Mucopolysaccharidoses

Prof Izelle Smuts, Paediatric Neurologist and Head of the Paediatric Neurology Unit at Steve Biko Academic Hospital and University of Pretoria

A group of **7** progressive, multi-system disorders with at least **11** different lysosomal enzyme deficiencies.

These enzymes are responsible for the degradation of mucopolysaccharides also known as glycosaminoglycans (GAGs) which are large unbranched polysaccharides. Polysaccharides are chains of repeating disaccharide units made up of an amino sugar and uronic sugar or galactose.

There are four groups of GAGs depending on the structure of the disaccharide unit and comprise of heparin sulphate, chondroitin sulphate/dermatan sulphate, keratin sulphate and hyaluronic acid.

The urinary excretion of GAGs varies in the different mucopolysaccharidoses (MPS) groups and are useful for screening purposes. The diagnosis of the specific MPS is confirmed with enzyme analyses in serum, leukocytes or cultured fibroblasts and mutational analyses.

CLINICAL VIGNETTE

A six-year-old girl presented with hazy corneas and stiff joints. She was the single child of unrelated parents and had an umbilical hernia which was repaired previously. She was short and her height was on the -1.69 z-score.

Her body mass index was 14.2 and on the z-score -0.73 for her age. It was observed that she had coarse facial features, corneal clouding and a marked increased lumbar lordosis with limited range of movement at the wrists and shoulders.

Although the thenar muscles were atrophied, she did not have carpal tunnel syndrome. She did not have palpable hepatosplenomegaly, but mild hepatomegaly with normal parenchyma was found sonographically.

She had mild mitral valve regurgitation and the ejection fraction was 63% with a shortening fraction of 34%. The forced vital capacity was 72%. She had normal hearing and her polysomnogram was normal. The urinary GAGs were positive and the diagnosis of MPS I (Hurler-Scheie syndrome) was confirmed on enzyme analysis. The alpha-iduronidase level was 15.94pmol/spot (normal 200-2614pmol/spot˙20h). Molecular testing confirmed two missense mutations namely c.[235G>A];[1883G>A].

SYNOPSIS

Although MPS are still classified according to the more prominent clinical features and specific enzyme deficiencies, they form a continuum of clinical phenotypes. It is also evident that a specific phenotype may have different enzyme deficiencies and a single enzyme deficiency may have different clinical features. This is the result of diverse mutations at the same locus or other epigenetic factors.

The shared clinical features for all the MPS are coarse facial features, cardiovascular abnormalities, chronic upper respiratory tract symptoms e.g. rhinorrhoea, sinusitis and otitis media and obstructive respiratory disease.

MPS form a continuum of clinical phenotypes

The majority of MPS patients will also have short stature (except MPS IS and II), joint stiffness (except MPS IV), hepatosplenomegaly (except MPS IX), corneal clouding (except MPS II, III and IX) and skeletal abnormalities (except MPS IS).

The skeletal abnormalities may vary from dysostosis multiplex, the more common form, to multiple bone dysplasias in MPS IV and acetabular erosions in MPS IX . MPS I H, the severe form of MPS II and the entire group of MPS III are associated with significant cognitive impairment.

A range of secondary complications is described and include deafness, hydrocephalus and spinal cord compression. It is the result of collagenosis in the tissue where the mucopolysaccharides are accumulating. If the duramater thickens in the cervical area the spinal nerve roots are compressed. Hydrocephalus develops if the intracranial meninges thicken and carpal tunnel syndrome is the result of peripheral nerve entrapment.

All the MPS syndromes, except MPS II are inherited in an autosomal recessive manner. The inheritance pattern of MPS II is X-Linked recessive.

Although a distinction has been made between the three MPS I syndromes (Hurler, Scheie and Hurler-Scheie) previously, they are now classified as severe or attenuated MPS I, because there is no known measurable biomarker to distinguish between the phenotypes.

Severe MPS I patients are normal at birth and then present with non-specific features including hernia or frequent respiratory infections before the age of one year. Coarsening of the facial features and gibbus formation are observed around one year of age.

It is followed by progressive skeletal involvement and the linear growth pattern start to decline at three years of age. Deafness develops often and cognitive impairment is progressive. These patients may die within the first decade of life due to cardiorespiratory failure.

The disease course in attenuated MPS I is less aggressive and patients may have a normal lifespan, but they may die as teenagers or in their twenties. Symptoms may develop between in the first decade with onset at around three years and disabling joint disease and cardiorespiratory involvement are common. The cardiac valves may also be affected and deafness as well as learning disabilities may be occur.

Enzyme replacement is available for MPS I, II, IV and VI. Haematopoietic stem cell transplantation is currently recommended as standard of care for paediatric patients with severe MPS I. Enzyme replacement for MPS I with laronidase is available for the non-central nervous system manifestations.

The development of comorbidities requires vigilant surveillance to ensure timeous intervention of specific manifestations e.g cardiac valve replacement, infective endocarditis prophylaxis, joint replacement, early decompression of the median nerve, ventriculoperitoneal shunt for hydrocephalus, tonsillectomy and adenoidectomy to improve the Eustachian tube function, tracheostomy and many more.

CONCLUSION

Clinicians should be aware of the phenotypic variation of MPS in general in order to identify patients qualifying for specific treatment options that will optimise outcome and quality of life.

References available on request. SF