SPINAL PROBLEMS IN MUCOPOLYSACCHARIDOSIS I (HURLER SYNDROME)

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Bone-marrow transplantation has increased the survival of patients with mucopolysaccharidosis-I. We describe the spinal problems and their management in 12 patients with this disorder who have been followed up for a mean of 4.5 years since transplantation.

High lumbar kyphosis was seen in ten patients which was associated with thoracic scoliosis in one. Isolated thoracic scoliosis was seen in another. One patient did not have any significant problems in the thoracic or lumbar spine but had odontoid hypoplasia, which was also seen in three other children. Four of the eight patients in whom MRI of the cervical spine had been performed had abnormal soft tissue around the tip of the odontoid.

Neurological problems were seen in two patients. In one it was caused by cord compression in the lower dorsal spine 9.5 years after posterior spinal fusion for progressive kyphosis, and in the other by angular kyphosis with thecal indentation in the high thoracic spine associated with symptoms of spinal claudication.

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The mucopolysaccharidoses are inherited lysosomal storage disorders caused by deficiency of the enzymes required for the degradation of glycosaminoglycans. In mucopolysaccharidosis-I (MPS-I), the Hurler syndrome, the enzyme alpha-L-iduronidase (Bach et al 1972) which is necessary for the degradation of dermatan and heparan sulphate, is deficient. These substances are deposited in the tissues with the excess excreted in the urine. The incidence of MPS-I is about 1 in 100 000 live births (Lowry and Renwick 1971).

It is inherited in an autosomal-recessive manner and various mutations in the alpha-L-iduronidase gene are responsible for the heterogeneity which is seen in the disorder.

Bone-marrow transplantation (BMT) has altered the natural history of the disease, but the deposition of metabolites in bone is not reversed to the same extent as that in soft tissue. The relative avascularity of the ground substance in bone may isolate the cells so that diffusion of alpha-L-iduronidase from the leucocytes is insufficient for the clearance of heparan and dermatan sulphate (Field et al 1994).

The extent and nature of involvement of the spine vary in MPS-I. We have made a retrospective review of the clinical and radiological changes seen in the spine in 12 patients with MPS-I who had received BMT. Neurological problems after posterior spinal fusion in MPS-I and significant scoliosis requiring treatment have not been described previously.

PATIENTS AND METHODS

The 12 patients with MPS-I had treatment by BMT between 1981 and 1995. The mean age at review was 5 years 10 months (10 months to 14 years and 5 months). The mean period since BMT was 4 years and 6 months, and the mean age when this was undertaken was 16 months (3 to 55). There were 5 boys and 7 girls. Eleven had the Hurler syndrome and one was thought to have a milder variant. Alpha-L-iduronidase deficiency had been confirmed biochemically in all the patients by leucocyte enzyme assay.

The children had had a regular, systematic clinical review and were seen at least annually if they were asymptomatic and more often if necessary. Radiographs of the dorsolumbar spine had been taken annually. If the odontoid process was found to be hypoplastic on the initial films, flexion-extension views of the cervical spine were taken and the radiographs repeated annually. MRI of the cervical and lumbar spine was done if indicated.

RESULTS

Table I shows the clinical findings.

Dorsal and lumbar spine. All 12 patients showed the infantile biconvex shape of the vertebral bodies on plain radiographs. A high lumbar kyphosis was seen in ten patients with the apex at L2 in eight, at L2/L3 in one and at D11 in one. The apical vertebral body had a prominent

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Fig. 1

Lateral radiograph of the dorsolumbar region showing antero-inferior beaking of the vertebral body, poorly developed superior facets, kyphosis and retrolisthesis.

anteroinferior beak with hypoplasia of the anterosuperior aspect. Hypoplasia of the superior facets was seen (Fig. 1), and in one patient there was also hypoplasia of the inferior facets. Similar features were seen to a less extent in the levels above and below this vertebra. As a result of these anomalies these patients all had retrolisthesis between the vertebrae at the apex of the kyphosis (Fig. 1). In nine it was less than 25% and in one between 25% and 50%. This patient also had scalloping of the posterior borders of L3 to L5.

The kyphosis was progressive in all six patients for whom serial radiographs were available, although the symptoms and rate of progress of the deformity varied. One child had had a posterior spinal fusion at the age of 2 years and 9 months because the Cobb angle had increased to 80°. Another had been operated on when she was 3.5 years old with an angle of 40° and a third had had fusion at 10 years 3 months with an angle of 56°.

One patient had progressive scoliosis with a right thoracic curve extending from D6 to L1. The curve was noticed at the age of two years, about eight months after BMT, and is

Fig. 2

MRI of the spine showing an upper thoracic kyphus. An extradural collection of fat is seen posteriorly.

being controlled by a brace; the Cobb angle is 70°. Another girl aged 2.6 years, five months after BMT, had a left thoracic curve which extended from D5 to D10 with a Cobb angle of 40°. She also had a dorsolumbar kyphosis from L1 to L3.

Kyphosis was seen at the cervicodorsal region in three patients due to antero-inferior beaking of the D1 to D3 vertebrae. The angle was almost 90° in one patient in whom a posterior hemivertebra was thought to be present as seen by MRI (Fig. 2).

MRI had been performed in three patients. A 13-year-old girl had had posterior spinal fusion of the dorsolumbar region when she was 3.5 years of age. At 12 years she was noticed to have a clumsy gait with reduced exercise tolerance. She had increased ankle reflexes with bilateral ankle clonus. The angle of kyphosis was static at 40° and MRI showed evidence of cord compression at the D10/D11 level where the cord was flattened with little high signal. Another child had a grade-II retrolisthesis at L1 to L2; MRI showed the cauda equina to be stretched over this area but there was no compression (Fig. 3). The third patient had had MRI of the spine at the time when she was having imaging for odontoid hypoplasia. She had had a posterior fusion from L1 to L3 six months earlier. The scan showed an adequate canal in the lumbar spine but also demonstrated a

Table I. Details of 12 patients with mucopolysaccharidosis I

Case	Age	Gender	Age at BMT (mth)	Spinal problem	Cervical spine	Dorsolumbar spine	Treatment
1	3 yrs 2 mths	F	15	Progressive high lumbar kyphosis	Hypoplastic odontoid Platyspondyly MRI: increased soft tissue around tip of odontoid	Kyphosis 80°. Apex at L2 (L1 to L3). L2 most dysplastic. L1 to L2 retrolisthesis grade 1. MRI: adequate canal, D1 to D4 level: severe kyphosis 90°. Cord stretched around this. Epidural fat collection at this level	Posterior spinal fusion L1 to L3 at 2 years and 9 months. Advised spinal fusion for high thoracic kyphosis
2	14 yrs 3 mths	M	27	Progressive high lumbar kyphosis	Triangular odontoid Platyspondyly	Kyphosis 40° in 3/1995. Apex at L2 (L1 to L3). L2 most dysplastic. Kyphosis 65° in 11/1995. L1/L2 retrolisthesis grade 2. Posterior scalloping of L3/L4/L5 MRI: cauda equina stretched. No compression	Advised posterior spinal fusion
3	1 yr	M	9	High lumbar kyphosis ? progressive		Kyphosis 22°. Apex at L2 (D12 to L3). L2 most dysplastic. L1/L2 retrolisthesis grade 1	Observation
4	2 yrs 6 mths	F	25	High lumbar kyphosis ? progressive. Scoliosis	Triangular odontoid Platyspondyly. MRI: increased soft tissue around tip of odontoid	Kyphosis 28°. Apex at L2 (L1 to L3). L2 most dysplastic L1/L2 retrolisthesis grade 1. Scoliosis D5 to D10. Convex to left 40°	Observation
5	14 yrs 4 mths	F	17	Progressive high lumbar kyphosis. Low back pain and anterior leg root pain Claudication symptoms after walking 100 yards	Odontoid hypoplastic at 9 years and 8 months but normal at 12 years and 4 months. Fusion C2 to C3. Platyspondyly. MRI: thecal indentation at C7/D1 due to kyphosis (anteroinferior beaking D1).	Kyphosis 56°. Apex at L2 (D11 to L4). L2 most dysplastic	Posterior spinal fusion at 10 years and 3 months

6	7 yrs 4 mths	F	23	Minimal odontoid hypoplasia and morphological vertebral changes. Increased soft tissue around tip of odontoid	Beaking of anteroinferior aspect of D12. Also, to less extent of D10, D11	Observation
7	13 yrs	F	9	Progressive high lumbar kyphosis. Paraparesis. Reduced exercise tolerance. Bilateral ankle clonus at 12 years. Worse after 11 months. Repeat MRI advised	Kyphosis 40°. Cord flattened at D10, D11 with little high signal. Cord compression. Also, D2 anterior wedging	Posterior spinal fusion at 3 years and 6 months
8	3 yrs 2 mths	F	16	Progressive scoliosis	Anteroinferior beak C4, C5, D2. Local kyphus D2. MRI: dural thickening at C2. Canal tight with loss of CSF fluid signal from foramen magnum to C5 but with no cord compression	Underarm brace
9	6 yrs 6 mths	M	12	Dorsolumbar kyphosis. Progressive	Platyspondyly with anteroinferior beak. Hypertrophy of posterior longitudinal ligament at C2/C3 but with no cord compression. Increased soft tissue around tip of odontoid	Observation
10	2 yrs 4 mths	F	17	Dorsolumbar kyphosis. Triangular odontoid	Kyphosis 23° in 1/94. 28° in 3/1995. Apex at L2 (L1 to L3) L2 most dysplastic. L1/L2 retrolisthesis grade 1	Brace
11	1 yr 7 mths	M	16	Dorsolumbar kyphosis. ? progressive	Kyphosis 20° in 10/1994. 40° in 3/1995. Apex at L2 (L1 to L3). L2 most dysplastic. L1/L2 retrolisthesis grade 1	Brace
12	10 mths	M	7	Dorsolumbar kyphosis. Platyspondyly ? progressive	Kyphosis 30° in 8/1995. Apex at L2/L3 (D12 to L3). L2 most dysplastic. L1/L2 retrolisthesis grade 1	Observation

Fig. 3

MRI of the dorsolumbar spine in a patient with grade-II retrolisthesis showing stretching of the cauda equina over this segment.

Fig. 4

MRI of the upper spine showing indentation of the theca at the site of a kyphus. An extradural collection of fat is seen posteriorly.

severe kyphotic deformity in the upper thoracic spine which had been previously undiagnosed. The cord was stretched over the kyphus and there was an abnormal collection of epidural fat locally (Fig. 2). There were no clinical features suggestive of cord compression.

Another girl aged 16 years had had posterior spinal fusion from D11 to L4 at the age of ten years for progressive kyphosis. She complained of claudication in the lower limbs after walking 100 yards. MRI showed thecal indentation at C7 and T1 at the site of another kyphus with no evidence of cord compression (Fig. 4). This patient also had an abnormal collection of epidural fat at the site of the kyphus.

Cervical spine. Platyspondyly of the cervical vertebra was seen in eight patients with prominent anteroinferior beaking in three. Four patients had hypoplasia of the odontoid process on the initial radiographs. Of these, two subsequently developed to the normal size by the ages of 5 years and 9 months and 12 years and 4 months, respectively. In three other patients the odontoid was triangular in shape but the ossification was described as normal. In another the bodies and neural arches were fused from C1 to C3.

MRI of the craniocervical junction was available in eight patients of whom four showed increased soft tissue around the tip of the odontoid (Fig. 5). One was a 16-year-old girl with a mild variant of alpha-L-iduronidase deficiency and radiological evidence of odontoid hypoplasia but the MR

scan showed that the hypoplasia was in fact minimal. The other patient with persistent odontoid hypoplasia also had increased soft tissue around the tip.

There was no clinical or radiological evidence of cord compression in the cervical spine but the patient with compression at the D10/D11 level also had a tight canal with loss of the CSF signal between the foramen magnum and C5. This patient is under treatment for scoliosis and showed hypertrophy of the posterior longitudinal ligament at the C2/C3 region on MRI but no cord compression. Three patients had evidence of cervical disc degeneration on MRI and thickening of the cervical meninges or pachymeningitis cervicalis was seen in another.

DISCUSSION

In 1981 Hobbs et al described BMT as a method of treating storage disorders. This has increased the life expectancy of patients with MPS-I considerably but has brought attention to other clinical problems.

The management of spinal abnormality in MPS-I is complicated by the learning difficulties of the children, the delay in treatment necessary while they undergo BMT,

Fig. 5

MRI of the cervical spine showing a soft-tissue collection around the tip of odontoid.

accompanying medical problems and the psychological difficulties which the parents experience with the prolonged treatment. The natural history of spinal problems in MPS-I and the effectiveness of treatment such as bracing and posterior fusion have yet to be established.

Anteroinferior beaking of the vertebral bodies has been ascribed to herniation of the nucleus pulposus into the superior aspect of the vertebra below. Swischuk (1970) suggested that hypotonia led to exaggeration of the normal physiological kyphosis in utero or in the neonate to cause the herniation. The abnormality is also seen in the Morquio syndrome (MPS-IV), cretinism, achondroplasia, the Down syndrome, phenylketonuria, Niemann-Pick disease, Werdnig-Hoffmann disease and in other mentally retarded, hypotonic children, and has been described in infants who have been abused. Field et al (1994), however, examined two specimens at postmortem and found that the endplate formation was normal but that there was a failure of ossification in the anterosuperior quadrant of the vertebral body. There may therefore be more than one mechanism involved in anteroinferior beaking. A mechanical cause may explain its occurrence in abused infants with brain damage and chronic hypotonia, but an underlying bony abnormality appears to be the principal factor in skeletal dysplasias. The posterior elements of the vertebrae also have a grossly

abnormal anatomy and a failure of ossification appears to affect the primary centres of the vertebral body and the two neural arches.

Progressive high lumbar kyphosis is the commonest clinical problem. The apex of the kyphus is usually located at the L2 vertebra which has a prominent anteroinferior beak. The rate of progression of the kyphosis is variable. Posterior spinal fusion of the involved segment in the lumbar spine is effective in stopping an increase in the deformity, but deposition of glycosaminoglycans in the tight canal may cause the later development of cord compression.

Short-segment kyphosis in the upper thoracic spine was diagnosed clinically in one of our patients and was seen coincidentally on MRI in another two. These children have short necks, high shoulders and a large head, making clinical diagnosis difficult and giving poor definition of the spine on lateral radiographs. In one patient the deformity measured 90° at the time of diagnosis with the cord stretched over this segment. Claudication in the legs of another child was thought to be due to thecal indentation and a tight spinal canal at the site of this kyphosis. Anteroinferior beaking of the vertebrae and the resulting kyphosis usually occur at the junction of the rigid thoracic and mobile cervical and lumbar spines, suggesting the importance of mechanical factors. We are using bracing to attempt to delay the progress of dorsolumbar kyphosis in two of the five patients seen recently, but it is too early to assess its effectiveness.

Scoliosis was first noticed at about two years of age in two patients. No obvious vertebral abnormality was seen in the affected segment. The application of repeated corrective plaster jackets under anaesthesia can be difficult due to associated anaesthetic (Walker et al 1994) and medical problems.

Atlantoaxial instability is not seen as often in MPS-I as in MPS-IV (the Morquio syndrome). None of the patients in our series had any evidence of atlantoaxial instability, but we have recently seen a 16-year-old girl with a mild variant of MPS-I who had not had BMT. She presented with a sudden onset of quadriparesis, atlantoaxial instability and cord compression at the craniocervical junction and at C1/C2. She was treated by C1/C2 laminectomy and fusion from the occiput to C3.

Ossification of the odontoid process was normal in eight patients and delayed in two. In three of the eight patients the odontoid process was triangular in shape. Wynne-Davies et al (1989) reported odontoid hypoplasia in four of six patients with MPS-I.

An increase in the soft tissue around the dens in MPS-I was described by Kulkarni et al in 1987 and attributed to the abnormal deposition of mucopolysaccharide. Hughes et al (1996) carried out MRI on the soft-tissue mass in the Morquio syndrome and suggested that it is composed of unossified fibrocartilage and fibrous tissue and is related to the craniocervical instability. Biopsy of the increased soft

tissue around the dens seen in degenerative disease with craniocervical instability has shown it to be composed of fibrous granulation tissue (Sze et al 1986). Ransford (personal communication, 1995) is of the opinion that this soft-tissue mass in the mucopolysaccharidoses will eventually disappear if the cervical spine is immobilised by a halo device. In our study, increased soft tissue was seen around the dens in four of the eight patients in whom MRI of the cervical spine was available, but its significance remains uncertain as odontoid hypoplasia was present only in two of these four patients.

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