorders in which pain may be a common complaint. Certain disorders, including familial amyloidosis, porphyria, mitochondrial, and trigeminal neuralgia, are not discussed owing to the infrequency of these disorders presenting in childhood or the infrequency of pain being one of the primary complaints.

Pain can be divided into the following multiple pathophysiologic categories: nociceptive, neuropathic, mixed, and psychogenic. Nociceptive pain is owing to damage to a tissue caused by overuse, trauma, pathologic invasion, or compression. Most of the pain experienced overall is nociceptive pain. This type of pain is typically aching, sharp, or throbbing. Pain receptors for tissue injury (nociceptors) are located mostly in the skin or in internal organs. The pain may be constant or intermittent, often worsening when a person moves, coughs, laughs, or breathes deeply. Most of the pain owing to cancer is nociceptive. When a tumor invades bones and organs, it may cause mild discomfort or severe and unrelenting pain. Pain relievers (analgesics), including nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, are usually effective.

Neuropathic pain is owing to nerve injury causing signal dysfunction. The cause of injury is broad and includes structural, nutritional, toxc, infectious, or autoimmune. The pain usually has qualities of burning, lancinating, heaviness, or numbness along the distribution of the affected nerve. In some diseases, there is a combination of nociceptive and neuropathic pain. An initial nervous system dysfunction or injury may trigger the neural release of inflammatory mediators and subsequent neurogenic inflammation. For example, migraine headaches probably represent a mixture of neuropathic and nociceptive pain. Myofascial pain is another subtype that is probably secondary to nociceptive input from the muscles, but the abnormal muscle activity may be the result of neuropathic conditions.

Psychophysiologic pain may be a more accurate term for psychogenic pain because the pain results from interaction of physical and psychological factors. Psychophysiologic pain is far less common than nociceptive or neuropathic pain, though it may be underrecognized in some circumstances. Any of the

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other types of pain described earlier may be complicated by psychological factors. Psychological factors often contribute to chronic pain and to pain-related disability. In such cases, the pain, disability, or both usually have a physical cause, but psychological factors exaggerate or enhance the pain, making it worse than what most people with a similar physical disorder experience.

Neuropathic Pain

There is a broad array of hereditary motor and sensory, along with sensory and autonomic neuropathies based on genetic etiologies. A few of these disorders present with pain as a dominant symptom.

Genetic

Fabry Disease

Fabry disease is an X-linked recessive disorder causing a deficiency of the lysosomal enzyme alpha-galactosidase A, encoded by the *GLA* gene.[1,2] The enzyme deficiency leads to an accumulation of glycolipids in the kidney, heart, and nervous system. In the past, the diagnosis was made based on electrodiagnostic studies,[3] nerve biopsy findings,[4] and enzyme activity levels.[5] Genetic testing is now commercially available and can confirm the diagnosis in typical and atypical cases. The accumulation of glycolipids in the small neurons leads to the painful neuropathy, but also disrupts autonomic neurons leading to dysfunction in blood pressure regulation. The pain usually presents in early adolescence in boys and slightly later in girls. The pain is described as episodic lancinating and burning sensations in the hands and feet. In some cases the patient complains of dysesthesia, an unpleasant, abnormal sense of touch.[6] Commonly, the pain is exacerbated by exertion, temperature extremes, stress, and fatigue. As this disease affects multiple systems, patients can present with symptoms other than pain, such as hypertension, renal dysfunction, and idiopathic stroke. The physical examination can reveal skin lesions of nonblanching clusters of ectactic blood vessels known as angiokeratomas, cardiomegaly, and rhythm abnormalities, as well as vascular lesions of the conjunctiva.

Recent work has revealed the potential molecular pathology that causes sensitization of small pain fibers. Choi et al were able to show that accumulating molecules of globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3) appear to increase cytoplasmic levels of Ca^{2+} in nociceptive dorsal root ganglion neurons.[7] It is postulated that the molecules are altering the functions of specific sodium channels in these dorsal root ganglion neurons causing sensitization, but further work is needed. The mainstay of treatment for Fabry disease is intravenous enzyme replacement therapy infusions bi weekly.[8] The treatment has been thoroughly studied in adults, but a 2014 clinical trial confirmed safety and efficacy in children as well.[9] Enzyme replacement alleviates the mortality and morbidity of the disease, but it is impressive that this treatment can decrease pain in patients who have already developed neuropathic symptoms. A retrospective analysis of the Fabry Outcome Survey of more than 700 patients reported that the 60% receiving enzyme replacement therapy had lower pain scores.[10]

Erythromelalgia

Erythromelalgia is a clinical syndrome of intense burning sensations primarily of the extremities with accompanying erythema and increased skin temperature (related article is printed elsewhere in this volume). It is a rare condition that infrequently presents in the pediatric population. Most cases are idiopathic with a small percentage having autosomal dominant *SCN9A* mutations. Children appear to present similarly to adults, with pain crises that typically affect the feet most prominently, with hands and legs representing the next most frequently involved areas. Episodes are usually spontaneous, but heat can trigger or exacerbate an ongoing crisis.[11] Relief of symptoms with immersion into ice cold water is a universal feature of the disease and is considered pathognomonic. There is an increased female to male ratio of 2:1. In between episodes, the affected areas may be cool and cyanotic, which has been confirmed with documented changes in peripheral vascular function. Measurement of blood flow during the pain episodes reveals increased temperature and flow and subsequent decreases in between symptomatic periods. Electrodiagnostic studies reveal abnormalities in less than half the cases, which are typically characterized by findings suggestive of axonal neuropathy. Treatment ranges from topical creams to a multitude of medications including NSAIDs, opiate analogues, and tricyclic antidepressants with variable responses. A retrospective review of 32 pediatric patients revealed that lidocaine patches were helpful in many patients.[12] As pharmacologic treatments otherwise appear to be minimally successful, it is important to consider multidisciplinary pain rehabilitation as with other chronic pain syndromes. The primary treatment goal of pain rehabilitation is restoration of function by a cognitive behavioral therapy model. A retrospective case series of patients who received daily physical and occupational therapy and attended daily educational group sessions related to the adverse effects of chronic pain revealed increases in functional ability with this regimen.[13]

Acquired

Guillain-Barre Syndrome

Guillain-Barre syndrome (GBS) is a heterogeneous group of inflammatory neuropathies that includes multiple subtypes and variants. Owing to the numerous variations of this disorder, this review focuses on the most common subtype in Western countries, acute inflammatory demyelinating polyneuropathy. The incidence is approximately 1 in 100,000 for the pediatric population.[14,15] In most GBS cases there is a preceding febrile illness within 4-6 weeks of symptom presentation, with rare links to vaccinations.[16,17] The proposed pathophysiology is immune-related damage to the myelin or axon owing to molecular mimicry. The immune system is