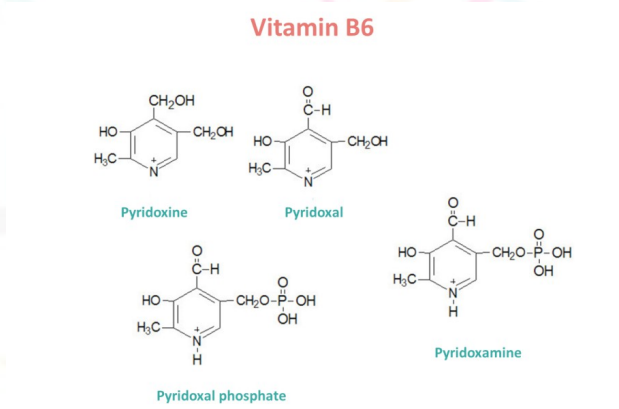
PNPO DEFICIENCY

WHAT IS THE DEFICIENCY OF PYRIDOX(AM)INE 5'-PHOSPHATE OXIDASE (PNPO)?



Pyridox (am) ine 5'-phosphate oxidase (PNPO) deficiency is **an inborn error of vitamin B6 metabolism**, which causes an **epileptic encephalopathy responsive to pyridoxal-5-phosphate (PLP).**

This deficiency is caused by mutations in the ***PNPO* gene** encoding this enzyme.

WHAT IS PYRIDOXAL-5-PHOSPHATE (PLP)?

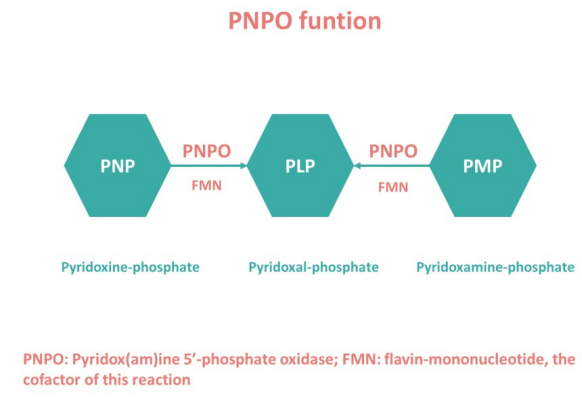
Vitamin B6 is a group of six soluble vitamers: pyridoxine, pyridoxamine and pyridoxal, and their phosphorylated esters: pyridoxine-5'-phosphate, pyridoxamine 5'-phosphate and **pyridoxal 5'-phosphate (PLP).**

Although they all show the same biological activity, **PLP is the physiologically active form of vitamin B6** and the main component of human plasma.

PLP is the cofactor of more than 140 enzymatic reactions in the body, many of them involved in the **synthesis and degradation of amino acids and amines**, which serve as **neurotransmitters or neuromodulators** in the brain.

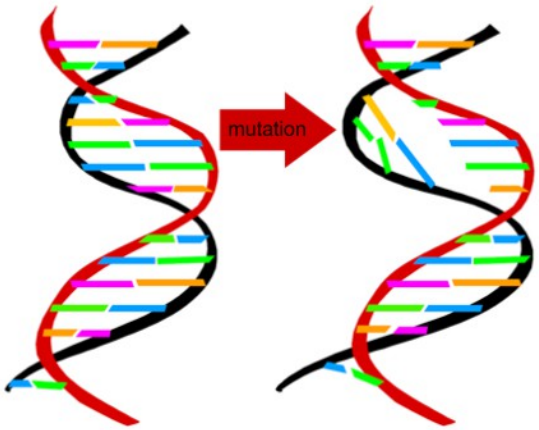
WHAT IS THE ROLE OF THE PNPO ENZYME?

The **PNPO enzyme** is a flavin mononucleotide (FMN) dependent oxidase and acts in the **synthesis of PLP** from phosphorylated esters of pyridoxine and pyridoxamine.



PNPO: Pyridox(am)ine 5'-phosphate oxidase; FMN: flavin-mononucleotide, the cofactor of this reaction

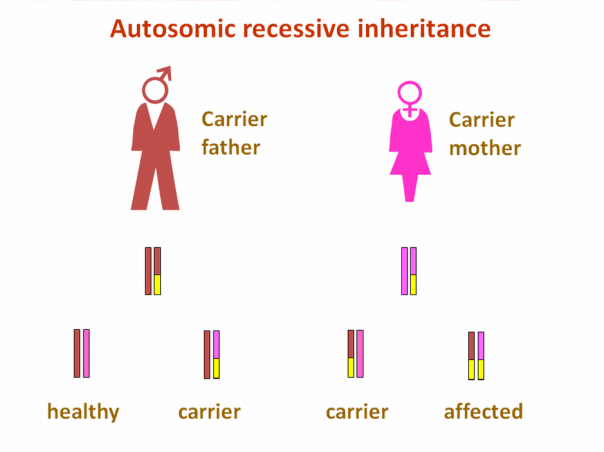
WHY PNPO DEFICIENCY OCCURS?



PNPO deficiency occurs due to **mutations** (stable and heritable changes) in the ***PNPO* gene** encoding this enzyme protein.

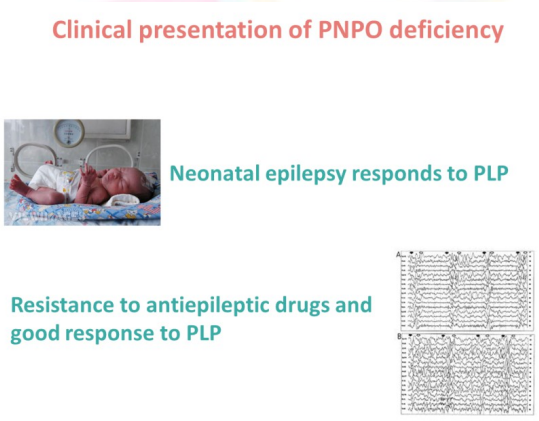
PNPO deficiency is transmitted with an **autosomal recessive inheritance**, i.e., both parents carry a mutation in the ***PNPO* gene**, although they do not suffer from any clinical manifestation due to it.

If both parents pass the child a mutated allele of this gene, he/she will suffer a **PNPO deficiency**.



CLINICAL SYMPTOMS OF PNPO DEFICIENCY

The first patients described showed a **neonatal encephalopathy refractory to drugs and responsive to PLP**. However, a recent study has shown that the clinical spectrum of PNPO deficiency is much broader, particularly as regards the response to PLP.



In some patients with mutations in PNPO, prematurity of birth has been observed, as well as certain neonatal respiratory difficulties, which might require intubation and assisted ventilation. However, many children are born at term and have no disease at birth.

Seizures usually start during the first hours of life, although in a few patients seizures present on the first months of life. Hypotonia and irritability may accompany them. Abnormal movements and signs of intrauterine fetal distress have also been described in some patients.

Some factors that may influence the clinical presentation are the severity of the mutations that allow some residual PNPO activity and the vitamin status (riboflavin as well as pyridoxine) of the newborn, since the PNPO enzyme depends on flavin mononucleotide (FMN), a riboflavin derivative.

Infertility and premature abortions have been described in some families carrying mutations in the gene PNPO.

Resistance to antiepileptic drugs is total in more than a half of the patients and partial in the rest of them, and contrasts with good response to PLP.

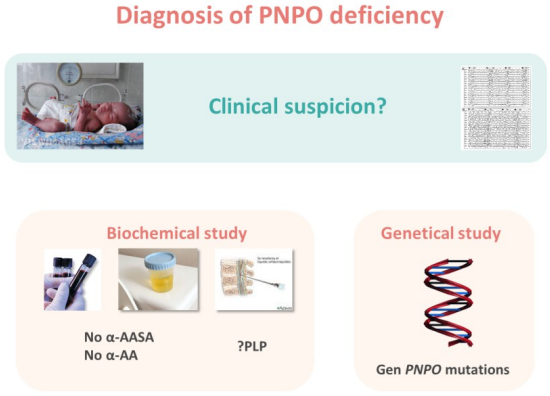
Most patients treated with PLP survive and the spectrum of neurological sequelae is wide from a clear psychomotor retardation to mild disorders such as dyslexia or other learning problems.

DIAGNOSIS OF PNPO DEFICIENCY

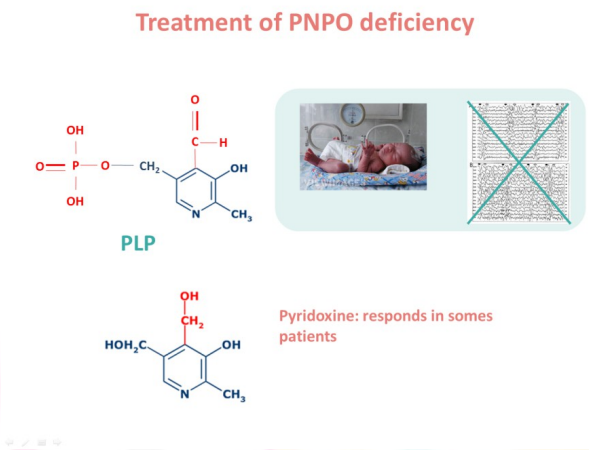
In front of the clinical suspicion and positive response to treatment, the diagnosis is based on **the exclusion of other biochemical markers of neonatal epileptic encephalopathies**, especially antiquitin deficiency (which causes elevation of α-aminoadipic semialdehyde and α-aminoadipic acid in plasma, urine and CSF).

Quantification of PLP in CSF shows decreased values of this vitamin B6 vitamer, but in spite of being very sensitive, this data is not very specific.

The definitive diagnosis is based on **the study of PNPO gene mutations** that allows genetic counseling and prenatal diagnosis if required.



TREATMENT OF PNPO DEFICIENCY



The first patients described only responded to treatment with PLP and not with pyridoxine. However, recent studies identified three groups of patients in relation to their response to treatment:

- Patients with neonatal epilepsy responsive to treatment with PLP
- A patient with infantile spasms beginning at 5 months, responsive to PLP
- Patients with epilepsy who responded to pyridoxine.

The treatment with PLP to pyridoxine therapy can worsen seizure control in some patients. This reaction seems paradoxical, but it may be explained because a high concentration of PLP inhibits PNPO residual enzyme activity.

Elevated levels of PLP can be toxic to the liver, so clinicians should monitor liver function in patients undergoing treatment.

In general, untreated PNPO deficiency has very poor prognosis.

Pyridoxine response in patients with PNPO deficiency is due to the residual enzyme activity of some PNPO mutations, which allows transforming pyridoxine to PLP. However, this pyridoxine responsiveness may also be influenced by other factors such as prematurity, patient age and riboflavin status, since PNPO is flavin mononucleotide dependent enzyme.

PNPO deficiency causes severe epileptic encephalopathy. Early diagnosis and treatment improve the prognosis and quality of life of patients.

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