Hunter's syndrome

Synonyms: Hunter syndrome, mucopolysaccharidosis type II (MPS II), MPS 2, iduronate 2-sulfatase deficiency, IDS deficiency, mild form known historically as gargoylism

The mucopolysaccharidoses are a group of inherited lysosomal storage diseases.

- There is an accumulation of incompletely degraded glycosaminoglycans (acid mucopolysaccharides) in tissues, in this case heparan and dermatan sulfate.
- Glycosaminoglycans are polysaccharide chains containing amino-sugars that are part of the structure of proteoglycans.
- Proteoglycans play an important structural and functional role throughout the body. They consist of a central protein core with multiple glycosaminoglycan polysaccharide chains attached.
- Proteoglycans are found intracellularly, on the cell surface, as part of the extracellular matrix and in basement membranes. Their roles are thought to be varied and largely undefined, predominantly of structural importance.

Genetics

In cartilage, proteoglycans play an important role in its 'shock-absorber' function by retaining water to form a yielding sponge-like structure. They have a complex biosynthetic pathway and are degraded by specific enzymes, one for each particular type of glycosaminoglycan chain. In Hunter's syndrome the deficient enzyme is *iduronate 2-sulfatase*.[1]

The condition is X-linked recessive (Xq28) and there are a range of mutations/chromosomal abnormalities causing the syndrome.[2] Thus it is seen almost exclusively in boys, but rare sporadic cases in females do occur.[3]

How common is Hunter's syndrome? (Epidemiology)

Hunter's syndrome is a rare genetic disorder, with an incidence rate ranging from 0.38 to 1.09 per 100,000 live male births.[4]

Hunter's syndrome symptoms (presentation)[5]

There are two clinical manifestations of Hunter's syndrome:

Type A - severe form

This has relentless progression towards profound intellectual disability. It usually presents in late infancy and is progressive, leading to neurological impairment, deafness and somatic dysfunction, with death by adolescence/third decade.

Problems usually start before age 3, and common presenting features include:

- Coarsening of facial features.
- Thickening of the tongue.
- Decline in intellectual function.
- Hearing problems.
- Swollen and stiff joints.
- Abdominal hernias.
- Hepatosplenomegaly.

Skin features

- Pebble-like ivory-coloured papular skin lesions occur in a reticular pattern between the angles of the scapulae and the posterior axillary line, and over the pectoral area and lateral aspects of the upper arms and legs. The skin changes are virtually pathognomonic for the disease.
- The skin may also show hypertrichosis and excessive Mongolian spots.[6]

Other features

- Macrocephaly - common with a short trunk length compared to the extremities.
- Short stature - develops gradually after the age of 3.
- Airways obstruction - from accumulation of heparan and dermatan sulfate in the trachea.
- Cardiomyopathy and valvular abnormalities (eg, aortic regurgitation - from cardiac infiltration).
- Flexion contractures.
- Progressive deafness - usually mixed sensorineural/conductive variety.
- Abnormal retinal pigmentation and papilloedema - leading to visual impairment.

Type B - mild form

This usually presents later and may not be noticed until adulthood. Life expectancy can be near-normal in this group, with relatively normal intellectual abilities but impaired reading and verbal skills. Some patients may only have involvement of one organ.[7]

- Diagnosis is often not made until later childhood or even adulthood.
- Physical features are similar to those in type A but there is an absence of, or much less severe, neurocognitive involvement.
- May also be dysplasia of the pelvis or femoral head and/or small carpal bones, and early osteoarthritis.
- Life expectancy varies from the fourth through to the seventh decade.

Behavioural problems such as aggression, restlessness and sleep disturbance may occur in both forms of the illness.

Differential diagnosis

- Hurler's syndrome (MPS IH) - corneal clouding present.

- Scheie's syndrome (MPS IS).
- Multiple sulfatase deficiency (mucosulfatidosis).

Investigations

- Urine - glycosaminoglycan variants in the urine suggest the diagnosis (namely chondroitin sulfate B and heparan sulfate).[5]
- Measuring iduronate 2-sulfatase activity in fibroblasts/leukocytes will confirm diagnosis.
- Deposition products can be shown in biopsy samples with special stains.
- X-rays - show features of *dysostosis multiplex* which are due to disordered ossification at varied sites.
- Audiometry.
- Brain CT/MRI - characteristic cerebral changes.
- Spirometry to look for airflow obstruction.
- Echocardiography - to reveal cardiac abnormalities.

Hunter's syndrome treatment and management

- No curative therapy is currently available.
- Treatment is supportive and symptomatic and often focuses on cardiac complications.
- Trials of haematopoietic stem cell transplantation have had mixed results with evidence of biochemical/dermatological amelioration which does not necessarily translate into clinical improvement.[8] [9]
- The current evidence regarding enzyme replacement therapy is limited. It has been shown that enzyme replacement therapy with idursulfase is effective in relation to functional capacity (distance walked in six minutes and forced vital capacity), liver and spleen volumes and urine glycosaminoglycan excretion.[10]

- Much progress has been made in applying gene therapy for Hunter's syndrome, from cellular models to human clinical trials.[11]

Complications

Carpal tunnel syndrome due to median nerve hypertrophy may become a problem, particularly in older people with the mild form.

Prognosis

Early detection of the disease and appropriate multidisciplinary management improves the quality of life.[12] [13]

Death is usually as a result of cardiorespiratory complications. Severe variant sufferers have average onset 2.5 years with an average age of death of ~12 years. However, some may survive into their thirties.

Mild variant sufferers have an average age of onset of 4.3 years with average age of death 21.7 years. However, some may survive into their fourth decade and beyond. Cognitive impairment is associated with reduced life expectancy.[14]

Hunter's syndrome prevention

Genetic counselling with prenatal diagnosis may be helpful within families already with a child already affected by Hunter's syndrome.

Further reading

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