ANTIQUITIN DEFICIENCY

WHAT IS ANTIQUITIN DEFICIENCY?
The deficiency of the enzyme α-aminoacidic semialdehyde dehydrogenase (also called antiquitin) is due to mutations in the ALDH7A1 gene encoding this enzyme. Cause the most common pyridoxine (vitamin B6) dependent epileptic encephalopathy.

Its estimated prevalence is from 1: 20,000 to 1: 600,000 alive newborns, according to geographical areas and diagnostic possibilities.

WHAT IS ANTIQUITIN?
Antiquitin is an enzyme in the catabolism of the amino acid lysine, which catalyzes the conversion of α-aminoacidic semialdehyde (αAASA) to α-aminoacidic acid (αAA), in a redox reaction that requires the nicotinamide adenine dinucleotide (NAD) cofactor. The name "antiquitin" derives from the apparent ancient origin of this protein.

Lysine is metabolized by two pathways, a peroxisomal one, resulting in pipecolic acid in the brain and a mitochondrial one, resulting in saccharopine and α-AASA, which operates primarily in the liver. The α-AASA becomes αAA by antiquitin action.

Both pathways are in equilibrium and converge in the formation of Δ-piperideine-6-carboxylic acid (P6C).

WHY DOES ANTIQUITIN DEFICIENCY OCCUR?
Antiquitin deficiency occurs due to mutations in the ALDH7A1 gene encoding this enzyme protein. Antiquitin deficiency is transmitted by autosomal recessive inheritance, i.e., both parents often carry a mutation in the ALDH7A1 gene, although they don’t suffer from any clinical manifestation for it.

If both parents transmit the son a mutated allele of this gene, the child will suffer antiquitin deficiency.
WHICH ARE THE METABOLIC CONSEQUENCES OF ANTIQUITIN DEFICIENCY?

The deficiency of antiquitin activity interferes in the conversion of αAASA in αAA.

Consequently, αAASA accumulates, becoming P6C. P6C excess condensed with pyridoxal phosphate (PLP, which is the active form of vitamin B6 or pyridoxine), causing a secondary deficiency of vitamin B6. Pipecolic acid also accumulates.

In summary, the metabolic consequences are due on the one hand to the accumulation of αAASA and P6C, which cause vitamin B6 deficiency. Vitamin B6 acts as coenzyme in many transamination and decarboxylation reactions of amino acids and neurotransmitter precursors. Moreover, accumulated pipecolic acid may contribute to seizure since it is a modulator of the inhibitory neurotransmitter GABA.

CLINICAL SYMPTOMS OF ANTIQUITIN DEFICIENCY

Antiquitin deficiency causes an epileptic encephalopathy resistant to antiepileptic drugs. Typically, it starts in the neonatal period or in infancy with seizures or epileptic encephalopathy resistant to common drugs, but sensitive to high doses of pyridoxine. The type of seizures varies even individually, being myoclonic, clonic or tonic-clonic or partial seizures, with propensity to develop status epilepticus (situation of almost continuous crises for a long time).

The clinical spectrum of antiquitin deficiency is wide and extends from ventriculomegaly detected in abnormal fetal ultrasound fetal movements, neonatal multisystem disorder until the onset of seizures and autistic traits after the first year of life, although the latter presentation it is rather unusual.

Brain MRI may be normal or show some nonspecific structural abnormalities such as corpus callosum hypoplasia, megacisterna magna, enlarged ventricles and diffuse cerebral atrophy of the white and gray matter.

Despite good control of epilepsy, some patients have long-term developmental delay and intellectual disability.
DIAGNOSIS OF ANTIQUITIN DEFICIENCY

The clinical diagnosis of antiquitin deficiency can be challenging because sometimes there is a partial response to common antiepileptic drugs. On the other hand, in children with a multisystem disease, the response to pyridoxine may not be immediate and obvious, and structural abnormalities of the brain can coexist and be considered a sufficient cause of epilepsy, and may not be related to a possible antiquitin deficiency.

Clinical suspicion is very important because it is a treatable disorder.

There are two biochemical diagnostic markers: αAASA and pipecolic acid in urine, plasma and CSF. Pipecolic acid is a highly sensitive but not very specific marker because it may be also increased in other metabolic diseases and treatment with pyridoxine reduces pipecolic acid levels.

They described other secondary biochemical abnormalities such as elevated some amino acids (possibly secondary to the defect pyridoxine), lactic acidemia, hypoglycemia and low levels of GABA and glutamate high.

Differential diagnosis with other causes of epilepsy responsive to pyridoxine or its vitamers is important, especially piridox (am) ine phosphate oxidase (PNPO) deficiency responsive to pyridoxal phosphate (PLP, the active form of vitamin B6), which it is also presented with neonatal epileptic encephalopathy. The different response to treatment with pyridoxine or PLP but especially mutational study is the basis for the differential diagnosis.

Diagnostic confirmation by ALDH7A1 gene mutational analysis allows genetic counseling and prenatal diagnosis, if required.

TREATMENT OF ANTIQUITIN DEFICIENCY

Treatment is based on lifelong supplementation with pharmacological doses of pyridoxine.

To stop seizures an intravenous dose of pyridoxine is administered which should be done with proper monitoring of vital signs (heart rate, respiration, oxygen saturation ...) in an intensive care unit. If this is not possible, it may be administered orally (or by nasogastric tube).

The response may be delayed or masked, so that treatment by oral / enteral pyridoxine should continue until antiquitin deficiency is excluded by negative genetic or biochemical tests.

Doses of long-term treatment varies between 15 and 30 mg / kg / day in infants or up to 200 mg / day in infants and 500 mg / day in adults.
In front of the doubt of PNPO deficiency (another cause of vitamin B6-dependent epilepsy, in this case PLP-responsive) or antiquitin deficiency, PLP can be administered directly to the patient. Both defects (PNPO and antiquitin) respond to treatment with PLP, which is the active form of pyridoxine. Sometimes is useful to treat first for 3 days with pyridoxine (easier to get in some countries) and if there is no response, administer then PLP, after an increased suspicion of a PNPO deficiency.

Antiquitin deficiency is an organic aciduria caused by poor lysine degradation. Therefore, a lysine restricted diet could improve the potential toxicity of αAASA, P6C and piperolic acid accumulation. However, a multicentre study on the long-term results is needed to document the potential benefits of this additional treatment.

Antiquitin deficiency is a neurometabolic disease with potentially serious consequences. Early diagnosis and treatment improve the prognosis and quality of life of affected children.