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Clinical Perspective

Clinical assessment and treatment of carpal tunnel syndrome in the mucopolysaccharidoses

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Abstract. The mucopolysaccharidoses (MPS) are a common cause of carpal tunnel syndrome (CTS) in children and adolescents. As the MPS diseases are progressive in nature, it is essential that CTS in these children is readily diagnosed and treated, before damage to the median nerve becomes irreversible. Currently, no standards for diagnosing and treating CTS associated with MPS exist. Proper diagnosis of CTS generally involves the assessment of clinical signs and symptoms, in combination with nerve conduction studies. As the clinical signs and symptoms of CTS described for adults are often absent in children with MPS, early diagnosis of CTS in these children requires recognition of subtle findings such as decreased sweating, nocturnal waking, gnawing of hands, and manual clumsiness. Sensory tests could also be useful for detecting early CTS when the integrity of the nerve is still relatively intact. Nerve conduction velocities, which are the gold standard for diagnosing CTS, can be difficult to perform in patients with MPS and should be adapted to the patients' clinical characteristics such as their abnormally small hands and young age. Ongoing monitoring for CTS is indicated for all MPS patients, including those treated with hematopoietic stem cell transplantation or enzyme replacement therapy.

Keywords: Carpal tunnel syndrome, diagnosis, hand, mucopolysaccharidoses, neural conduction

1. Introduction

The mucopolysaccharidoses (MPS) are a group of rare and clinically heterogeneous lysosomal storage disorders, with each MPS type being characterized by a deficiency of one or more of the enzymes involved in glycosaminoglycan (GAG) metabolism. The accumulation of unprocessed GAGs in connective tissue of patients with MPS progressively leads to tissue and organ dysfunction. Patients with MPS share, to different degrees, certain clinical features such as coarse facies, visual impairment, hepatosplenomegaly, joint stiffness, skeletal dysmorphisms and cardiorespiratory disease. Most MPS disorders are also associated with mental retardation, except MPS IV Types A and B, and MPS VI and mild forms of MPS I and MPS II. There is a wide spectrum of progression rates within each MPS type.

A common finding in MPS is carpal tunnel syndrome (CTS) [11,20]. CTS is a result of compression of the median nerve in the carpal canal at the wrist, which is formed anteriorly by transverse carpal ligament and posteriorly by the carpal bones, and is shared with nine flexor tendons and their associated synovial sheaths. The median nerve innervates five muscles: the first two lumbricals, the opponens pollicis, the abductor pollicis brevis and the flexor pollicis brevis. CTS traditionally

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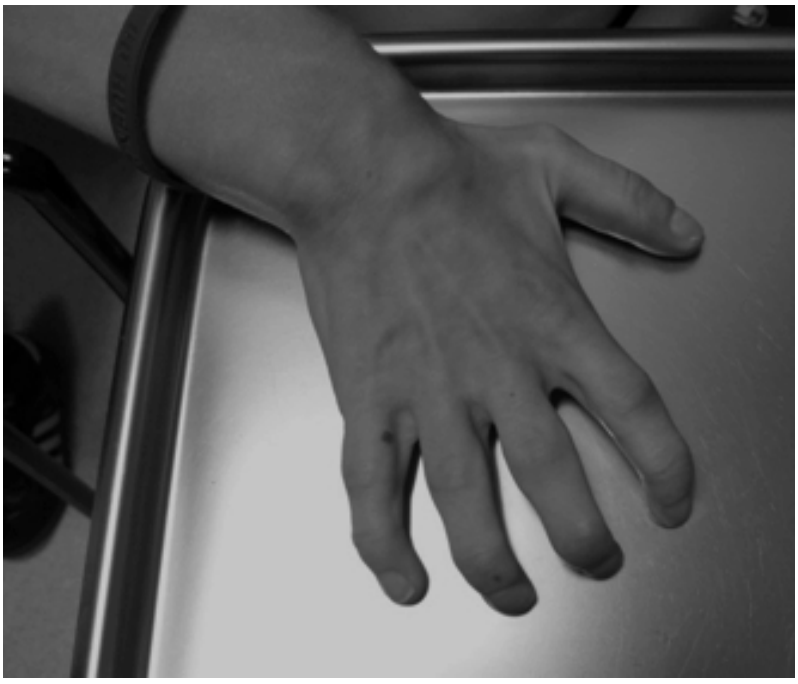

Fig. 1. Photograph showing a clawed hand of a 14-year-old boy with mucopolysaccharidosis II and carpal tunnel syndrome. Note the clawing and generalized atrophy. Given the intrinsic muscle wasting, he likely suffers from ulnar neuropathy as well.

affects middle-aged adults and is rarely seen in children and adolescents. Consequently, many physicians are unfamiliar with its presentation and treatment in children and young adults. In this age group, MPS (mainly I, II and VI) and mucolipidoses (II and III) are, in the absence of trauma, a common cause of CTS [1]. In MPS and related disorders, CTS is thought to be due to a combination of bone deformity, tenosynovial deposits, and excessive GAG storage in the connective tissue of the flexor retinaculum (Fig. 1) [18,19]. This paper discusses the diagnosis, treatment, and follow-up of CTS, with focus on patients with MPS disorders.

2. Diagnosis

Early diagnosis of CTS is indicated in children with MPS as these patients tend to have a good functional and neurophysiological recovery after surgery [11, 18]. Several tests for diagnosing CTS exist, but none of them are diagnostic independently. Proper diagnosis of CTS generally involves the evaluation of clinical signs and symptoms in combination with neurophysiological tests. Due to important differences in disease characteristics between adults and children with MPS, the procedures used for diagnosing CTS in adults are not always suitable for these children. Although there is currently no consensus on which method should be used to screen MPS patients for CTS, electrodiagnostic testing provides the most objective testing that is currently available.

2.1. Signs and symptoms

Typical signs of median nerve compression in adults are burning pain, tingling and numbness (paresthesia/lack of sensation) in the distribution of median nerve distal to the wrist [3]. The part of the hand involved in CTS is usually the thumb, index and middle fingers, and the radial half of the ring finger. Some patients experience finger weakness or clumsiness. A late sign of CTS is thenar atrophy (wasting), which is associated with significant loss of thumb abduction and opposition strength, suggesting permanent damage of the median nerve [2].

The reported ages for presentation of CTS in MPS has ranged from two years of age to adulthood. The diagnosis of CTS in children with MPS is often delayed because typical symptoms such as nocturnal pain, numbness, tingling, Tinel's sign and Phalen's test tend to be absent [11,19] (Fig. 2). It is likely that signs of CTS in MPS are masked by other features of MPS

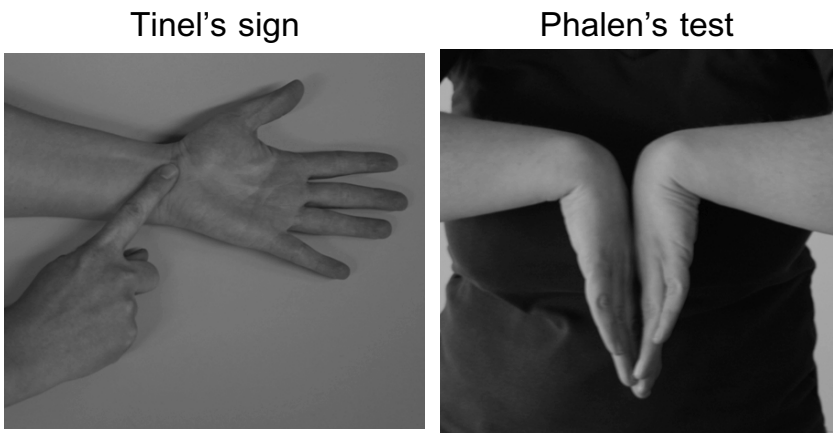

Fig. 2. Photographs showing Tinel's sign (left) and Phalen's test (right). Tinel's sign involves light tapping over the site of the median nerve at the distal wrist crease, which can elicit tingling or discomfort in the fingers of patients with CTS [12]. In Phalen's test, the wrist is flexed until compression of the nerve between the transversal carpal ligament and flexor tendons in the carpal tunnel causes paresthesia in the median nerve distribution [16].

such as joint stiffness and skeletal dysplasia, or ignored because of more severe complaints. In addition, the onset is very gradual which may contribute to the lack of subjective complaints and the recognition of clinical signs and symptoms can be confounded by the inability of the children to communicate their problems; this certainly applies for very young children and those with developmental delays.

Because of the lack of typical symptoms, CTS is often not recognized in children with MPS before thenar wasting and loss of function become apparent. Therefore, more subtle clinical signs such as alterations in grasp or playing pattern, increasing difficulty with fine motor tasks, withdrawal of hands from the touch of others, gnawing of hand and manual clumsiness should be looked for in these patients together with more typical signs such as decreased sweating and impaired sensation of pinprick [11,20].

2.2. Electrodiagnostic tests

Electrodiagnostic tests that are used to evaluate peripheral nerve function include nerve conduction studies and electromyography. The current standard for diagnosing CTS in patients with MPS is with nerve conduction studies. We recommend routine screening in all patients with an MPS disorder for the development of CTS by a yearly clinical evaluation. Those children or adolescents with an inability to clearly communicate due to age or developmental delay should be considered for nerve conduction studies every one to three years, in addition to clinical examination. We recommend that monitoring for CTS should begin at the time of diagnosis and continue thoughout life.

Nerve conduction studies evaluate the site and the severity of a lesion by measuring the sensory and motor nerve conduction velocity in the median nerve at the level of the wrist using surface electrodes. In early CTS, demyelination of the median nerve will cause a delay in the conduction velocity of the sensory nerve at the site of the compression [2]. This delay can be measured by stimulating the median nerve and recording the latency of the electrical pulse by placing an electrode near the base of the ring finger. Motor nerve conduction studies are performed by recording the nerve conduction velocity and the size of the response (amplitude) from a peripheral nerve to the muscle supplied by this nerve. For diagnosing CTS, the motor nerve conduction velocity is measured from wrist to the thenars. Prolonged distal motor latency suggests nerve compression.

There remains considerable controversy about the use of nerve conduction studies for identifying patients with CTS as they are associated with false-positive and false-negative results, with sensitivities ranging between 49% and 84% in non-MPS adult populations (and therefore may not be transferrable to pediatric populations). Therefore, some authors advocate using clinical history and physical examination rather than electrodiagnostic tests for diagnosing CTS [4,9]. Nerve conduction studies, specifically in children with MPS, may be difficult for several reasons. Often, the children are unwilling to cooperate. As the studies may be painful, the examination may require sedation. In our experience, children undergoing nerve conduction studies do not require sedation, but if anesthesia is desired (generally

Table 1
Classification system for nerve-conduction defects in children with mucopolysaccharidoses. Reprinted from Haddad et al. [11], with permission from the British Editorial Society of Bone and Joint Surgery

Sensory studies	A = normal median sensory action potential from the middle finger
	B = double peak sensory action potential from the ring finger
	C = no recordable median sensory action potential from the middle finger
Motor studies	1 = normal distal motor latency to abductor pollicis brevis
	2 = prolonged distal motor latency to abductor pollicis brevis
	3 = no recordable motor response to abductor pollicis brevis

when EMG is included in study), it should be administered by an anesthesiologist with experience in MPS diseases. Another problem is posed by the patients' abnormally small hands, which can confound the results of the test. Minor variations in the distance between stimulating and recording electrodes may cause errors in velocity measurements [11].

Currently, no accepted standard procedure for performing nerve conduction studies in patients with MPS exists. Comparative normal data for these tests depend on several variables, including the patient's age and limb length and are usually based on comparisons to the unaffected contralateral hand. As children with MPS tend to have CTS syndrome in both hands, normative data are difficult to obtain. As such, comparison to the ipsilateral ulnar nerve over the same length segment has also been described and is our preferred mode [13].

Nerve conduction studies and electromyography have also been used for monitoring patients after surgery with MPS or mucoplipidosis with variable success. In a study by Wraith and Alani only two of 16 patients showed electrophysiological improvement after median nerve decompression, whereas most patients and parents reported symptomatic improvement [19]. In contrast, all patients showed normalized or improved electrophysiological results after surgery in a study by Van Heest et al. [18].

A simple classification system for evaluating nerve conduction studies in children with MPS VI was proposed in a study by Haddad et al. [11]. Nerve conduction studies were performed using "standard techniques" (Orthodromic recording of sensory action potentials (SAP) using ring finger stimulations with a ring electrode and a recording electrode over the wrist between the median and ulnar nerves. When possible the median nerve was isolated by stimulating the middle finger and placing the recording electrode over the median nerve. Motor studies of the median nerve involved stimulation at the wrist and elbow with recording electrodes over the abductor pollicis brevis). The classification system is described in Table 1. The study, which included 48 children with MPS, showed that sensory conduction velocity tended to improve more than motor latency after surgery. Whereas full recovery was common in patients with grade C sensory conduction, none of the three patients with grade-3 motor deficit recovered [11]. Although simplistic, outcomes assessed by this system indicate that early diagnosis and treatment results in improved return of nerve function.

2.3. Sensory tests

Several sensory tests exist for assessing peripheral nerve injury (Fig. 3). The practical use of these tools may be limited in MPS patients, but can provide a useful adjunct in clinical monitoring for CTS in adult patients, when used in addition to physical examination and electrodiagnostics. Threshold tests, such as vibration tests and monofilament tests (Fig. 3A), and density tests, including static and moving two-point discrimination (2pd) tests (Fig. 3B), may be attempted, but again, in this patient population are likely to be of limited clinical value, due to an inability to effectively participate in the examination.

3. Treatment

Non-surgical techniques for treating CTS include splinting and non-steroidal anti-inflammatory drugs and may be considered for symptomatic treatment of mild cases of CTS [2]. Surgery is indicated in almost all cases with clinical and electrodiagnostic evidence of compressive neuropathy, and consists of division of the transverse carpal ligament.

Historically, surgery was recommended as a proactive approach to treat CTS in children with MPS before the median nerve was irreversibly damaged [6, 17]. Several studies have shown clinical improvements in hand function after carpal-tunnel release in children with MPS [11,17,19], but neurophysiological recovery was often not demonstrated [19]. Haddad et al. described the outcome of early decompression in 48 children with CTS associated with MPS or mucolipi-

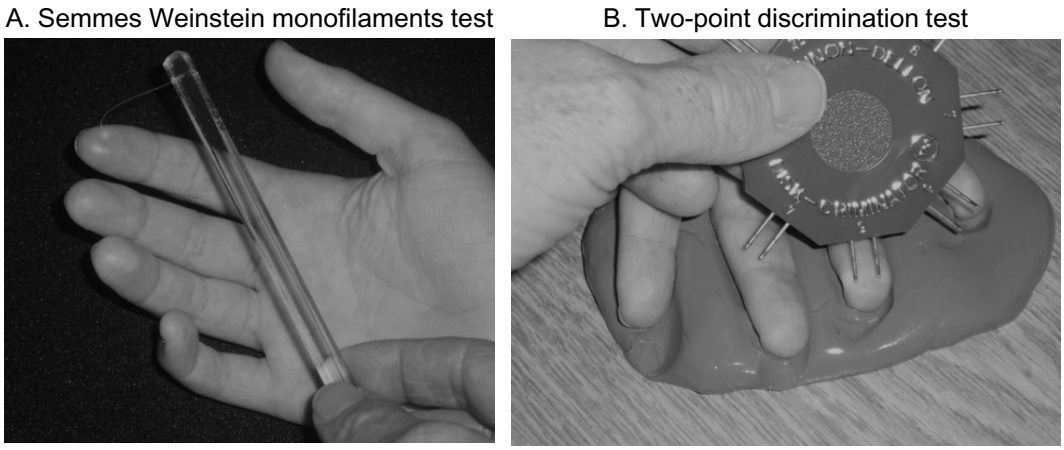

Fig. 3. (A) The Semmes Weinstein monofilaments test measures the sensory threshold of each finger by pressing monofilaments of increasing diameter perpendicularly against each finger until the monofilament bends. (B) Two-point discrimination tests evaluate the number of nerve cells and their receptors in a given area of the skin.

dosis [11]. They demonstrated that mild cases of CTS have a better neurophysiological recovery than more severe cases. The latter finding supports performing early carpal-tunnel decompression in MPS patients.

The advent of hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) for the treatment of several MPS types has considerably changed the outcomes of MPS patients, but has thus far failed to prevent the development of CTS in these patients. Several studies have reported the effect of HSCT on CTS in MPS patients. A study by Guffon et al. evaluated the effect of HSCT in nine patients with Hurler syndrome [10]. Eight patients developed CTS during the course of their disease. They all required median nerve release, including five after HSCT was started. Similarly, 12 of the 17 MPS patients in a study by Van Heest et al. who had previously received HSCT ultimately developed CTS [18]. Surgical treatment in this series emphasized the need for adequate exposure and open release of the transverse carpal ligament as well as debridement of hypertrophic tenosynovium. A more favorable effect of HSCT on CTS in these children was documented in a study by Khanna et al. [13]. Transplantation of 43 children with Hurler syndrome before the age of two years reduced the risk of developing CTS by 46%. The risk decreased by 78% in children who had enzyme activity in the normal range after HSCT. Despite this positive evolution, the children remained at risk of developing CTS and the authors recommended regular monitoring with nerve conduction studies. Little information currently exists on the impact of the recently introduced ERT on CTS in children with MPS. As this therapy is increasingly applied in patients with MPS, there is a need for clinical research on this topic. If therapy results in better life expectancies, proper treatment for CTS will become increasingly important to maintain hand function for as long as possible.

4. Unresolved issues

The diagnosis and treatment of children with CTS and MPS is slowly evolving. Several issues remain unresolved with regard to the diagnosis, follow-up and treatment of CTS in children with MPS. It is clear that patients with MPS require routine monitoring for the development of CTS. It is not clear, however, at what time interval they should be screened and what is the best screening method; to date, no standards exist for the technique or interpretation of nerve conduction studies and electromyography in MPS patients. There is a need for international guidelines for diagnosis, treatment, and follow-up of these patients.

Additionally the exact nature of CTS in MPS remains uncertain. There are indications that CTS in these children may also represent an intrinsic neuropathy. Consequently, surgical release may be inadequate for long-term benefit. The risk of recurrent CTS after surgical treatment has not been defined, and may be related to this intrinsic neuropathy. To clarify these issues, additional research is warranted to assess the impact of either HSCT or ERT on CTS, and to examine in which cases watchful waiting or surgery should be considered.

5. Summary

Despite being very common in the MPS disorders,

CTS, in our experience, is a frequently overlooked condition, which can lead to significant functional disability when left untreated. We recommend routine screening in all patients with an MPS disorder, by a yearly clinical evaluation, for the development of CTS. The majority of patients with MPS lack the ability to clearly communicate symptoms of CTS, and therefore should be considered for nerve conduction velocities in addition to clinical examination. Surgical decompression of the median nerve is the treatment of choice in patients with clinical or neurophysiological signs of median compressive neuropathy. There is still much to be learned about carpal tunnel syndrome in the mucopolysaccharidoses.

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Conflicts of interest

Klane White has received honoraria for educational lectures from BioMarin Pharmaceutical Inc., and Shire plc. Jacob A. Neufeld has received an honorarium for this lecture. Tiffany Kim received a travel award from BioMarin.

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