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Carpal Tunnel Syndrome in Pediatric Mucopolysaccharidoses

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ABSTRACT

Background: Carpal tunnel syndrome (CTS) is rare in children but is a recognised complication of the mucopolysaccharidoses (MPS). Clinicians should have a low threshold of suspicion for CTS in patients with MPS, as their symptoms may be atypical or minimal. If untreated, CTS can cause significant loss of hand function. We present findings in 11 children with mucopolysaccharidoses and suspected CTS and propose guidelines for screening for CTS in children with these disorders.

Methods: Clinical and electrodiagnostic data of 11 children with mucopolysaccharidoses, suspected on clinical grounds to have CTS, was reviewed. All subjects underwent motor and sensory conduction studies of bilateral median and ulnar nerves. The presence of carpal tunnel syndrome and its severity was determined. Subsequent details regarding interventions and recurrence were noted.

Results: Three children had MPS I, five had MPS II, one had MPS III, and two had MPS IV. Seven had motor symptoms and three had sensory symptoms referable to median nerve compression. Nine of the eleven children (2 out of 3 with MPS I, 5 out of 5 with MPS II, 0 out of 1 with MPS III, 2 out of 2 with MPS IV) had median neuropathies at the wrist, (eight bilateral, one unilateral) which were mild in three, moderate in five, and severe in one. Three children presented with symptoms at five years of age. Six underwent median nerve decompression. Four of these had recurrent symptoms several years after surgery that were associated with changes in nerve conduction in two cases. To the best of our knowledge, this is the first report of carpal tunnel syndrome in MPS IV.

Conclusion: Some children with mucopolysaccharidoses experience early development of at least moderately severe carpal tunnel syndrome. We recommend screening for median neuropathies at the wrist starting at age four for children with mucopolysaccharidoses, particularly types I, II, and IV, regardless of their symptoms of CTS and of the treatment received for mucopolysaccharidosis.

Keywords: mucopolysaccharidosis; carpal tunnel syndrome; pediatric screening

BACKGROUND

Median neuropathy due to compression at the wrist, or carpal tunnel syndrome (CTS), is rare in children and, when present, is usually secondary to an underlying disorder. Previous reports have shown that the most common cause of CTS in children are lysosomal storage disorders, particularly the mucopolysaccharidoses (MPS) and mucolipidoses (ML) [1,2]. The mucopolysaccharidoses are a group of inborn errors of metabolism characterised by deficiency of a specific lysosomal enzyme, with resulting intra-cellular accumulation of various glycosaminoglycans leading to progressive tissue damage. Based on the specific enzyme deficiency, seven distinct types of MPS are known [3, 4] with several common features but variable severity [Table 1].

Carpal tunnel syndrome often presents in an atypical way in children. In contrast to adults with compressive median neuropathies at the wrist, many authors report lack of complaints of numbness, tingling, nocturnal pain, and absence of Tinel's and Phalen's signs in children [5, 6, 7, 8]. In those with underlying cognitive impairment, it becomes additionally important to recognize subtle symptoms such as decreased sweating, nocturnal waking (which is a feature of MPS), gnawing of hands, withdrawal of hands from touch of others, manual clumsiness, alterations in grasp or playing pattern, and increasing difficulties with fine motor tasks, which may be associated with classical signs of finger pulp atrophy (atrophy of the soft tissue on the palmar surface of distal phalanx of the thumb and index finger), wasting of the thenar eminence, and weakness of thumb abduction and opposition [5,6,8] .

Treatment options for MPS, including bone marrow transplantation and enzyme replacement therapy, have altered the natural progression of the disease in those affected and have placed additional emphasis on improving quality of life. The need to address the musculoskeletal complications of these disorders is evident, as they can cause significant morbidity if untreated. When severe, CTS can be quite debilitating in limiting hand function and causing severe neuropathic pain. However, when diagnosed and treated early, CTS generally leaves no residual deficits.

Type of MPS	Deficient enzyme	Clinical features
MPS I (Hurler, Scheie, Hurler/ Scheie syndrome)	α-L-iduronidase	Spectrum from clinically severe to mild forms Variable mental retardation, coarse facial features, macroglossia, corneal clouding, hepatosplenomegaly, herniae and dysostosis multiplex
MPS II (Hunter syndrome)	Iduronate sulfatase	Severe and mild forms Similar clinical presentation to MPS I except for absence of corneal clouding
MPS III (Sanfilippo syndrome)	Glucosaminidase	Prominent neurocognitive deficits (developmental regression, hyperactivity) Minimal musculoskeletal problems
MPS IV (Morquio syndrome)	Galactosidase	Severe skeletal dysplasia, short stature
MPS VI (Maroteaux-Lamy syndrome)	N-acetyl-galactosamine sulfatase	Variable (mild to severe) skeletal dysplasia, short stature, heart defects Normal neurocognitive function
MPS VII (Sly syndrome)	β glucuronidase	Skeletal dysplasia, hepatomegaly, developmental delay, corneal clouding
MPS IX	Hyaluronidase	Peri-articular nodular painful masses, mild facial features, normal intelligence

Table 1. The Mucopolysaccharidoses

The association between MPS and pediatric CTS has been recognised for many years, but there are no established guidelines for neurophysiologic screening in these conditions. We report neurophysiologic findings in 11 children with MPS assessed at a single tertiary centre and propose guidelines for neurophysiologic screening in children with these conditions.

METHODS

This was a retrospective study in which clinical and electrodiagnostic data of children with mucopolysaccharidoses attending a single tertiary referral centre between the years 2001-2012 was reviewed. All children had a mucopolysaccharidosis, with diagnosis based on urine metabolic screens, analysis of enzyme activity in blood, or fibroblasts and/or mutation testing. All were suspected to have carpal tunnel syndrome based on the history of a recent onset of loss of hand function, clawing of hands, and/or sensory features. A detailed history, including type of MPS, treatment received for MPS, symptoms suggestive of median nerve compression, age of first presentation with these symptoms, surgical intervention for CTS, recurrence of symptoms, and subsequent management, was noted.

All subjects underwent nerve conduction studies using a Dantec system. Sensory studies were performed by stimulating the median and ulnar nerves orthodromically in the mid-palm at a distance of 7 cm distal to the wrist recording electrodes with application of supramaximal stimulus of 0.1 ms duration. The latency to onset, peak to peak amplitude, and sensory conduction velocity was measured. The values obtained on both motor and sensory studies were compared with the normal reference values for digital studies in children and adolescents of comparable ages, as normal values for palmar studies were not available [9]. An abnormal sensory response was identified where there was an absent or low amplitude median sensory action potential and/or a prolonged absolute median sensory latency and/or a median-ulnar latency difference of >0.3 ms [10] . The median and ulnar motor responses were recorded with surface electrodes over the abductor pollicis brevis and abductor digiti minimi, respectively, after giving a supramaximal stimulus at the wrist and elbow. The distal motor latency, peak compound muscle action potential (CMAP), amplitude, and motor conduction velocity was measured. The presence of a prolonged distal median motor latency, with and without low amplitude or absent median compound motor action potential, was considered to be an abnormal motor response. The electrodiagnostic data was then analysed to determine the presence or absence of median neuropathy at the wrist and, where present, its severity was determined using the following neurophysiologic criteria based on the scale proposed by the American Association of Neuromuscular and Electrodiagnostic Medicine [11] :

- Mild – Prolonged (relative or absolute) sensory latencies with normal motor studies. No evidence of axon loss.
- Moderate – Abnormal median sensory latencies and prolongation of median motor distal latency. No evidence of axon loss.
- Severe – Any of the above features with evidence of axon loss as defined by either a) an absent or low amplitude SNAP, b) a low amplitude or absent median CMAP, or c) a needle EMG with fibrillation potentials or motor unit potential changes (where performed).

Some patients then underwent decompression surgery of the median nerve based on the clinical symptoms and sever-

Subject	Diagnosis (syndrome)	Age at presentation with CTS (y)	Sensory latency (ms)/ SNAP amplitude (μV)		Distal motor latency (ms)/ CMAP amplitude (mV)		Median-Ulnar sensory latency difference (ms)
			Right	Left	Right	Left	
1	Morquio	15	**3.2**/27.8	**3.3**/22.4	2.5/8.0	2.5/7.6	0.2 L, **0.4 R**
2	Morquio	12	0.8/190	1.0/110	0.8/8.0	1.7/9.2	**0.4 L**, 0.2 R
3	Hunter	10	**Absent**	**Absent**	**3.3/6.4**	**2.7/0.7**	**Absent**
4	Hunter	5	**3.4**/29.2	0.8/54.2	**4.2/4.7**	**5.8/3.6**	0.2 L, **1.6 R**
5	Hunter	5	1.0/12.4	1.0/31.9	**3.3/3.7**	**5.0/4.8**	0.3 L, **0.4 R**
6	Hurler	10	**Absent**	**Absent**	**3.5/7.8**	**4.1/8.3**	**Absent**
7	Hurler	5	**4.2**/27	**3.75**/83	**4.2/3.2**	**3.3/6.6**	0.25L, **0.7 R**
8	Sanfilippo	15	0.9/30	0.8/66.2	1.2/10.3	1.4/8.9	0.1 L, 0.2 R
9	Hunter	12	**Absent**	**Absent**	0.9/9.5	1.3/10.2	**Absent**
10	Hurler	8	1.0/30.5	1.52/45.8	2.4/9.5	2.17/9.7	0.2 L, 0.2 R
11	Hunter	8	**4.1**/12.9	**4.0**/12.3	1.67/**0.3**	1.67/**0.6**	**1.2 L, 0.9R**

Table 2. Sensory and Motor Nerve Conduction Findings in Children with MPS
Abnormal values are highlighted in bold [9].

ity of median neuropathy on the neurophysiologic studies. The subsequent clinical course and findings on repeat nerve conduction study, where performed, were noted.

RESULTS

Eleven boys with MPS, aged 5 to 17 years old, were studied. Three had Hurler syndrome (MPS I), five had Hunter syndrome (MPS II), one had Sanfilippo syndrome(MPS III), and two had Morquio syndrome (MPS IV). The mean age of presentation with symptoms referable to CTS was 9.5 years (range 5-15 years) with three children presenting at 5 years of age.

The most common symptom, noted in seven children, was a loss of hand function characterized by difficulty writing and loss of fine motor function associated with wasting of the thenar muscles. Sensory features ,hand numbness and pain, were present in one subject with MPS IV, while one child with MPS II had only numbness of both hands. One child with MPS I syndrome presented with a history of persistent gnawing at his fingers and had mild clawing of both hands. The only patient with Sanfilippo syndrome (MPS III) had decreased sensation over the right hand in the radial distribution with a previous history of right radial nerve palsy secondary to a supracondylar fracture of the humerus with no other symptoms directly referable to CTS.

Two children (one with MPS I and one with MPS II) were receiving enzyme replacement therapy for 1 and 4 years, respectively, before presenting with symptoms of median nerve compression. One child with MPS I had undergone bone marrow transplantation at 17 months of age before presenting with symptoms of median neuropathy at 5 years old. Two children were started on enzyme replacement therapy three years after bilateral surgical median nerve decompression for moderate CTS but had recurrence of clinical symptoms of CTS, having been on enzyme replacement therapy for more than six years.

On nerve conduction studies, nine of the eleven patients studied (two with MPS IV, five with MPS II, and two with MPS I) had neurophysiologic evidence of median neuropathy at the wrist based on absent or prolonged median sensory latencies, prolonged distal motor latencies, or low amplitude of median CMAPs [Table 2]. In patients with mild changes, only the median sensory responses were abnormal. Of these nine subjects, eight had bilateral changes while one had only unilateral CTS. Three had mild, five had moderate, and one had severe CTS. Electromyography was not performed on any of the subjects.

Six subjects with either moderate or severe CTS underwent surgical decompression of the median nerves on both hands (patients 3, 4, 5, 6, 7, and 11). Two underwent surgery at age 5 years old with no subsequent recurrence (patients 4 and 5). The remaining four, who underwent surgery between ages 7 and 10 years old with initial clinical recovery, had subsequent recurrence of symptoms of CTS 5, 7, 8, and 10 years after surgery, respectively (patients 3, 6, 7, and 11). Two of these subjects received enzyme replacement therapy for more than six years before the recurrence. Three of those with recurrent symptoms underwent repeat nerve conduction studies, of whom two had neurophysiologic evidence of CTS – moderate unilateral in one (patient 6) and mild bilateral in the other (patient 11). To date, no subjects have undergone repeat surgery.

DISCUSSION

Carpal tunnel syndrome has been reported in association with the storage disorders MPS I, MPS II, MPS VI, and mucolipidoses II and III [12, 13] . It has a reported eventual prevalence of over 90% in MPS types I and II [14]. Development of CTS in MPS is thought to result from excessive deposition of glycosaminoglycans within the flexor retinaculum along with dysplasia of the underlying bones, causing compression of the median nerve in the carpal tunnel. Mucolipidoses are also a common cause of childhood CTS [2]. The clinical features of mucolipidoses mimic those of some of the mucopolysaccharidoses [7]. CTS is sometimes the first presenting feature of type III mucolipidosis, which is also known as pseudo-Hurler syndrome [15]. Carpal tunnel syndrome is only rarely seen in MPS III (Sanfilippo syndrome) [16]. The present series includes subjects with a variety of mucopolysaccharidoses but no mucolipidoses. The only subject with Sanfilippo syndrome was suspected to have CTS but had normal nerve conduction studies. Two subjects with MPS IV in this study had CTS. To our knowledge, this is the first report of this association in MPS IV (Morquio syndrome).

Children with MPS may have very early compression of their median nerves, often presenting before five years of age. Bona et al reported four children with MPS (two with MPS I and two with MPS II) who presented before 5 years of age with bilateral claw hands and were diagnosed with CTS on the basis of median nerve conduction studies and electromyography [17]. In the present study, three children (two with MPS II and one with MPS I) were diagnosed with moderate CTS affecting both hands at 5 years of age and requiring surgical release.

Classical symptoms suggesting CTS in adults, such as nocturnal paresthesias, pain, or sensory disturbance over the hands, are rare in children [8]. Moreover, children with MPS who have intellectual disability may find it difficult to localise and describe their symptoms. Signs of median nerve compression, such as wasting of thenar muscles, decreased hand function, and clawing of the fingers, are the main presenting features in children. In one large series of 42 MPS patients, specific symptoms of CTS were much less common than relatively non-specific complaints, such as decreased sweating, pulp atrophy (defined as atrophy of the soft tissue on the palmar surface of distal phalanx of the thumb and index finger), thenar muscle wasting, and manual clumsiness [18] . Another study identified difficulty in fine motor tasks as the most frequent complaint in childhood CTS [19]. These signs develop only when axon loss has occurred, and hence are seen only late in the course of compressive median neuropathies. Sensory symptoms, such as gnawing of the hands, were seen in a minority of children in this series with most subjects presenting with decreased hand function and clawing of the hands. These findings can develop in MPS syndromes independent of CTS as a result of bone and soft tissue involvement. The frequency of atypical clinical presentations of CTS in children with MPS, coupled with their lack of expression of symptoms in those with intellectual disability, increases the importance of having a low threshold for suspicion and early screening for CTS in children affected by these conditions.

Enzyme replacement therapy and bone marrow transplant for MPS do not prevent development of CTS in those children who already have bone abnormalities as part of their disease. There is insufficient data to comment on the effect of enzyme therapy for MPS in prevention of bone abnormalities and carpal tunnel syndrome if treatment is started from birth. Field and colleagues reported musculoskeletal development in 12 children with Hurler syndrome who underwent bone marrow transplantation before two years of age [20]. All twelve children developed progressive thoracolumbar kyphosis and hip subluxation, while seven developed carpal tunnel syndrome more than five years after the transplant. Surgical decompression for CTS was needed in all affected children at an average age of 112 months. The authors concluded that the benefit of BMT as a treatment for skeletal disorders of Hurler syndrome is limited by the poor penetration of musculoskeletal tissues by leukocyte-derived enzymes. In another series, five of eight patients with MPS underwent surgery for CTS one to nine years after bone marrow transplantation [21]. In the present series, one child with Hurler syndrome (MPS I) had undergone BMT at age 17 months but developed CTS by age 5 years, and four other affected children had been on enzyme replacement therapy for 1 to 6 years. Enzyme therapy started later in the course of the disease does not completely prevent bone disease in MPS but may slow its progression [22]. Enzyme replacement therapy with recombinant idursulfase is commonly used to treat Hunter syndrome (MPS II). In a randomised, placebo-controlled clinical trial, intravenous administration of idursulfase to 32 patients was associated with significant improvement in pulmonary function, decreased liver and spleen volumes, increased growth velocity, mild improvement with joint mobility, and reduction in urinary glycosaminoglycans [23]. However, it did not show any benefit in cognitive and behavioural manifestations of MPS. The study did not address the incidence of CTS in that series. The recent guidelines for enzyme replacement therapy in Hunter syndrome do not include data on its effect on prevention of CTS [24]. Future studies should systematically address the impact of early diagnosis and treatment of MPS with bone marrow transplantation or enzyme replacement therapy on the evolution of carpal tunnel syndrome. For the moment, regular screening for CTS is important even in those receiving these treatments.

Treatment of CTS mainly involves surgical decompression of the median nerve complemented by physiotherapy and splinting. The standard technique of median nerve decompression involves open division of the flexor retinaculum through a mid-palmar skin incision extended across the wrist crease, followed by complete exposure and release of the median nerve, with or without exploration of the thenar branch. Neurolysis of the median nerve, in addition to decompression, is advised by some authors [25], but a recent comparative study showed no additional long-term benefit from neurolysis [26]. The main histopathological feature of MPS-related CTS is the large quantity of glycosaminoglycans deposited within the flexor retinaculum, causing compressive injury to the median nerve. Direct damage to the nerve or its myelin sheath by glycosaminoglycan deposition has not been identified to date [5, 7]. This suggests that surgical technique plays a limited role in preventing recurrence of median nerve compression. Various authors have studied outcomes of surgical median nerve decompression in the MPS syndromes. Most have reported improved post-operative hand function and symptoms, with or without normalisation of nerve conduction studies [19, 27]. In a series of 48 patients with MPS and CTS, Haddad and colleagues reported improved hand function in all patients after surgery, particularly those with type II MPS [5]. Some authors have noted that early carpal tunnel release may prevent permanent nerve injury [28, 6]. Having discussed the importance of

early screening and surgical intervention, none of the previous reports have recommended ideal ages for screening for CTS in this population.

Analysis of surgical data from the large cohort of patients enrolled in the MPS I registry revealed that almost 11% of patients with Hurler syndrome had undergone surgery for CTS at a median age of 4.1 years, 21% of those with Hurler-Scheie at median age of 8.8 years, and 43% of those with Scheie at 14.9 years [29]. The authors noted that this procedure often preceded the diagnosis of MPS, especially among patients with milder forms of the disease. According to the data on orthopaedic manifestations in patients with MPS II enrolled in the Hunter Outcome Survey of 2009, CTS affected 27.4% of patients and began at a median age of 7 years old (10th-90th percentile 3.6-17.3 years) [30]. Surgery for CTS was the most common surgery performed in this cohort of patients. Almost a quarter of the children in the present study presented before 5 years of age with clinical signs suggestive of at least moderately severe median nerve compression. These subjects underwent surgery soon after diagnosis and have generally had excellent outcomes. This suggests that children with storage disorders predisposing to compressive median neuropathies at the wrist (MPS I, MPS II, MPS IV, MPS VI, ML II, and ML III) should be screened by neurophysiologic testing at or before 4 years of age, even in the absence of symptoms, or earlier if suggestive signs or symptoms are seen irrespective of specific treatment(s) received for MPS. Those with moderate to severe neurophysiologic changes should be referred for early surgery. Where changes suggestive of mild median nerve compression are demonstrated, or after decompressive surgery, children with the storage disorders listed above should undergo neurologic review at least annually with a view to repeat nerve conduction studies every two years, unless clinical suspicion prompts earlier re-assessment.

One of the limitations of this study was that only symptomatic patients were screened with nerve conduction studies for presence of median neuropathy at the wrist. We cannot comment on the frequency of median neuropathy in patients without symptoms or signs suggestive of this condition.

A methodological issue with this study is that historically, in this centre, mid-palmar values were measured for sensory and motor studies. Normal values for these studies are not available in children; hence, the values recorded in the subjects studied were compared with established norms for digital studies. Because these are recorded over a longer distance, they should be associated with greater distal latencies. However, in this series, patients' distal latencies were prolonged even in comparison with norms for digital studies, demonstrating the severity of the abnormalities in the subjects studied. Future studies will include establishment of normal values for palmar studies in children.

It is important to screen children at risk of CTS from MPS by neurophysiologic testing, even in the absence of symptoms and signs of median neuropathy. This will facilitate early diagnosis and intervention where required. This testing may be confined to sensory studies where there is concern about patient distress, but inclusion of motor studies adds additional information regarding disease severity. Those who have no neurophysiologic evidence of median neuropathy, and those who have already undergone decompression surgery, should still be followed regularly by clinical and neurophysiologic evaluation to better delineate the evolution and progression of median neuropathy and its recurrence in different types of MPS with age. With this intention, a prospective study of clinical and neurophysiologic monitoring of children with lysosomal storage disorders (mucopolysaccharidoses and mucolipidoses) is being planned.

CONCLUSIONS

1. Children with mucopolysaccharidoses can have very early development of median neuropathy at the wrist, often presenting with moderately severe nerve compression by 5 years of age.
2. Early diagnosis and prompt surgical intervention has shown good long-term outcomes.
3. All children with mucopolysaccharidoses, particularly types I, II, and IV—which particularly causes compressive median neuropathy—should undergo regular neurophysiologic screening from 4 years of age, if not earlier, irrespective of symptoms or specific treatment received for the storage disorder.
4. With very young children, or if the procedure is poorly tolerated, neurophysiologic testing can be limited to sensory responses, but testing of motor responses confers additional information regarding severity of median nerve involvement.
5. Those with no evidence of median neuropathy and those who have undergone surgery should be assessed annually by a neurologist and at regular intervals by neurophysiologic testing for evolution of compressive median neuropathy.

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Competing interests

None

Author contributions

TM Jadhav – Conception of design, acquisition of data, analysis of data and drafting the manuscript.

AJ Kornberg, H Peters, J Lee – Patient ascertainment and data collection and critical revision of manuscript.

MM Ryan – Conception of design, interpretation of data, analysis of data and critical revision of manuscript.

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