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Review

Pain and spinal cord imaging measures in children with demyelinating disease

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ABSTRACT

Pain is a significant problem in diseases affecting the spinal cord, including demyelinating disease. To date, studies have examined the reliability of clinical measures for assessing and classifying the severity of spinal cord injury (SCI) and also to evaluate SCI-related pain. Most of this research has focused on adult populations and patients with traumatic injuries. Little research exists regarding pediatric spinal cord demyelinating disease. One reason for this is the lack of reliable and useful approaches to measuring spinal cord changes since currently used diagnostic imaging has limited specificity for quantitative measures of demyelination. No single imaging technique demonstrates sufficiently high sensitivity or specificity to myelin, and strong correlation with clinical measures. However, recent advances in diffusion tensor imaging (DTI) and magnetization transfer imaging (MTI) measures are considered promising in providing increasingly useful and specific information on spinal cord damage. Findings from these quantitative imaging modalities correlate with the extent of demyelination and remyelination. These techniques may be of potential use for defining the evolution of the disease state, how it may affect specific spinal cord pathways, and contribute to the management of pediatric demyelination syndromes. Since pain is a major presenting symptom in patients with transverse myelitis, the disease is an ideal model to evaluate imaging methods to define these regional changes within the spinal cord. In this review we summarize (1) pediatric demyelinating conditions affecting the spinal cord; (2) their distinguishing features; and (3) current diagnostic and classification methods with particular focus on pain pathways. We also focus on concepts that are essential in developing strategies for the detection, monitoring, treatment and repair of pediatric myelitis.

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1. Introduction

Injury to the spinal cord presents a significant clinical and therapeutic problem (Table 1) that includes significant neuropathic pain syndromes. While most spinal cord injuries are in adults, both traumatic and non-traumatic injuries present in children, with the most common being neoplasms and vascular (Citterio et al., 2004) and demyelinating diseases including acute transverse myelitis (Nair et al., 2005; Galvin et al., 2013). Transverse myelitis is "a neurological disorder caused by inflammation across both sides of one level, or segment, of the spinal cord" (National Institute of Neurological Disorders and Stroke (NINDS), 2015). The term 'myelitis' refers to inflammation of the spinal cord while the term 'transverse' refers to the location of the inflammation across the width of the spinal cord.

Acute transverse myelitis may occur as an isolated inflammatory process or as part of a chronic demyelinating disorder such as multiple sclerosis (MS), neuromyelitis optica (NMO), acute disseminated encephalomyelitis (ADEM) or a syndrome characterized as polio-like myelitis or acute flaccid myelitis (Greninger et al., 2015; Pfeiffer et al., 2015; Mirand and Peigue-Lafeuille, 2015). Transverse myelitis can be classified into two types: *complete or partial*. Complete transverse myelitis usually involves major bilateral loss in motor, sensory and sphincter function. It can be associated with a long spinal cord lesion exceeding three vertebral bodies in length, referred to as Longitudinally Extensive Transverse Myelitis (LETM).

Damage resulting from the inflammation to the fibers in the spinal cord tracts results in a constellation of symptoms and signs characteristic of spinal cord damage including pain, weakness or paralysis, urinary retention and loss of control of bowel function. In some patients there is complete recovery, while in others, these symptoms, including pain, may persist for years. Routine Magnetic Resonance Imaging (MRI) has been the imaging modality of choice in the detection of neuroinflammation; however, studies have shown it to have poor correlation with clinical status of patients with demyelinating injuries (Verhey and Banwell, 2013; Alper et al., 2011; Pidcock et al., 2007; Banwell et al., 2009). Finding more sensitive approaches to defining the location, severity and evolution (i.e., persistence or recovery) of regional demyelination may contribute to a more informed approach to diagnosis and treatment.

Pain in spinal cord disease is frequently severe and disabling (Cardenas and Felix, 2009). The incidence of pain is reported in approximately 65% of patients with chronic SCI, with nearly one third of these patients rating their pain as severe (Yezierski, 1996; Siddall and Loeser, 2001; Schomberg et al., 2012). The pain may be musculoskeletal, neuropathic and less commonly visceral. In spinal cord demyelination, pain is believed to develop following damage to the spinothalamic pathways that under normal condition carry nociceptive information to the brain (Defresne et al., 2003; Siddall et al., 1997). Symptomatically, these changes result in pain at and below the level of the damage.

In this review we summarize (1) spinal cord demyelinating conditions in the pediatric population; (2) their distinguishing features; and (3) classification methods in spinal cord disease with particular focus on pain. We also focus on the current and developing approaches to objective measures of spinal cord damage and recovery using different MRI methods.

1.1. Search terms and methodology

English language literature search of demyelination of spinal cord in children and MRI measures in pain was undertaken using PubMed (http://www.ncbi.nlm.nih.gov/pubmed) from inception until March 2015. Keywords included the terms 'demyelination', 'myelitis', 'spinal cord', 'pediatric', 'neuropathic pain' and 'imaging'. Of note, using search terms "pediatric AND myelitis AND pain AND diffusion" yielded no results suggesting a paucity of information in the field.

2. Pediatric spinal cord demyelination

Inflammatory demyelinating myelopathies represent the majority of pediatric non-traumatic SCI (Nair et al., 2005; Verhey and Banwell, 2013). These are often grouped under the term "*myelitis*" which comprises acute transverse myelitis, NMO and spinal cord relapses in MS. Each year, an estimated 1400 new cases of acute transverse myelitis occur in the United States (Banwell et al., 2009). Among these cases, 20% are reported in children less than 18 years of age (Alper et al., 2011). Transverse myelitis was believed to affect males and females equally with a reported 1.04 ratio (Pidcock et al., 2007). However a more recent study showed a slight male predominance (ratio = 1:0.9) in children less than 10 years of age and a female predominance (ratio = 1:1.2) in patients older than 10 years (Banwell et al., 2009). The reason for these disparities remains unclear. Demyelination is believed to be the pathological basis in transverse myelitis and presents acutely in children, with symptoms appearing over 24–48 h (National Institute of Neurological Disorders and Stroke (NINDS), 2015; Chitnis, 2013).

Table 1
Incidence rates and etiology in non-traumatic spinal cord injuries.

	Sample characteristics			Etiology (n)				Pain assessment
Reference	Size (n)	Mean age (years)	Male/female ratio	Inflammatory	Vascular	Neoplasm	Degenerative	
McKinley et al., 1999	86	61.2	1:1	10	7	22	Not available	Not performed
Scivoletto et al., 2003	177	54.0	1.7:1	40	36	39	61	Reported by 42%
Citterio et al., 2004	330	55.2	1.7:1	63	81	81	60	Not performed
New et al., 2005	70	69.0	0.8:1	12	10	23	18	Not performed
Nair et al., 2005	297	32.0	1.07:1	192	3	85	Not available	Reported by 49.3%
Galvin et al., 2013	68	8.3	1.8:1	15	Not available	40	Not available	Not performed