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A PERSPECTIVE REVIEW ON CARNOSINEMIA

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ABSTRACT

An inherited metabolic condition characterised by extreme mental defect and myoclonic seizures. Serum Carnosinase Deficiency; Beta-Alanine-Pyruvate Aminotransferase; Hyper-Beta Carnosinemia. Just about ten cases have been reported. The mutation on 18q21.3 causes autosomal recessive transmission. In some of the instances, parental consanguinity has been reported. A deficiency in carnosinase function causes a progressive neurologic condition with a variable phenotype that includes extreme mental retardation, myoclonic seizures, tremor, and hypotonia. As a result of demyelinization and reactive fibrosis, autopsy findings in the central nervous system may include extreme axonal degeneration, loss of Purkinje fibres, and neuraxonal spheroids in the grey matter. Meat contains large amounts of carnosine, a dipeptide of histidine and alanine. A strict meat-free diet can help to alleviate symptoms but does not cure the disease. Carnosine levels in the blood and urine are elevated when carnosinase is deficient.

Keywords: Carnosinase, Autosomal recessive transmission, myoclonic seizures, tremor.

INTRODUCTION

Carnosinemia is a rare autosomal recessive[3] metabolic disorder[4] caused by a lack of the dipeptidase carnosinase (a type of enzyme that splits dipeptides into their two amino acid constituents). [5] Carnosine is a dipeptide that is present in skeletal muscle and nervous system cells and is made up of beta-alanine and histidine. [number six] An accumulation of carnosine is found in the urine,

cerebrospinal fluid, blood, and nervous tissue as a result of this condition. [nine] Carnosinemia ("carnosine in the blood") and neurological disorders associated with a deficiency of carnosinase are common. [3][8][9].

Genetics

Carnosinase is encoded by a gene on chromosome 18,[3] an autosome. Carnosine dipeptidase-1 (CNDP1) is a gene that regulates tissue and serum carnosinase. [nine] Carnosinase deficiency is caused by mutations in the CNDP1 gene, resulting in carnosinemia. [three] Carnosinemia is an autosomal recessive condition, which means the abnormal gene is found on an autosome and the disorder must be inherited in two copies - one from each parent. Both parents of a person with an autosomal recessive disorder have one copy of the defective gene, but they normally have no signs or symptoms of the disorder.

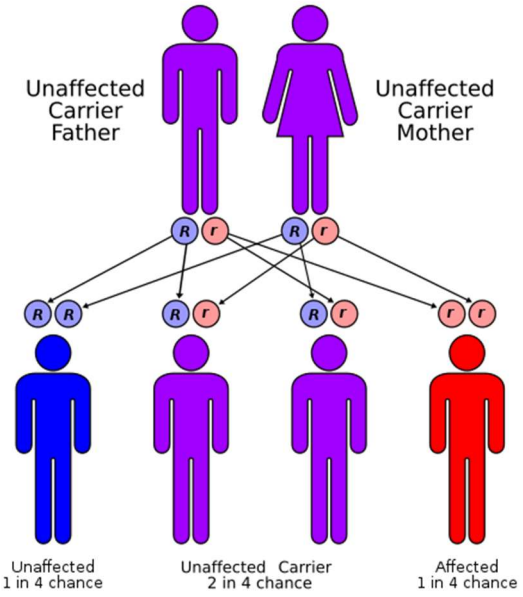

Fig 1: Carnosinemia has an autosomal recessive pattern of inheritance.

Causes

Although the exact nature of the biochemical abnormality that causes carnosinemia is unknown, carnosinase, the enzyme that breaks down carnosine, is known to be present in both the brain and the blood. Studies of muscle tissue from affected people show that the enzyme carnosinase is abnormal in its metabolism of two dipeptides found in meats, carnosine and anserine. Carnosinase is an enzyme that breaks down carnosine into two basic components. Carnosineuria (abnormally high levels of carnosine in the urine) and abnormally low levels of the enzyme carnosinase in the blood are common in those who are affected. It's also unclear how the disorder's neurological symptoms are linked to low carnosinase and/or high carnosine levels in the body.

The CNDP1 gene encodes carnosinase, an enzyme that degrades histidine-containing dipeptides including carnosine, anserine, and homocarnosine. Carnosinase deficiency has been identified in a small number of patients with extremely high blood carnosine levels, but it is uncertain if the wide range of clinical symptoms experienced by these people is caused by carnosinase deficiency.

Carnosinemia is thought to be passed down through the family in an autosomal recessive pattern. When a child inherits an abnormal gene from both parents, he or she develops recessive genetic disorders. If a person is born with one regular and one abnormal gene for a disease, he or she will be a carrier for the disease but will not display symptoms. For each birth, there is a 25% chance that two carrier parents will both transfer the abnormal gene and, as a result, have an affected infant. For each birth, there is a 50% chance of having a child who is a carrier, much like the parents. A child has a 25% chance of inheriting normal genes from both parents. Males and females are equally at risk. [10].

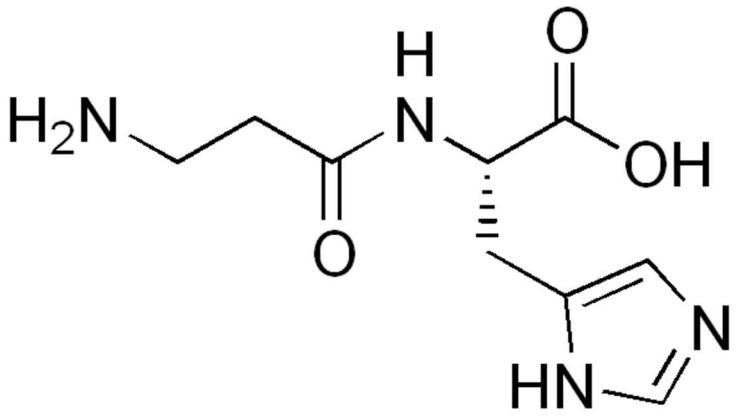

Fig 2: Carnosinemia

Signs & Symptoms

Extreme drowsiness and seizures are common symptoms of carnosinemia in children under the age of one year. Children with this condition have slowed growth, low muscle tone, motor delays, and intellectual development delays. Myoclonic seizures can occur alongside seizures. Affected children show varying degrees of intellectual deficit by the age of two, leading to intellectual disabilities and developmental regression. Some of the children who are affected also have muscle weakness (congenital myopathy). An abnormal electroencephalogram (EEG) is a test that detects electrical activity in the brain. This disorder has been documented in a few patients who have few to no symptoms. [10]

Diagnosis

In humans, there are two types of carnosinase: Carnosinase, cellular or tissue: [nine] [12] This enzyme can be present in all bodily tissues. It is a dimer that hydrolyzes both carnosine and anserine, with a preference for dipeptides with a histidine monomer at the C-terminus. (12) Because of its ability to hydrolyze a variety of dipeptide substrates, including those belonging to prolinase [16], tissue carnosinase is often referred to as a "nonspecific dipeptidase"[13-15].

Carnosinase present in the blood plasma is called serum carnosinase. The most common metabolic measure of systemic carnosinase deficiency is carnosinuria ("carnosine in the urine"), which is caused by a lack of this form of carnosinase. [3] [8] [17] The glycoprotein serum carnosinase breaks free carnosine and anserine in the blood. [9] This form of dipeptidase isn't present in human blood until late infancy, and it takes a long time to reach adult levels by the age of 15. [14] Serum carnosinase, unlike tissue carnosinase, hydrolyzes the GABA metabolite homocarnosine as well. [9] Homocarnosinosis, a neurological disorder resulting in an excess of homocarnosine in the brain, though unaffected by tissue carnosinase, is caused by a deficiency of serum carnosinase in its ability to hydrolyze homocarnosine.[18] A deficiency of tissue and serum carnosinase, with serum being an indicator, is the underlying metabolic cause of carnosinemia.[7][9].

Clinical aspects

Perinatal and early postnatal development may appear normal, but the condition may manifest with myoclonic seizures and the loss of previously acquired milestones by the age of 4 to 5 months. One of the patients was severely mentally retarded and had spastic athetoid quadriparesis by the age of two. He had tonic-clonic seizures, optic atrophy, and suprabulbar symptoms when he was 3 to 4 years old. A carnosinase deficiency causes extreme mental retardation, myoclonic seizures, tremor, sensory peripheral neuropathy, and hypotonia in this progressive neurologic condition with variable phenotype. As a result of demyelinization and reactive fibrosis, autopsy findings in the central nervous system may include extreme axonal degeneration, loss of Purkinje fibres, and neuraxonal spheroids in the grey matter. Meat contains large amounts of carnosine, a dipeptide of histidine and alanine. Carnosine levels in serum and urine are elevated when carnosinase is deficient. A strict meat-free diet can help to alleviate symptoms but does not cure the disease.

STANDARD THERAPIES

Since there is no appropriate drug treatment for carnosinemia, it is treated symptomatically and supportively. A vegetarian diet lowers serum carnosine levels by reducing the amount of carnosine and anserine presented to the body. However, it's unclear whether this will have any impact on symptoms or disease progression. Carnosinemia patients and their families should seek genetic therapy.

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