CARPAL TUNNEL SYNDROME IN THE MUCOPOLYSACCHARIDOSES AND MUCOLIPIDOSES


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Children with a mucopolysaccharidosis or mucolipidosis suffer progressive disability of the hands, particularly in relation to dysfunction of the median nerve. This is an increasing problem because bone-marrow transplantation has dramatically improved survival without apparently changing the musculoskeletal manifestations. We have reviewed 48 children with these syndromes who required carpal tunnel decompression, recording symptoms, signs, radiological, electrophysiological and operative findings, histology and upper-limb function. In these children the carpal tunnel syndrome differs from that seen in adults. Symptoms are rare but signs such as decreased sweating, pulp atrophy, thenar wasting and manual clumsiness are much more common. At operation, the flexor retinaculum was thickened and a mass of white tenosynovium engulfed the flexor tendons. Most patients had some definite nerve constriction with a thickened epineurium.

Functional improvement was seen after early decompression, with some benefit from simultaneous tendon release. Regular physiotherapy helped to maintain increased hand movement.

We describe our assessment protocol, the physiotherapy and operative regime and the standard functional review which helps to maximise function in the hands and upper limbs of these children.

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The mucopolysaccharidoses (MPS) are inherited intracellular lysosomal storage disorders in which the deposition of glycosaminoglycans leads to cell, tissue and organ dysfunction (Table I). The mucolipidoses (ML) are similar disorders caused by abnormal lysosomal enzyme transport in cells of mesenchymal origin. The two groups of conditions share many clinical features with multisystem involvement, abnormal facies, organomegaly, dysostosis multiplex and a chronic progressive course. Visual, auditory and cardiorespiratory abnormalities are common. Many of the children have normal intellectual ability, but mental retardation is seen in the Hurler syndrome (MPS IH) and in the Sanfilippo syndrome (MPS III). There is a wide spectrum of severity within each disorder.

The quality of life and the longevity of these children have been greatly improved by bone-marrow transplantation and supportive care, particularly with regard to cardiorespiratory and auditory complications, and this is increasingly uncovering the importance of the musculoskeletal complications. Progressive disability of the upper limbs is recognised in both MPS and ML, and the carpal tunnel syndrome has been reported in association with MPS I, MPS II, MPS VI, ML II and ML III.1-10 Many authors have advised decompression, but there are few objective data on the precise cause, natural history, neurophysiology and functional outcome after operation in these children.

We have reviewed 48 children with mucopolysaccharidoses and mucolipidoses and have developed a standard system for assessment, operation and postoperative review.

PATIENTS AND METHODS

We studied 48 consecutive children with mucopolysaccharidoses and mucolipidoses (Table I) using clinical, radiological and neurophysiological assessment. There were 28 boys and 20 girls with a mean age of 9.8 years (8 months to 16 years) at the most recent review. We excluded children with severe intellectual impairment because they were unable to tolerate thorough neurophysiological or clinical assessment. In addition, their limited lifespan and poor independent function usually precluded musculoskeletal operations.

Clinical review. Clinical assessment was by a surgeon (FSH or DHAJ) and a physiotherapist, using previous detailed clinical and physiotherapy case notes for those patients who were specially reviewed only after operation. Special note was made of symptoms and signs of hand
dysfunction and of median-nerve function. The children were asked to perform a series of tasks of increasing difficulty (Table II) to help to determine their functional status before operation, when possible, at six weeks after operation and then at six-monthly intervals. The minimum follow-up was six months, and was for up to six years in some cases.

**Radiology.** All patients had a full skeletal survey at initial diagnosis. Plain radiographs of the hand and wrist were repeated before operation. MRI was carried out before surgery in some of the older children to assess the carpal tunnel.

**Neurophysiology.** We performed nerve-conduction studies on a Dantec counterpoint machine using standard techniques. Sensory action potentials (SAP) were recorded orthodromically, stimulating the ring finger by ring electrodes with the cathode proximal and the recording electrode over the wrist between the median and ulnar nerves. The appearance of a double peak in the SAP is abnormal: it indicates different conduction velocities for the median and ulnar nerves over the same distance. When possible we also recorded the SAP and conduction velocity for the median nerve alone, stimulating the middle finger and recording over the median nerve. Motor studies of the median nerve involved stimulation at the wrist and the elbow, with active recording electrodes over abductor pollicis brevis.

The neurophysiologists (MCP, NK) developed a simple classification system for nerve-conduction defects as follows:

<table>
<thead>
<tr>
<th>Sensory studies</th>
<th>Motor studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>A = normal median SAP from the middle finger</td>
<td>1 = normal distal motor latency to abductor pollicis brevis</td>
</tr>
<tr>
<td>B = double peak SAP from the ring finger</td>
<td>2 = prolonged distal motor latency to abductor pollicis brevis</td>
</tr>
<tr>
<td>C = no recordable median SAP from the middle finger</td>
<td>3 = no recordable motor response to abductor pollicis brevis</td>
</tr>
</tbody>
</table>

**Surgical technique.** Surgery was recommended when neurophysiological abnormality was present in association with clinical symptoms or signs. A few children with no clinical signs of median-nerve dysfunction were kept under close clinical and neurophysiological review. In most, both sides were affected and simultaneous bilateral decompression was needed.

Our standard treatment had been simple open division of the flexor retinaculum and exposure of the nerve with or without exploration of the thenar branch. Neurolysis has been advised by some, but this has not been usual. We have now modified our technique on the basis of our own experience and that of others and the rationale of management of the condition in adults having renal haemodialysis.

An extended midpalmar skin incision is stepped across the wrist crease. The flexor retinaculum is divided and a sample sent for histological examination and electron microscopy. The median nerve is located and fully released both proximally and distally, including its motor branch. The flexor tendons are always covered with thickened shiny white tenosynovium, which is cleared as one mass. This releases some of the flexor clawing, improves tendon excursion, and eliminates any triggering while clearing the space within the carpal tunnel. A limited external neurolysis is then performed, and samples of perineurium and of tenosynovium are also sent for histological examination. The wound is closed with 4-0 Ethilon sutures; a dry dressing is covered with wool and crepe.

Patients leave hospital the next day, having started passive stretching exercises, followed by active finger movement as soon as this is comfortable. The sutures are
removed at ten days, and mobilisation continues under physiotherapy supervision.

RESULTS

No patient under the age of two years showed any clinical or neurophysiological evidence of median-nerve compression. When there was evidence of compression on one side, the contralateral side always developed similar findings in time. Both clinical and neurophysiological deterioration may be rapid, even within the period of a six-month review. The presentation of symptoms was similar in the MPS and the ML, and we therefore discuss the whole group together and comment on subgroups only if there are particular features.

Symptoms. Most of our patients denied any symptoms, even when there were florid signs and severe neurophysiological deficits. Parents, teachers and regular physiotherapists occasionally reported hand shaking or gnawing, increased difficulty with fine motor tasks and manual clumsiness. An exception to this finding was that some patients with the Hunter syndrome complained of severe pain, numbness and tingling.

Clinical signs. These children usually have small clawed hands (Fig. 1), and with definite median-nerve compression there is an obvious deficit in thumb function, which may become very disabling in a skeletal dysplasia with stiff joints. Pulp atrophy, thenar wasting, thumb weakness and decreased sweating are common; impaired sensation to pinprick and trophic changes are seen less often. When these are present there is always severe impairment of nerve conduction.

Radiology. Plain radiographs showed many previously reported abnormalities such as distal radio-ulnar dissociation, small irregular carpal bones, short tubular metacarpals and phalanges, and tapering distal phalanges (Figs 2 and 3). We could not establish a relationship between the carpal width/height ratio and the severity of median-nerve compression. MRI provided no useful additional information, but did show abnormal signals around the flexor tendons.

Neurophysiology. No patient become worse after operation. The sensory conduction velocity usually improved more than distal motor latency. Several patients with grade-C sensory conduction had full recovery, but none of the three patients with grade-3 motor deficit recovered. Despite this we found no fixed relationship between motor and sensory recovery: some patients had remarkable motor improvement and almost no sensory recovery. The best neurophysiological response to decompression was seen in patients with MPS I and MPS VI. The data from patients with MPS VI are shown in Table III to illustrate some of the results.

Operative findings. Typical findings were a very thickened flexor retinaculum over a large mass of shiny white tenosynovium which engulfed the flexor tendons and restricted both single tendon and differential motion. There was a

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**Table III. Neurophysiological data for seven patients with MPS VI**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
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<th>Nerve conduction</th>
<th>Preoperative</th>
<th>Postoperative</th>
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</thead>
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<tr>
<td>1</td>
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<td>A1, A1</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>14.0</td>
<td>M</td>
<td>A1, A1</td>
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<td>A2, A2</td>
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</tr>
<tr>
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<td>3.0</td>
<td>F</td>
<td>C1, C2</td>
<td>B1, B1</td>
<td></td>
</tr>
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<td>3.7</td>
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<td>A1, A1</td>
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<td>15.0</td>
<td>M</td>
<td>C2, B2</td>
<td>C2, B1</td>
<td></td>
</tr>
</tbody>
</table>

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Fig. 1
Photograph showing a clawed hand in a child with the Maroteaux-Lamy syndrome.

Fig. 2
Radiographs showing oblique views of both hands in a child with the Hunter syndrome. There is clawing, the fingers are semiflexed and the fifth metacarpophalangeal joint is slightly extended.

Fig. 3
Radiograph of the forearm of a child with ML III showing radio-ulnar dissociation with irregular carpal bones and misshapen metacarpals.
variable amount of nerve constriction (Figs 4 and 5) and a thickened epineurium in most cases. There were no problems of wound healing and no scar pain.

Associated pathology. Six patients had triggering in association with a carpal tunnel syndrome. In four, this was at the carpal tunnel and was cured by tenosynovectomy and tendon release. In the other two the triggering was at the A1 pulley or more distally. One of them had a standard A1 pulley release in two fingers with a volar proximal interphalangeal joint release in one finger. The other patient is unwilling to have another operation.

Functional outcome. All the patients and their families reported improved hand use after surgery. This was most noticeable in the patients with MPS II who had symptoms, but was also true in others with few subjective complaints. We cannot separate the effect of the surgery from that of intensive physiotherapy and exercises. We have abandoned the use of splints, originally used to maintain passive extension, since compliance was very low. Our new functional scoring system will help to monitor the long-term outcome of carpal tunnel decompression.

Histological examination. Electron microscopy of the flexor retinaculum, tenosynovium and of epineurium showed numerous foamy macrophages and fibroblasts containing empty membrane-bound vacuoles, in a loose connective-tissue matrix (Fig. 6). Portions of nerve which we studied showed occasional vacuolation of fibroblasts but no evidence of damage to myelinated or unmyelinated fibres (Fig. 7).

Individual syndromes

The Hurler/Hurler-Scheie syndrome (MPS I). This repre-
resents the largest group, and all the patients with confirmed diagnoses over the age of two years ultimately developed carpal tunnel syndrome. They rarely had definite symptoms and some developed florid clinical signs with triggering at the carpal tunnel and the A1 pulley.

The Hunter syndrome (MPS II). All the patients with the Hunter syndrome over the age of two years developed severe symptoms of carpal tunnel compression. Pain and clumsiness, the rapid progression of clinical signs and rapid deterioration of nerve conduction were seen. There was an excellent clinical response after operation, which seemed to persist for a number of years in spite of a slow decline in nerve conduction. All three patients over 12 years showed grade-B1 or grade-B2 nerve-conduction studies.

Sanfilippo syndrome (MPS III). All these children have severe mental retardation, but clinical assessment showed no evidence of carpal tunnel syndrome, and the one child who tolerated nerve-conduction tests had normal results.

Morquio-Brailsford syndrome (MPS IV). None of the children with this syndrome showed any clinical or neurophysiological evidence of median-nerve compression at the wrist.

Maroteaux-Lamy syndrome (MPS VI). All but one of these patients over the age of two years showed symptomatic evidence of carpal tunnel syndrome. They all also had finger clawing which was passively fully correctable and responded well to surgical decompression.

Mucolipidosis III (ML III). Four of the six children had clinical and neurophysiological evidence of severe carpal tunnel syndrome. The other two were teenage siblings. In spite of severe clawing, thenar wasting, pulp atrophy and decreased sweating in the median-nerve distribution, none of these children complained of pain or sensory deficit. All four had neurophysiological evidence of severe median-nerve compression (grades C1 to C3). At operation, severe narrowing of the median nerve was noted in all (Fig. 4).

After operation there was a definite improvement in clawing and in function, but no neurophysiological recovery.

DISCUSSION

The carpal tunnel syndrome was first reported in children by Lettin in 1965. It is rare and usually has an underlying cause. Occasional idiopathic or familial cases have been reported, but the usual causes are anomalous anatomy, trauma, repetitive activity, bleeding disorders, and, most frequently, connective-tissue disorders. The relationship to the mucopolysaccharidoses is recognised and it has been reported in MPS I, MPS II, MPS VI, ML II and ML III. The carpal tunnel syndrome may be the first presenting feature of MPS or ML; this was true of one of our patients with ML III.

In 1974, Fisher, Horner and Wood described dysfunction of the upper limbs in children with mucopolysaccharide disorders. They suggested early carpal tunnel release in anticipation of problems before permanent changes occurred. They also advised soft-tissue releases to improve the range of movement in the wrist and fingers. Pronicka et al prospectively assessed three children with the Hurler syndrome, six with the Hunter syndrome and two with the Maroteaux-Lamy syndrome. All had preoperative and postoperative nerve-conduction studies, and surgery was followed by intensive rehabilitation. They found an improvement in motor activity in all, but the better results were in the more intelligent children. They reported no correlation between postoperative improvement and nerve-conduction changes; they even postulated nerve injury at the time of surgery, but nonetheless advised early carpal tunnel decompression regardless of intellectual disability. Wraith and Alani reported a series of 18 patients with MPS and related disorders, studying clinical and neurophysiological changes in the 17 patients with median-nerve...
dysfunction. Most patients and parents reported functional improvement, but only two showed evidence of neurophysiological recovery.

The diagnosis of median-nerve dysfunction in children with mucopolysaccharidoses and mucolipidoses may be delayed because symptoms are rare, and the signs are masked by other features of the disease, such as joint stiffness and skeletal dysplasia. Signs may be ignored because of more pressing cardiorespiratory, auditory and visual complaints. With the notable exception of some patients with MPS II, we found a striking lack of symptoms. Numbness, tingling, nocturnal pain, Tinel's sign and Phalen's signs were absent. Minimal symptoms in the presence of typical signs are well documented, but Norman-Taylor et al reported definite symptoms in three children with MPS II.

Subtle clinical changes include alterations in grasp or playing pattern, increasing difficulty with fine motor tasks and manual clumsiness. These should be sought, together with the classical findings of pulp atrophy, thenar wasting, weakness of abduction and opposition, decreased sweating, impaired sensation to pinprick and trophic changes. These are always associated with severe nerve-conduction deficits, and should become increasingly rare as median-nerve compression is diagnosed earlier by screening.

Craniocephalic instability is common in these children, but we have seen no evidence of double-crush lesions. Despite this, neurological symptoms in the upper limbs, particularly in MPS IV, in which the carpal tunnel syndrome has not been reported, should lead to careful clinical and radiological assessment of the cervical spine.

Neurophysiological assessment is difficult in these children because they are often unco-operative, have abnormally small hands and may find the procedures painful. Their small hands complicate longitudinal studies, since minor variation in the distance between stimulating and recording electrodes will cause errors in velocity measurements. This problem may explain the previous reports of no clear evidence of neurophysiological recovery. We also have found no recovery from severe nerve damage of C3 on nerve-conduction studies, which may also help to explain the earlier pessimism.

Johnson et al have shown that ‘square’ wrists in adults (those with a depth to width ratio of over 0.7) were associated with higher sensory conduction latencies, and a greater potential risk of carpal tunnel syndrome. We noted no such relationship in our patients. Britz et al have studied MRI findings in 43 adults with carpal tunnel syndrome and noted abnormalities in all cases. We did not use MRI in the younger children, since it would require general anaesthesia. In older children, it revealed only an altered signal in the tendon sheaths but no alteration in the median-nerve signal. In the future, with new-generation scanners, it will be possible to delineate denervated thenar muscles and intrinsic median-nerve damage, but this is unlikely to alter the indications for operation. MRI, CT or ultrasound can be used to assess the volume of the carpal tunnel; this may be useful in patients who do not respond to decompression or have recurrence after successful surgery.

The usual treatment for these children is straightforward decompression, but the addition of external neurolysis has been advised. This has been used in the treatment of carpal tunnel syndrome due to amyloidosis in patients on haemodialysis, and we now routinely perform synovectomy and external neurolysis.

An association between carpal tunnel syndrome and trigger finger has been described in two otherwise normal children, and a similar association is reported in the mucopolysaccharidoses and mucolipidoses. We saw this in six of our patients. Flexor tendon nodules have been described and we agree with MacDougal’s finding that division of the A1 pulley improves finger movement.

Brown and Coulson described triggering at the transverse carpal ligament with median-nerve compression in two adults; they found benign fibromatosis in one and a fibrosed angioma in the other. Robb has described triggering due to a neurilemmoma in the carpal tunnel, but the patient did not have carpal tunnel syndrome. Iqbal reported a similar case due to a tumour of a flexor digitorum profundus tendon. Four of our patients had triggering at the level of the flexor retinaculum; all were cured of this by excision of gross thickening of the flexor sheaths.

In the mucopolysaccharidoses and mucolipidoses an element of bony dysplasia alters carpal volume and morphology; this factor is being investigated. We found large quantities of glycosaminoglycan within the flexor retinaculum, which further reduces the space, and a similar deposition on a larger scale in the paratenon surrounding the flexor tendons also contributed to triggering. Another possible factor is direct damage to the nerve or its myelin sheath. We found no evidence of direct axonal infiltration, and no other peripheral nerve lesions or entrapments in these children have been reported. Swift and McDonald showed multivasculated endoneural fibroblasts on electron microscopy and inclusion bodies within Schwann cells in biopsy specimens of the sural nerve from a patient with MPS II, but we know of no other evidence of direct peripheral nerve damage in these conditions.

Median-nerve compression appears to be due to progressive deposition within the carpal tunnel. The better neurophysiological recovery in mild cases supports regular screening and early intervention. Many of the poor neurophysiological results previously reported may be due to severe preoperative nerve damage. We therefore advise clinical and neurophysiological screening for these children from the time of diagnosis. Children with a poor medical and intellectual prognosis can usually be predicted from their genotype, so that unnecessary surgery is avoided. We have not yet used prophylactic carpal tunnel decompression; we await our longer-term results and recognise that general anaesthesia for these children has problems in airway management. For this reason there should be full

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paediatric intensive-care back-up and carpal tunnel releases should be combined with other procedures such as grommet insertion or inguinal herniotomy.

We do not have enough data to assess the effect of bone-marrow transplantation on the development of median-nerve dysfunction and upper-limb disability in these children, but have seen a definite delay in intellectual deterioration after this procedure.34,35 Imaizumi et al.36 have reported improvement in skin, joint contractures and quality of life after bone-marrow transplantation in patients with MPS II and MPS VI. Field et al.37 found improved joint mobility and decreased clawing in 11 children with MPS IIH after transplants but the hands remained abnormally broad and the digits stubby. Seven of these children with carpal tunnel syndrome showed “considerable benefit”.

Conclusions. Bone-marrow transplants and improved cardiorespiratory support have greatly improved the prognosis for children with mucopolysaccharidoses and mucolipidoses, and many have normal intellectual function. The carpal tunnel syndrome is only part of their musculoskeletal and upper-limb disability, but can be treated by straightforward surgery. We now use a standard protocol for the assessment, surgery and postoperative follow-up which will help to assess the effect of bone-marrow transplant and future treatments such as gene therapy and directed enzyme replacement. At present, early surgery is advised to reduce irreversible damage.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

REFERENCES