CLINICAL QUIZ (p41-42) ANSWER

Mucopolysaccharidosis type I (MPS I): Our proband had mildly coarse facial features, restricted range of movement over large joints, splenomegaly, mitral valve regurgitation and umbilical hernia. The skeletal survey showed dysostosis multiplex. The vertebral bodies are flattened, more severely on the dorsal side. There were pointing proximal metacarpal bones as well as widening of the diaphysis of the proximal phalanges. Magnetic resonance imaging (MRI) scan demonstrated prominent perivascular spaces and J-shaped sella. Urine analysis for mucopolysaccharide was therefore performed and found elevated level of dermatan sulphate (32.8 mg/mmol Cr; reference: <13 mg/mmol Cr). Leukocyte enzyme analysis showed significantly reduced α-L-iduronidase activity (0.34 nmol/mg protein/hr; ref. 41.8±15.9 nmol/mg protein/hr). Molecular testing was done and 2 previously reported missense mutations in the *IDUA* gene were found in our proband.[1-3] The p.Arg89Gln:c.266G>A mutation was inherited paternally and the p.Trp626Arg:c.1876T>C mutation was inherited maternally. The diagnosis of MPS I was thus confirmed.

MPS I is a lysosomal storage disease with progressive multi-system involvement.[4,5] There were 3 MPS I syndromes including Hurler syndrome (MPS I-H), Scheie syndrome (MPS I-S) and Hurler-Scheie syndrome (MPS I-HS). However it is increasingly recognised as a continuum of disease with variable severity, rather than being 3 distinct syndromes. MPS I is now classified into 2 broader groups: severe (MPS I-H; OMIM#607014) and attenuated (MPS I-S; OMIM#607016 and MPS I-HS; OMIM#607015).[6] Both groups are affected by the same biochemical mechanism and have overlapping clinical phenotypes.[7] The prevalence of MPS I is estimated to be about 1 in 100,000 births.[8] However this estimate is biased towards the severe group since they are easier to be diagnosed comparing to the attenuated cases.[6]

Infants with MPS I can present with inguinal or umbilical hernias but some infants may appear normal at birth. The mean age of diagnosis for MPS I is approximately 9 months of age and most severely affected children are diagnosed before 18 months old. The attenuated cases usually present between 3 to 10 years of age.[9] Clinical phenotypes presented in both severe and attenuated MPS I are listed in Table 1.[10] Attenuated cases have normal development at 2 years of age and may have less somatic involvements.[9] It has been reported that even among patients with the same diagnosis, their clinical presentation may differ, one of the contributing factors is the type of underlying mutation.[7] Death, caused by cardiorespiratory failure, usually occurs within the first 10 years of life for severe cases. For the attenuated cases, some will die of life threatening complications in the 20s & 30s while some can have a normal life span.

Table 1 Clinical phenotypes associated with severe and attenuated MPS I and our proband

Clinical features	Severe cases	Attenuated cases	Our proband
Restricted range of movements of joints	+++	++	++
Skeletal abnormalities	+++	++	++
Carpel Tunnel syndrome	+++	++	−
Cardiac (valvular) disease	+++	++	++
Recurrent upper airway infections	+++	+	−
Obstructive airway disease/sleep apnoea	+++	+	+
Corneal clouding	+++	+	−
Spinal cord compression	+++	+	−
Hepatomegaly/splenomegaly	+++	+	+
Inguinal/umbilical hernia	+++	+	+
Hearing loss	+++	+	−
Intellectual disability	+++	−	−
Coarse facial features	+++	−	+
Communicating hydrocephalus	+++	−	−
Abnormally shaped teeth	+++	−	−

Modified from MPS I Registry webpage[10]

Skeletal survey is usually performed for patients with suspected MPS I. In the axial skeleton, characteristic radiological features in the skull include the J-shaped sella turcica, where it appears wide with long clinoid apophyses and horizontal orientation on the lateral skull X-ray. On chest X-ray, ribs may appear widened at the anterior aspects with tapering towards the posterior portion, leading to the characteristic oar-shaped ribs. Concerning the spine, atlantoaxial subluxation and anterior inferior vertebral beaking involving the thoracolumbar vertebrae may be present. Progressive thoracolumbar kyphosis could eventually lead to gibbus deformity, which is particularly more common in MPS I compared to the other types of MPS. At the appendicular skeletal system, long bones usually show enlargement/widening of diaphysis, while metacarpal bones are proximally pointed, shortened and thickened.

In terms of the central nervous system, prominent perivascular spaces may be seen on MRI scans in patients with MPS I. Cerebral atrophy is also a feature, leading to widening of cerebral sulci. It usually develops earlier in MPS I, II, III and VII, and becoming clinically detectable during the first few years of life.

However, only a few features are demonstrated in our proband: the skeletal X-rays showed pointing proximal metacarpal bones and enlargement of the diaphysis of the proximal phalanges, MRI scan demonstrated prominent perivascular spaces and J-shaped sella. Still the evaluation of these imaging findings is essential and helpful: 1. for considering and supporting MPS I as the possible diagnosis; 2. as tools for monitoring the disease progress; and 3. as guide to any medical or surgical intervention in the future. Detailed radiological features detectable in MPS I are summarised in Table 2.[11-14]

The *alpha-L-iduronidase* (*IDUA*; OMIM#252800*)* gene is responsible for MPS I and is located in the short arm of chromosome 4 (4p16.3). The mutations found in our proband are reported to be associated with the milder MPS I subtypes in which Trp626Arg is associated with MPS I-HS and Arg89Gln is associated with MPS I-S.[3] These may explain the lack of distinguishable clinical features and therefore suggest that our proband in fact has attenuated MPS I. *IDUA* instructs the production of the IDUA enzyme that is involved in the breakdown of sugar molecules

Table 2 Radiological features detectable in MPS I[11-14]

X-ray	
Skull	• J-shaped sella • Macrocephaly • Frontal bossing
Spine	• Atlanto-axial subluxation • Anterior inferior vertebral body beaking • Thoracolumbar kyphosis
Chest	• Widening of anterior ribs (oar-shaped/paddle ribs)
Hands	• Shortening and widening of long bones • Pointing of proximal metacarpals • Swelling/enlargement of diaphyses
Pelvis	• Flared iliac wings • Inferior tapering of ilium
Magnetic resonance imaging	
Brain	• Prominent perivascular spaces • Cerebral atrophy • Macrocephaly • J-shaped sella
Ultrasound	
Abdomen	• Hepatosplenomegaly

called glycosaminoglycans (GAGs), more specifically dermatan sulphate and heparan sulphate.[7] GAGs were called mucopolysaccharides originally and this is how MPS I was named. Mutations in the *IDUA* gene reduce or stop the function of the IDUA enzyme completely. The lack of IDUA enzyme activity causes accumulation of GAGs within cells, especially in lysosomes, where different types of molecules are digested and recycled. This accumulation of GAGs increases the size of the lysosomes, which leads to organomegaly in patients with MPS I. Excess GAGs are excreted in urine, therefore marked increase of GAGs in urine as well as decrease in IDUA enzyme activity are good indicators to prompt for a diagnosis of MPS I.

Managements

MPS I is a disease with multi-organ involvement and has variable disease severity. Clinical examination, skeletal survey and urine GAGs analysis with electrophoresis to determine GAGs species are usually used as first line tests to make the initial diagnosis which may then be confirmed by IDUA assay and molecular testing. One method of molecular testing is by targeted mutation analysis where a panel of mutations known for causing MPS I are sequenced and this method has a 100% detection rate for the known mutations. There are more than 200 different *IDUA* mutations listed in the Human Gene Mutation database,[15] for mutations that failed to be detected by targeted mutation analysis, sequencing analysis of the *IDUA* gene is the second method. If the sequencing analysis fails as well, deletion/duplication analysis may be considered.

Treatment for MPS I include enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT).

Table 3 Multidisciplinary management care for MPS I patients

Neurological/behavioural/developmental

- MRI cranial imaging to assess hydrocephalus
- MRI spine to assess spinal cord and peripheral nerve involvement
- Developmental assessment.

Ophthalmologic

- Ophthalmologic examination to measure visual acuity and intraocular pressure, slit lamp examination of the cornea, and retinal function assessment.
- Counter measures should be used to reduce glaring from corneal clouding.
- Corneal transplant may be considered but corneal will turn cloudy eventually.

Ears, nose, and throat

- Assessment and consideration of ventilating tubes for recurrent otitis media as well as hearing test and sleep study.
- Placement of ventilating tubes is recommended in severely affected individuals and hearing aids should also be considered.

Pulmonary

- Sleep apnoea may require tracheotomy or high-pressure continuous positive airway pressure with oxygen supplement.

Cardiac

- Echocardiography to assess ventricular size and function.
- Valve replacement may be considered but should be done early.

Musculoskeletal

- Skeletal survey to determine the extent of involvement of the spine and the joints.
- Early referral to physiotherapy for mobilisation to preserve joint functions.
- Nerve conduction study for Carpal Tunnel syndrome identification and determining the best timing for surgical treatment.

MRI=magnetic resonance imaging

ERT treatment with laronidase is used in treating patients with non – CNS phenotypes of MPS I. However it is only effective if diagnosis was made early and if treatment was started early.[9] For HSCT, stable engraftment and graft-versus-host disease are limitations to the success of treatment.[16] Due to a high mortality and morbidity, HSCT should only be proceeded after extensive pre-transplantation assessment.[17] It was reported that the survival rate in HSCT treated patients is 67% higher than those without HSCT.[18] With good timing and donor match, HSCT for MPS I-H patients have an event-free survival rate up to 81% at 5 years.[19] As shown on Table 3, multidisciplinary clinical management should be provided for patients of MPS I. Full discussion on treatment and management suggestions of MPS I is beyond the scope of this clinical quiz. For more details, readers are suggested to read the guideline published by Muenzer et al in 2013.[6]

Apart from clinical managements, proper genetic counselling should also be provided to the patients as well as the families. MPS I is inherited in an autosomal recessive pattern in which both copies of the genes in chromosome 4 are mutated. Parents of affected children are likely to be carriers. Their offsprings (siblings of patient) have 25% chance of having MPS I and 50% chance of being carriers. Therefore genetic testing should be provided for the parents as well.

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