Hunter syndrome (also known as Mucopolysacchridosis type II or MPS 2)

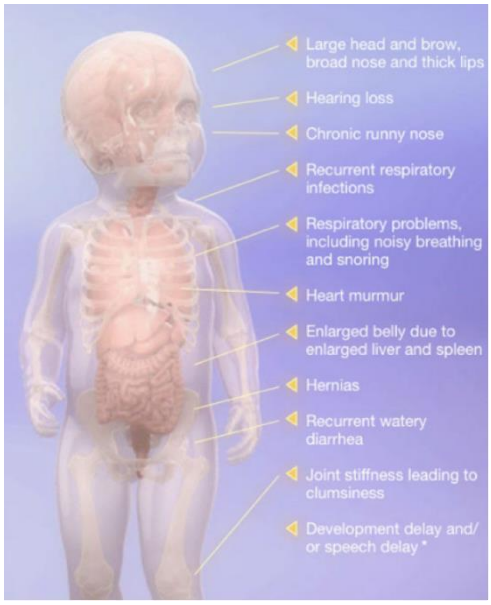
What is Hunter syndrome?

Hunter syndrome is an inherited lysosomal storage disorder, a type of inborn error of metabolism. It is a caused by errors in the IDS gene located on X-chromosome. The IDS gene carries instructions to make a protein (enzyme) known as iduronate-2-sulfatase (I2S). In Hunter syndrome I2S enzyme is missing as a result of an error in the IDS gene. I2S is required to break down two types of complex sugar molecules called mucopolysaccharides or glycosaminoglycans: dermatan sulfate (DS) and heparan sulfate (HS). In absence of I2S, partially broken-down products of DS and HS get stored in the body cells. As large quantities of DS and HS collect in body cells over time, the cells get damaged and symptoms become evident.

What is the mode of inheritance in Hunter syndrome?

The mode of inheritance of Hunter syndrome is X-linked recessive. Only boys are affected by Hunter syndrome as boys have a single X-chromosome and therefore a single copy of the IDS gene. Malfunction of this solitary IDS gene in boys causes Hunter syndrome by reducing functioning of I2S enzyme. Girls are usually not affected by Hunter syndrome as they have two copies of the X-chromosme and thereby have two copies of the I2S gene. If one out of the two copies of the IDS gene malfunction in girls, such girls are carriers. As seen in the figure carriers can transmit the malfunctioning IDS gene to 50% of their sons who will then be affected.

What are the manifestations of Hunter syndrome?



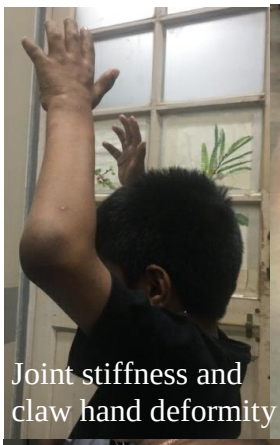
Babies with Hunter syndrome appear healthy at birth and could have large size at birth. They may have excessive number and large size of blue spots known as Mongolian spots on the buttocks and back. Severity of symptoms vary among individuals: some have mild disease whereas others have severe disease with brain involvement.

[Source of figure: https://www.efpia.eu/news-events/the-efpia-view/blog-articles/26102017-hunter-syndrome-mucopolysaccharidosis-type-ii-eu-incentives-behind-omps/, accessed on 18 July 2021]

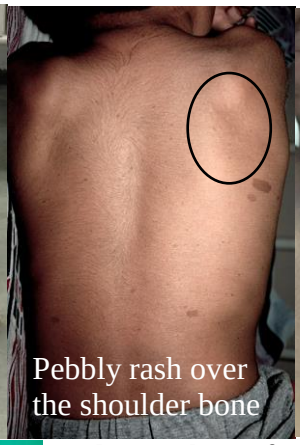
Signs of Hunter syndrome:

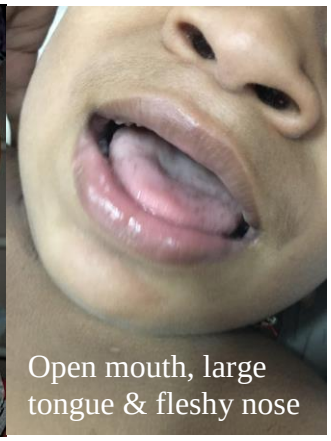
- Inguinal or umbilical hernia
- Short stature
- Coarse face (thick lips, broad nose, flared nostrils)
- Large head
- Large protruding tongue (macroglossia) and thickened gums.
- Frequent upper respiratory tract infection (runny nose, cough, nose block)
- Hoarse voice
- Obstructed breathing during sleep (obstructive sleep apnea) due to enlarged tonsils/adenoids, macroglossia, blocked nasal passage and narrow windpipe.

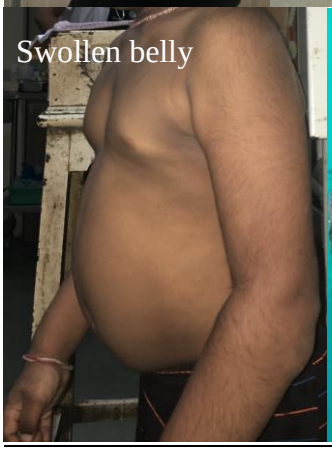
- Skeletal involvement: involvement of skeleton in form of large head involvement of spine causing deformity and thickening of the long bone diaphysis.
- Abdomen is distended due to enlargement of the liver and spleen
- Recurrent ear infections and hearing loss
- Involvement of heart
- Delayed development, intellectual disability, behavioral problems, loss of attained development
- Pearly skin 'rash' resembling pebbles usually over the scapula
- Joint involvement: stiffness, contractures, carpal tunnel syndrome due to compression of median nerves at the wrist
- Heart enlargement and leaky heart valves

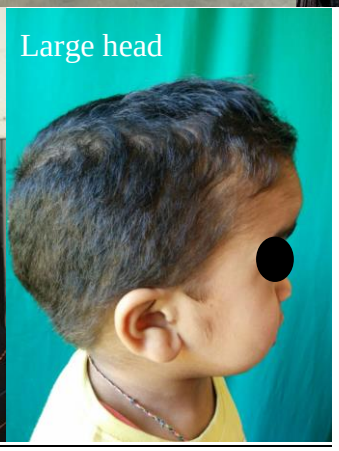

Joint stiffness and claw hand deformity


Deformity of both knee joints

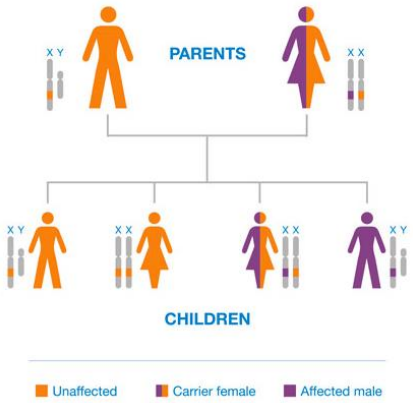

Pebbly rash over the shoulder bone


Open mouth, large tongue & fleshy nose


Swollen belly


Large head

Pedigree chart of X-linked recessive inheritance in Hunter syndrome



[Source of figure for pedigree: https://www.hunterpatients.com/what-is-hunter-syndrome/genetics-of-hunter-syndrome/, accessed on 18 July 2021

Complications:

- CNS complications:
  - Fits (seizures)
  - Cervical spinal cord compression may result in irreversible cord damage and paralysis of upper and lower limbs.
  - Excessive fluid collection in the ventricular system of the brain (hydrocephalus)
- Cardiac complications:
  - Progressive cardiac involvement can lead to high blood pressure and heart failure.
- Respiratory failure

How is Hunter syndrome diagnosed?
In a boy suspected to have Hunter syndrome, amount of glycosaminoglycans excreted in urine is measured in an early morning urine specimen. Bone x-rays will show abnormal shape and growth of several bones. Diagnosis of Hunter syndrome is confirmed by measuring activity of I2S enzyme in white blood cells or skin cells (fibroblasts) or by identification of an error in the IDS gene by DNA testing.

Is treatment available for Hunter syndrome?
Treatment of choice for Hunter syndrome is enzyme replacement therapy (ERT). The two products currently available are described below.

Therapeutic product	Manufacturer	Technology	Administration
Idursulfase alpha (Elaprase→)	Takeda Pharmaceutical Company (formerly Shire Human Genetic Therapies)	Recombinant DNA technology, human IDS gene expressed in human fibroblasts	Intravenous, infusion, every week
Idursulfase beta (Hunterase→)	Green Cross Corp	Recombinant DNA technology, human IDS gene expressed in chinese hamster ovary cells	Intravenous, infusion, every week
Hunterase ICV	GC Pharma (formerly Green Cross Corp)		Intraventricular

How effective is treatment with ERT?
ERT is not curative. The natural progress of the disease is altered by ERT. Therapy is lifelong. Disease manifestations are completely or partially reversed by ERT. Symptoms will recur if ERT is discontinued. Early initiation of ERT may markedly slow or prevent the development of some irreversible manifestations of Hunter syndrome, including coarse facial features, joint disease, and cardiac function. Urinary glycosaminoglycan excretion is reduced, spleen and liver size is reduced, growth is maintained in the normal range and joint mobility is either stabilized or improved.
ERT also improves cardiovascular clinical outcomes in patients with Hunter syndrome particularly those who receive early intervention. Brain involvement is not reversed with ERT.

Apart from ERT is any other treatment required for people with Hunter syndrome?
All people having Hunter syndrome require multi-disciplinary care. Those receiving ERT need additional therapy including surgeries as all the manifestations do not respond to treatment with ERT. Even those not receiving ERT require supportive therapy as untreated disease is progressive. Supportive care required is listed below.

- Hearing aids for hearing loss
- Grommet (ventilation) tube placement due to recurrent fluid collection in the middle ear (serous otitis media).
- Tonsillectomy and adenoidectomy to correct eustachian tube dysfunction and to decrease airway obstruction.
- Some of the common surgeries requied are hernia repair, cervical spinal cord stabilization, correction of bone and joint deformities, median nerve decompression for carapl tunnel syndrome and placement of shunt for drainage of excessive fluid from the brain (hydrocephalus).
- Support for breathing with non-invasive (BIPAP device) and invasive ventilation.

What is the outcome for people with Hunter syndrome without treatment?

Relentless progression of the disease decreases lifespan in untreated people with Hunter syndrome. Those with severe disease and brain involvement do not survive beyond the second decade of life due to fatal obstructed breathing or cardiac failure. Those having mild disease may live up to the sixth decade of life.

What is the approximate cost of treatment with ERT for Hunter syndrome?
Annual cost of treatment for a child weighing 10 kgs is approximately ₹ 65,00,000.

Can Hunter syndrome be prevented?

Families having affected children are encouraged to consult a clinical geneticist for counselling and prevention of recurrence in future pregnancies.

Link to Patient video

Write-up prepared on 19th July 19, 2021