Hartnup Disease

Hartnup disease is an autosomal recessive metabolic disorder caused by mutations in the SLC6A19 gene, which encodes a sodium-dependent neutral amino acid transporter in the proximal renal tubules and small intestine. This defect results in decreased absorption of neutral amino acids, such as tryptophan. Tryptophan is the most significant among the neutral amino acids affected due to its role as a precursor for niacin (vitamin B3) and serotonin. Niacin deficiency leads to pellagra-like symptoms such as diarrhea, dermatitis, and dementia. Another common symptom of Hartnup disease is cerebellar ataxia due to niacin deficiency, which is needed for cellular processes. Neutral aminoaciduria, characterized by increased excretion of neutral amino acids in urine, is a key diagnostic feature of Hartnup disease. Treatment includes a high-protein diet to ensure adequate amino acid levels and niacin supplementation to alleviate pellagra symptoms.



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Pathophysiology

Autosomal Recessive
Recessive-chocolate
This metabolic disorder is inherited in an autosomal recessive fashion.

Defective Sodium-Dependent Transporter
Broken Salt-shaker Transporter
Hartnup disease is caused by mutations in the SLC6A19 gene, which encodes a sodium-dependent neutral amino acid (such as tryptophan) transporter in the proximal renal tubules and the small intestine—leading to decreased absorption of neutral amino acids.

Neutral Amino Acids
Neutral A-mean-ol' Acidic-lemon
During Hartnup disease, multiple neutral amino acids are not absorbed in the kidney and small intestines. Reduced systemic levels of neutral amino acids result in different clinical manifestations.

Renal and Intestinal Cells
Kidney and Intestine
In Hartnup disease, the sodium-dependent neutral amino acid (such as tryptophan) transporter is defective. This transporter is primarily located in the proximal convoluted tubule of the kidney and the small intestines. So, absorption of amino acids in the kidneys and GI tract is decreased.

Tryptophan Deficiency
Tri-toe-fan Deficient
Tryptophan is one among other neutral amino acids not absorbed in those with Hartnup disease. This lack of absorption leads to decreased levels of tryptophan, which is the precursor of niacin (vitamin B3) and serotonin.

Impaired Synthesis of Niacin
Impaired Nice-sun
In Hartnup disease, tryptophan is the most significant amino acid affected because of its critical role in the body. It serves as a precursor for niacin (vitamin B3), and a deficiency of niacin can lead to various clinical manifestations, including pellagra-like symptoms.

Signs and Symptoms

Pellagra-Like Symptoms
Pelican
Hartnup disease leads to pellagra-like symptoms due to decreased levels of tryptophan, a precursor for niacin. The deficiency of niacin results in clinical manifestations such as dermatitis, diarrhea, and dementia.

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Diarrhea

Toilet

Niacin deficiency affects the gastrointestinal tract, leading to inflammation and dysfunction. This inflammation and dysfunction results in diarrhea, possibly abdominal pain, loose stools, and malabsorption.

Dermatitis

Dermatologist Examining Rash

Dermatitis in Hartnup disease is a photosensitive rash that typically occurs on sun-exposed areas of the skin. The most common locations are the neck (C3/4 dermatome), arms, and face. The rash is red, rough, and scaly, resembling a sunburn, and can progress to hyperpigmentation and thickening of the skin. The “Casal’s necklace” is a classic sign that a rash forms around the neck. Because of its location on the neck, it is also referred to as a “broad collar” rash.

Dementia

Demented-D-man

Dementia, which is a serious loss of global cognitive ability, is a characteristic symptom of niacin deficiency. Neurological symptoms arise due to niacin's role in cellular energy production and nervous system function.

Ataxia

A-taxi

Cerebellar ataxia is one of the symptoms of Hartnup disease. The cerebellum relies on adequate energy supplies for proper function. Niacin deficiency impairs energy production in neurons due to reduced NAD+ availability. This dysfunction in cerebellar neurons and pathways leads to ataxia.

DIAGNOSIS

Neutral Aminoaciduria

Neutral A-mean-ol'-acidic-lemon-urinal

A defective transporter in the proximal convoluted tubule of the kidney impairs the reabsorption of neutral amino acids, resulting in their increased excretion in the urine. Neutral aminoaciduria serves as a key diagnostic feature of Hartnup disease.

TREATMENT

High-Protein Diet

High-Mr. Protein Food

A high-protein diet ensures a normal supply of important amino acids for the body, including tryptophan. A well-balanced diet rich in vitamins and minerals is recommended to maintain overall health and minimize deficiency symptoms.

Niacin Supplementation

Nice-sun Pills

Niacin supplementations can alleviate pellagra symptoms because the main cause of the clinical manifestations in Hartnup disease is niacin deficiency.

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