I-cell Disease (Inclusion Cell Disease)

Inclusion cell (I-cell) disease is a lysosomal storage disorder, also known as mucolipidosis II. It is most commonly inherited in an autosomal recessive fashion and is caused by a defective N-acetylglucosaminyl-1-phosphotransferase enzyme which is involved in cellular trafficking. Without this enzyme, hydrolases and other catabolic enzymes destined for lysosomes are instead secreted into the bloodstream, leading to abnormal lysosome function and buildup of byproducts within cells. Specifically, mannose residues on newly synthesized glycoproteins are unable to be phosphorylated, which causes them to be secreted extracellularly instead of shuttled into lysosomes. This gives rise to clinical manifestations such as coarse facies, skeletal abnormalities, and corneal clouding. A diagnosis of I-cell disease is made when increased lysosomal enzyme levels are detected in the plasma, or inclusion bodies are visualized on microscopy. This disease has a poor prognosis with most patients dying in childhood from cardiac or respiratory failure.

PLAY PICMONIC

Pathophysiology

Mucolipidosis II

Mucous-lips and (2) Tutu

I-cell disease is also known as type II mucolipidosis, and is classified under the umbrella of lysosomal storage disorders. Other mucolipidoses include types I (aka sialidosis), III, and IV. The clinical features of I-cell disease closely resemble those of Hurler and Hunter syndromes, which are classified as mucopolysaccharidoses.

Autosomal Recessive

Recessive-chocolate

This disease is most commonly inherited in an autosomal-recessive fashion.

Defective N-acetylglucosaminyl-1-phosphotransferase

Broken Seagull-glue-amigo with (1) Wand Phosphate-P-train

N-acetylglucosaminyl-1-phosphotransferase (GlcNAc-1-phosphotransferase) is a key enzyme in the appropriate cellular trafficking of newly made proteins. GlcNAc-1-phosphotransferase normally phosphorylates mannose residues on newly-made glycoproteins in the Golgi apparatus, which tags them for transport to lysosomes. Without this enzyme, hydrolases and other catabolic enzymes destined for lysosomes are instead secreted into the bloodstream, leading to abnormal lysosome function and buildup of byproducts within cells. I-cell disease is typified by defective activity of the GlcNAc-1-phosphotransferase enzyme due to mutations in the $GNPTAB$ or $GNPTG$ genes.

Absent Mannose-6-Phosphate on Glycoproteins

Missing-poster of Man-nose (6) Sax Phosphate-P

Without the enzyme GlcNAc-1-phosphotransferase, newly made proteins won't have the lysosomal-specific mannose-6-phosphate tag added onto their glycoprotein components. Without this tag, these new proteins are inappropriately targeted for extracellular secretion instead of being shuttled into lysosomes. As such, lysosomes can't break down cellular debris, and elevated levels of lysosomal hydrolases in the bloodstream will be detected.

Accumulation of Lysosomal Debris

Lysol-can Full of Debris

In I-cell disease, lysosomes do not function properly due to lack of their normal catabolic enzymes (e.g. lysosomal hydrolase). This leads to the accumulation of cellular byproducts such as lipids and mucopolysaccharides within lysosomes. This buildup causes tissue dysfunction throughout the body and leads to clinical signs and symptoms. On microscopy, lysosomal debris is visualized as inclusions which gives I-cell disease its name.

Signs & Symptoms

Coarse Facies

Coarse Face

I-cell disease is a disease of infants and children, who will have thickening of the skin over the face and ears as well as large full cheeks, leading to a coarse appearance. Gingival hyperplasia may also be evident.

Corneal Clouding

Corn Clouds

Glycoprotein deposition in the eyes may lead to corneal clouding that progresses to blindness. This feature is also notable in Hurler syndrome, a related lysosomal storage disorder.

Skeletal Abnormalities

Abnormal Skeleton

Skeletal abnormalities can include joint contractures, clubfeet, kyphoscoliosis, and abnormal growth of the long bones. There may also be a characteristic “claw hand deformity” due to lysosomal enzyme deposition in soft tissues.

Diagnosis

Increased Plasma Lysosomal Enzymes

Up-arrow Plasma-TV Lysol-can and Enzyme

Postnatal diagnosis of I-cell disease is confirmed when increased levels of lysosomal enzymes are detected in the plasma or when inclusion bodies are visible on microscopic examination of peripheral blood lymphocytes. In the urine, high levels of oligosaccharides may be seen. Prenatal diagnosis involves confirmation of hypofunctioning GlcNAc-1-phosphotransferase via amniotic fluid analysis (amniocentesis) or chorionic villus sampling (CVS). Gene sequencing can also be utilized to detect pathologic variants of the *GNPTAB* gene.

Inclusion Bodies

Ink-blots

On microscopic examination of affected cells such as fibroblasts, distinctive inclusions will be seen within their lysosomes due to the accumulation of cellular byproducts.

Considerations

Poor Prognosis

Gravestone

I-cell disease is a disease of infancy and childhood. Only symptomatic treatment is currently available for patients with I-cell disease. Most die in childhood from respiratory failure due to abnormal respiratory musculature mechanics, or from cardiac failure due to cardiac valve thickening.