

Pyridoxine-Dependent Epilepsy: A Treatable Cause of Infantile Epileptic Encephalopathy

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Overview

- 1954 Pyridoxine-dependent epilepsy (PDE) described
- 1995 Folinic acid-responsive seizures (FARS) described
- 2006 Genetic defect in PDE identified
- 2009 PDE and FARS shown to be identical

Overview

- Clinical features: Classic/Variant
- Diagnosis
- Treatment
- Outcome

Pyridoxine-Dependent Epilepsy

- 1954 Hunt et. al report an infant whose treatment refractory seizures began at 3 hours of age
- Seizures stopped with the intramuscular administration of the multivitamin berocca C
- Fractionation of the multivitamin identified pyridoxine as the anti-convulsive agent

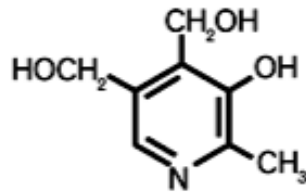
Pyridoxine-Dependent Epilepsy

- The child was dependent on pyridoxine (B6) to remain seizure-free
- She was given 2 mg of B6 orally q day
- Seizures recurred with illness
- At 20 months she could not stand, walk or talk

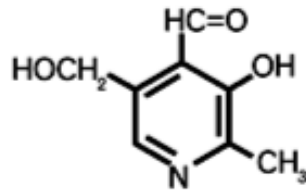
Pyridoxine-Dependent Epilepsy

- Pyridoxine deficiency was reported to cause seizures; in contrast, the author's termed the child's condition "**pyridoxine dependency**"
- *"Whatever the nature of the mechanism, it can best be described as an unusual metabolic aberration of the CNS in which there is a continuing high requirement for pyridoxine in excess of the normal dietary intake in order to maintain this infant in a seizure-free state."*

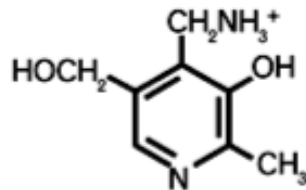
Forms of Pyridoxine - Vitamin B6



Pyridoxine

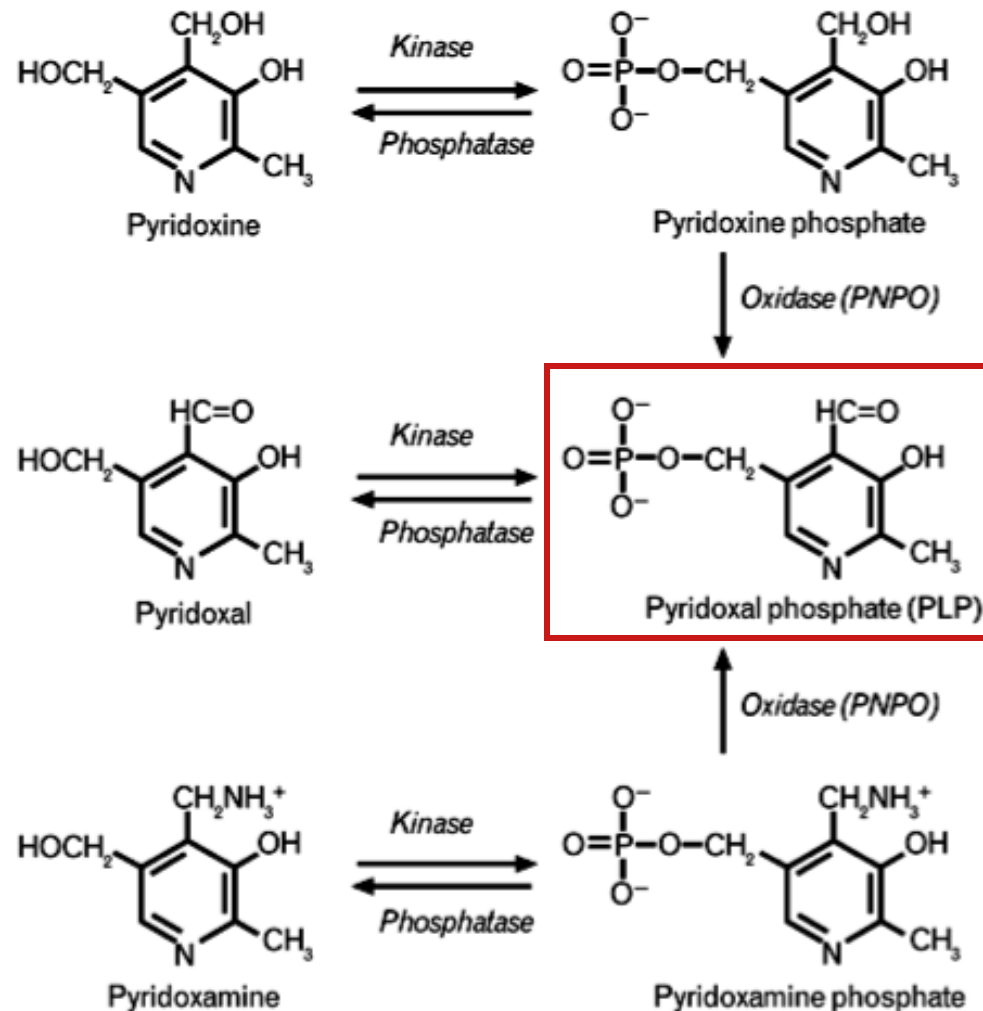


Pyridoxal



Pyridoxamine

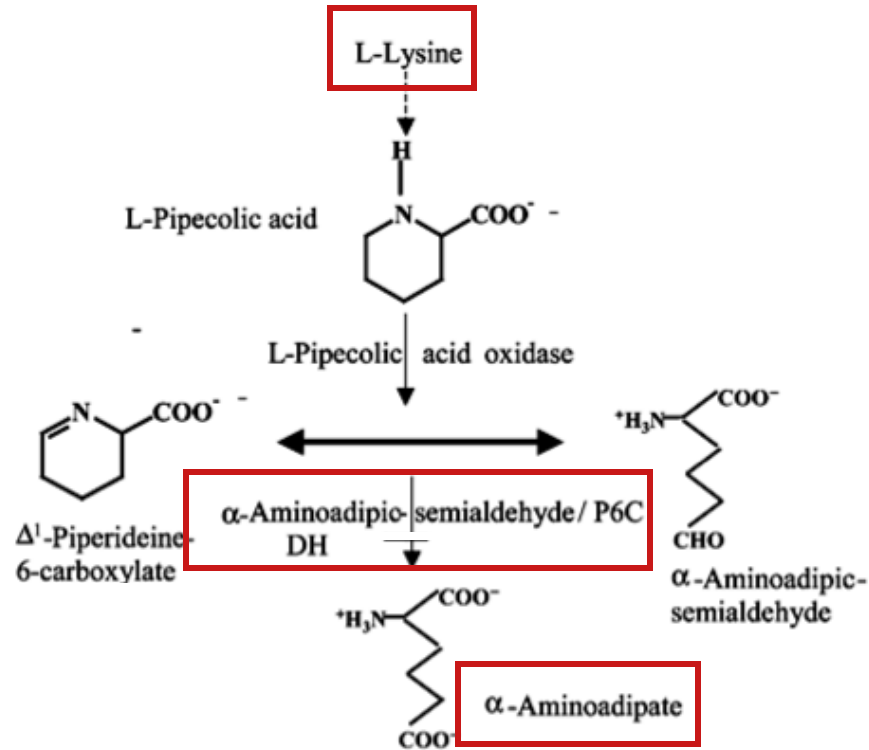
Forms of Pyridoxine - Vitamin B6



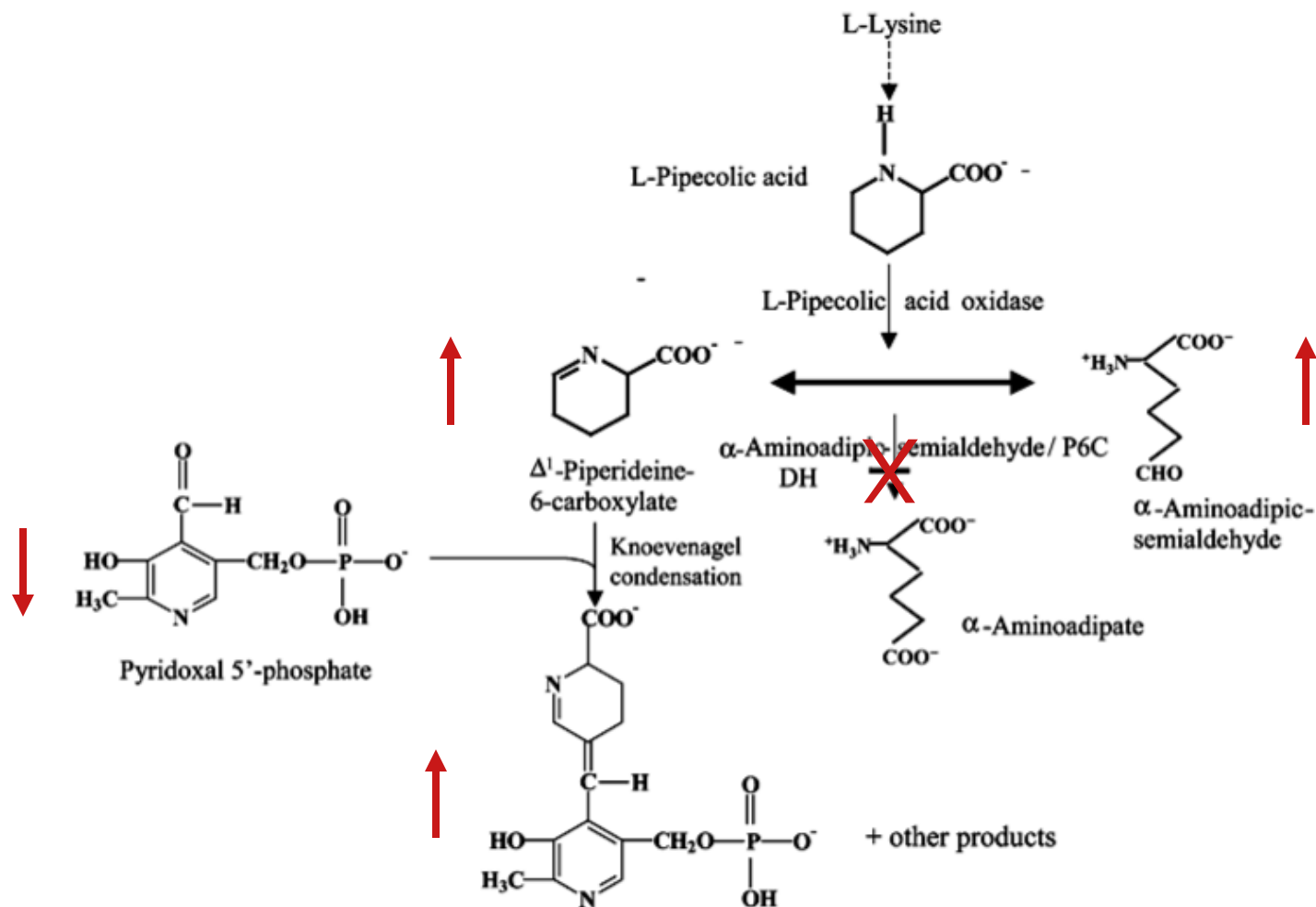
PLP is a Co-Factor in Many Reactions

- Glutamate decarboxylase
- Aromatic amino acid decarboxylase
- Glycine cleavage
- Serine racemase
- GABA transaminase
- Kynureninase

Proposed Pathogenic Mechanism: Pyridoxal 5'-Phosphate Sequestration



Proposed Pathogenic Mechanism: Pyridoxal 5'-Phosphate Sequestration



Antiquitin Deficiency in PDE

- Mutations in the *ALDH7A1* gene encoding antiquitin were found in PDE
- Testing for PDE became possible both through both biochemical and DNA sequencing techniques

Folinic Acid-Responsive Seizures

- Three individuals with early-onset seizures were found to have a novel marker in CSF
- Two of three had seizure cessation or amelioration with folinic acid therapy

Folinic Acid-Responsive Seizures

- CSF testing for the marker, and empiric trial of folinic acid was recommended
- Despite therapy with folinic acid the outcome was fatal in multiple cases
- The relationship with folate metabolism remained unclear

FARS and PDE are Identical

- Two children with early-onset seizures had the CSF marker of FARS, but were responsive to B6 - the hallmark of PDE
- α -AASA was elevated in CSF
- DNA sequencing of *ALDH7A1* identified two mutations in each child

FARS and PDE are Identical

- Retrospective evaluation of patients with the CSF biochemical marker of FARS identified elevated α -AASA and mutations in *ALDH7A1*
- Patients with PDE had the marker of FARs
- The same *ALDH7A1* mutations were found in both disorders

FARS and PDE are Identical

Table 2. Concentrations of α -Aminoadipic Semialdehyde and Pimecolic Acid in Cerebrospinal Fluid Samples from Patients Previously Classified with Folinic Acid-Responsive Seizures, and Mutations Detected in the *ALDH7A1* (*Antiquitin*) Gene

Subjects	α -AASA ($\mu\text{mol/L}$)	Pimecolic Acid ($\mu\text{mol/L}$)	Mutations	Deduced Effect
Patient 1 ^a	14.0	9.5	c.248G>A ^b /c.1208C>T	p.Gly83Glu ^b /p.Pro403Leu
Patient 2 ^a	8.2	3.0	c.750G>A ^c /c.1195G>C	r.748_787del ^c /p.Glu399Gln
Anonymous 1	11.7	6.9	c.1208C>T/c.1208C>T	p.Pro403Leu/p.Pro403Leu
Anonymous 2	12.6	4.8	c.890C>G ^b /c.1405+5G>A ^c	p.Thr297Arg ^b /splice error ^c
Anonymous 3	5.5	1.4	c.1195G>C/c.1195G>C	p.Glu399Gln/p.Glu399Gln
Anonymous 4	4.1	1.4	c.248G>A ^b /c.410G>T ^b	p.Gly83Glu ^b /p.Gly137Val ^b
Anonymous 5	4.9	5.2	c.107delA ^b /c.1274A>G ^b	p.Glu36GlyfsX14 ^b / p.Gln425Arg ^b
Anonymous 6	2.3	2.1	c.1263T>A ^{b/d}	p.Asn421Lys ^{b/d}
Anonymous 7	1.9	1.3	c.419_422delTCTT ^b / c.1197G>T ^b	p.Ile140SerfsX10 ^b / p.Glu399Asp ^b
Control subjects	<0.1	<0.12		

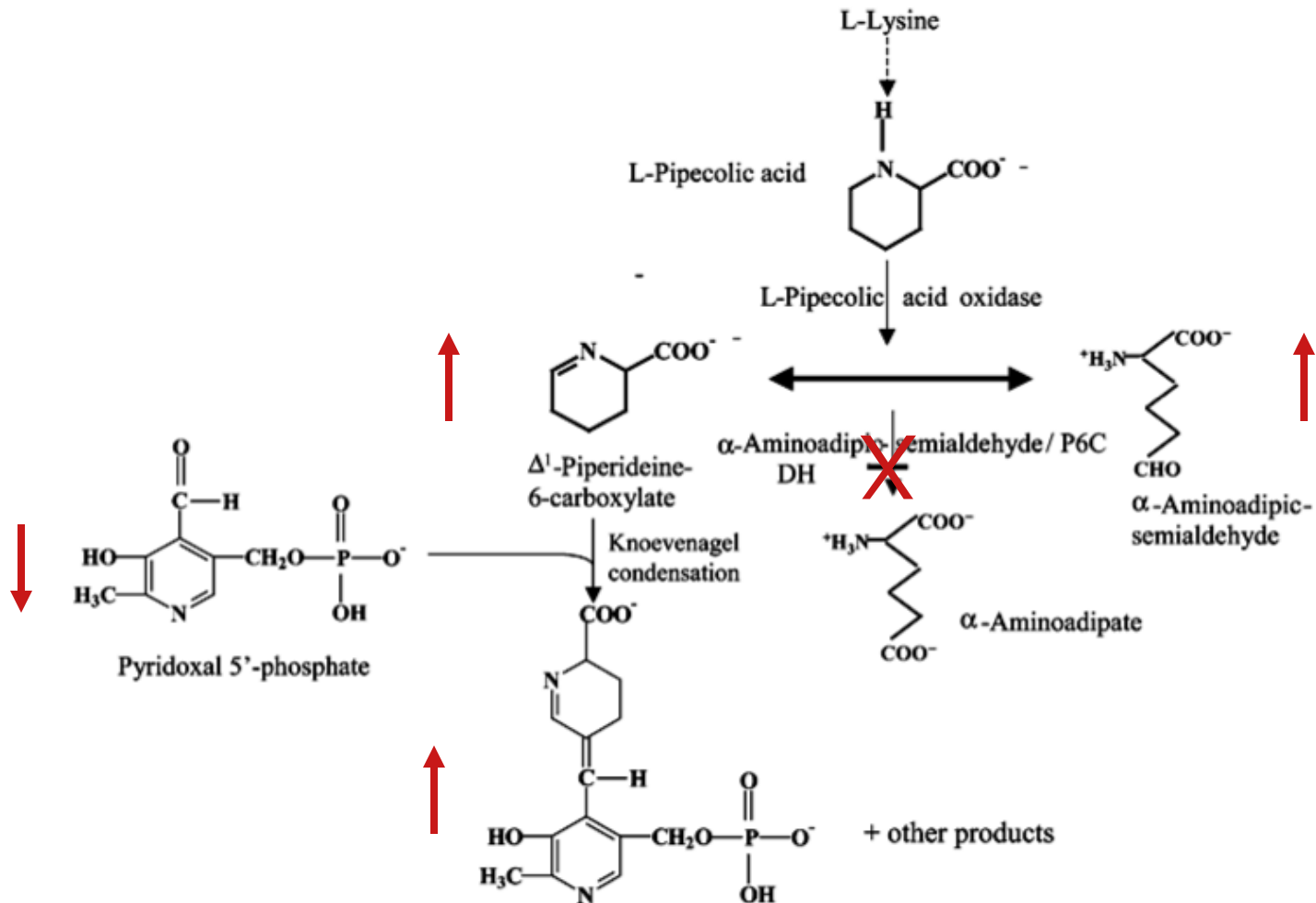
They are biochemically and genetically identical

Gallagher RC, Van Hove JKL, Scharer G, et al. Ann. Neurol. 2009, 65:5:550-556

FARS and PDE are Identical

- This suggests that empiric trial of both folinic acid and B6 should be performed
- This indicates the importance of B6 therapy in FARS
- Lysine restriction may be indicated

Pathogenic Mechanism: Pyridoxal 5'-Phosphate Sequestration



Clinical Features of PDE

- Classic
 - Seizure onset hours to days after birth
 - Treatment refractory
 - Burst suppression pattern on EEG
 - Resolution of seizures with B6 - IV or oral
 - Remains seizure-free after withdrawal of anti-epileptics
 - Recurrence of seizures with withdrawal of B6

Clinical Features of PDE

- Variant
 - Late-onset, up to 3 years of age
 - Initial response to AEDs, in some
 - Seizure-free without B6 therapy, in some
 - Absence of initial response to B6, in some

Seizure Types

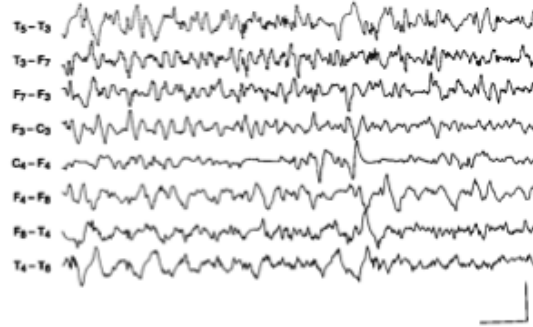
- Status
- Brief - generalized or partial
- Atonic
- Myoclonic
- Infantile spasms

EEG Findings

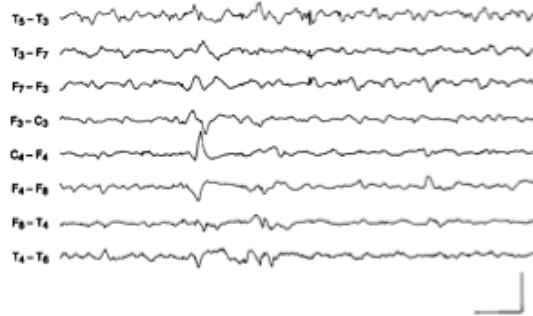
- Diffuse slow-wave activity, intermingled spike and polyspike foci
- Burst suppression - severe
- Normalization with pyridoxine therapy

EEG Findings

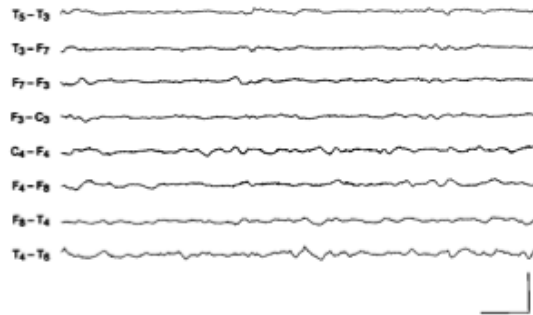
Clinical Seizure



5 minutes post-B6



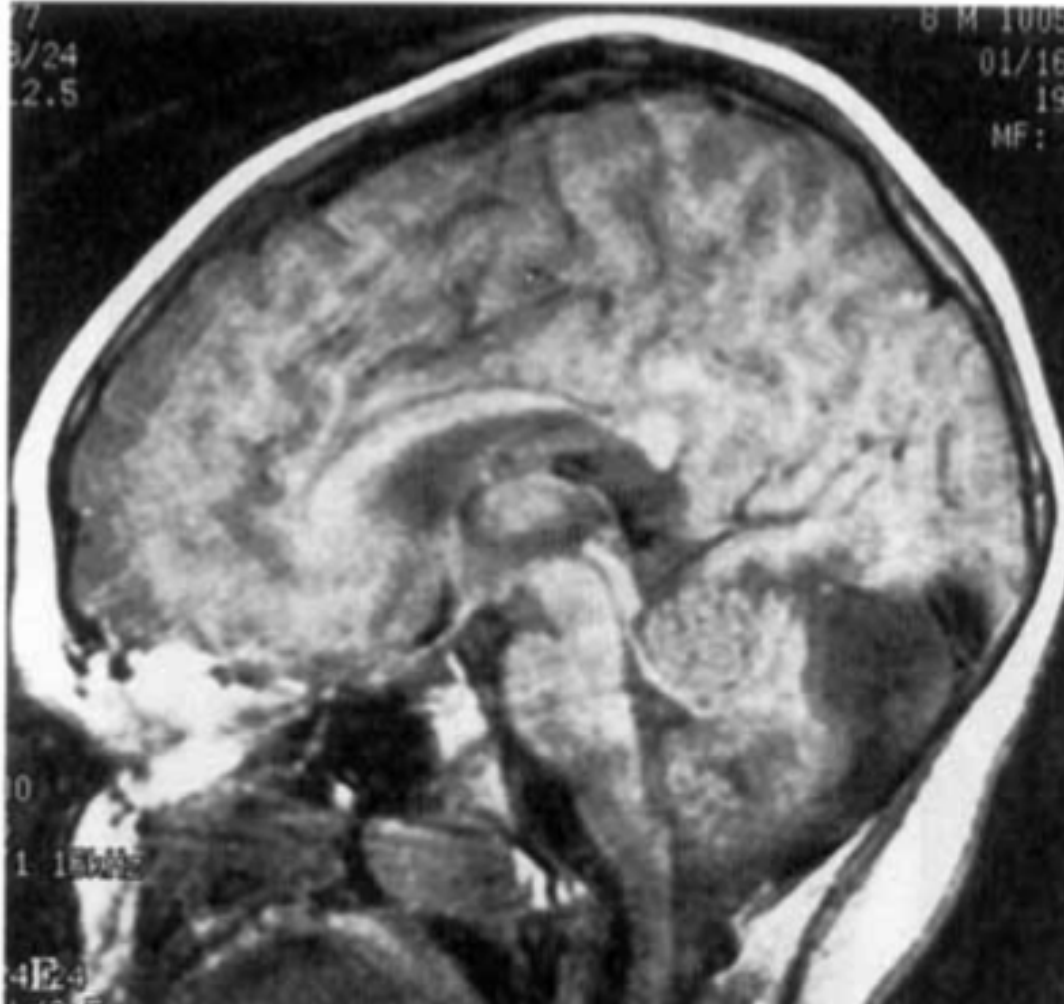
10 minutes post-B6



MRI Findings

- Mega cisterna magna
- Thin posterior corpus callosum
- Cerebellar hypoplasia
- Hemorrhage
- White matter abnormalities

MRI Findings



Gospe SM, Hecht ST. Neurology 1998, 51:74-78

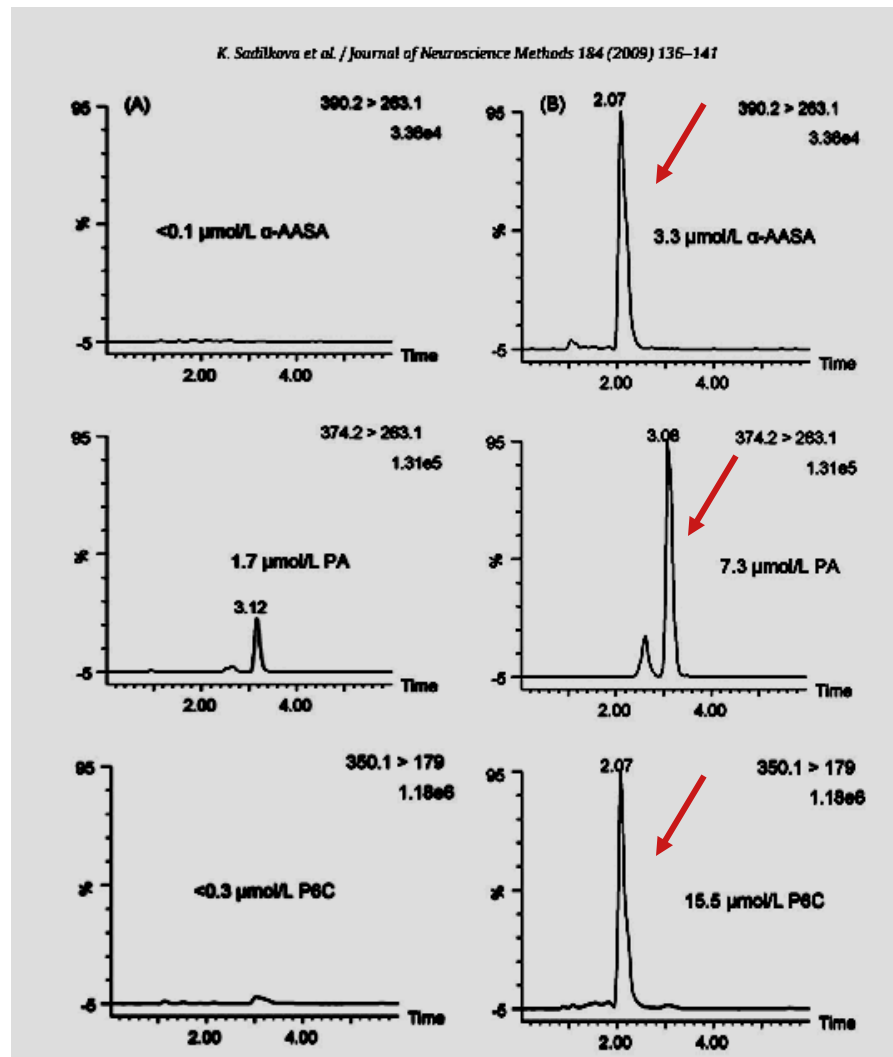
Diagnosis

- Plasma pipercolic acid (surrogate marker)
- CSF neurotransmitter studies (“FARS” marker)
- Urine, plasma or CSF α -AASA
- DNA sequencing for mutations in the *ALDH7A1* gene encoding the antiquitin dehydrogenase

α -AASA in Serum

Control

Affected



α -AASA

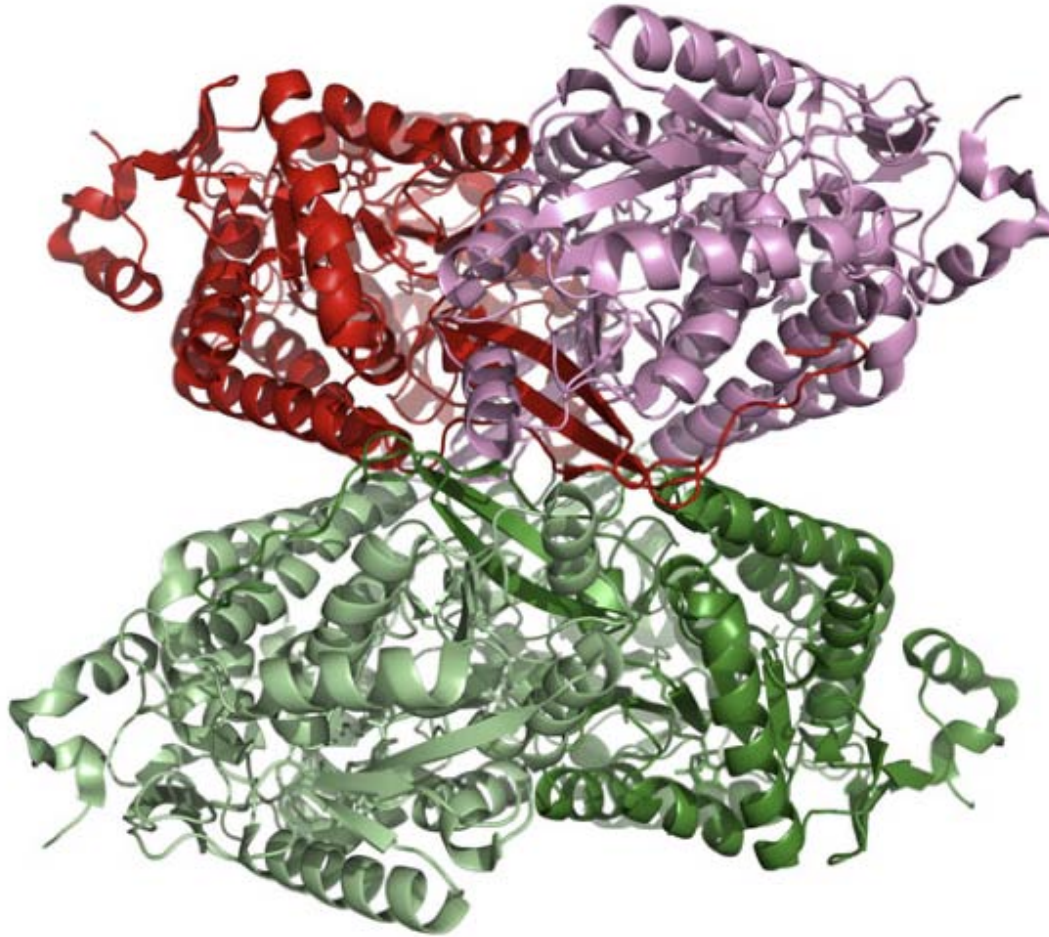
Pipecolic Acid

P6C



Antiquitin

Black Seabream

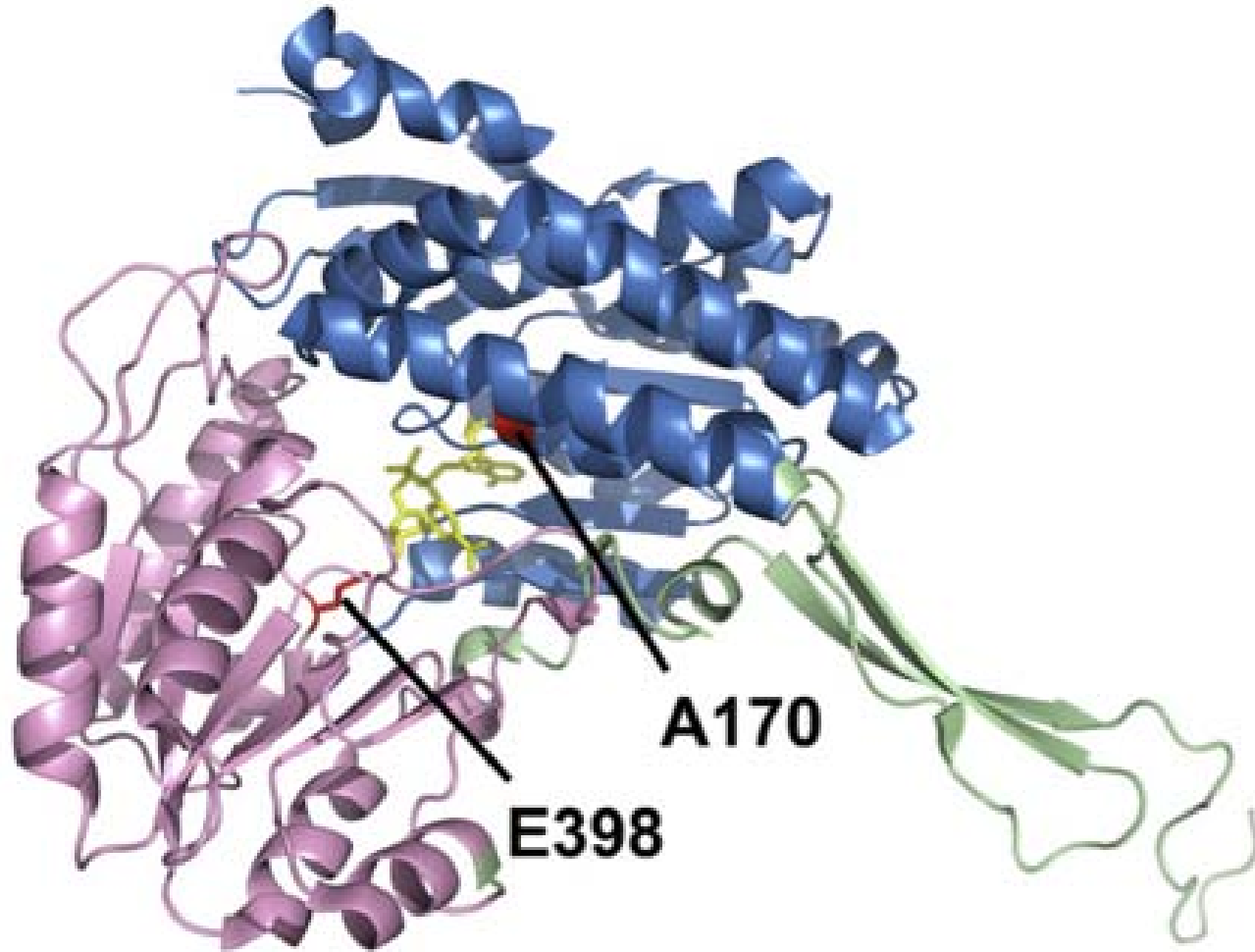


Tang WK, Wong KB, Lam YM. FEBS Letters 2008, 582: 3090-3096



Antiquitin

Black Seabream

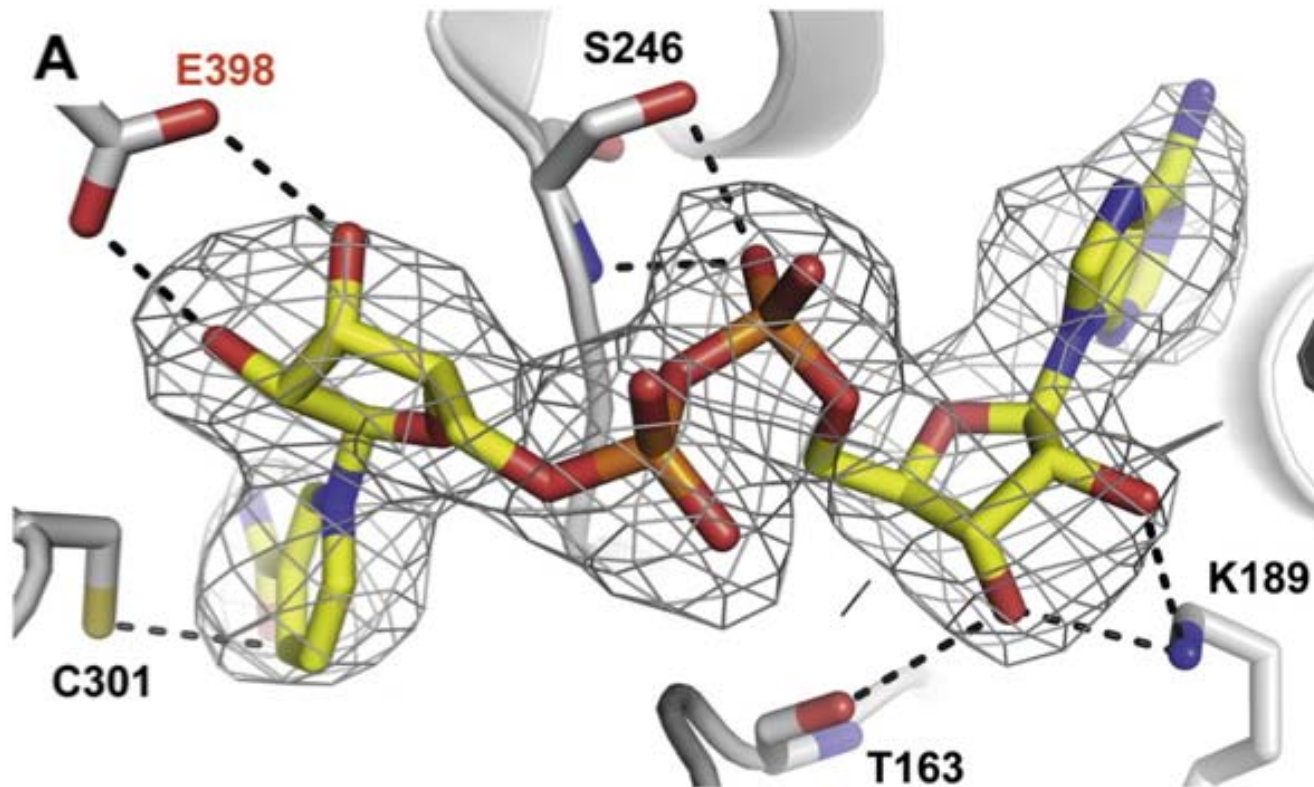


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Antiquitin

Black Seabream



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Treatment

- Pyridoxine 15-30 mg/kg/day
- AEDs as indicated
- Consider
 - Folinic acid 2-5 mg/kg/day
 - Lysine restricted diet with monitoring of α -AASA levels

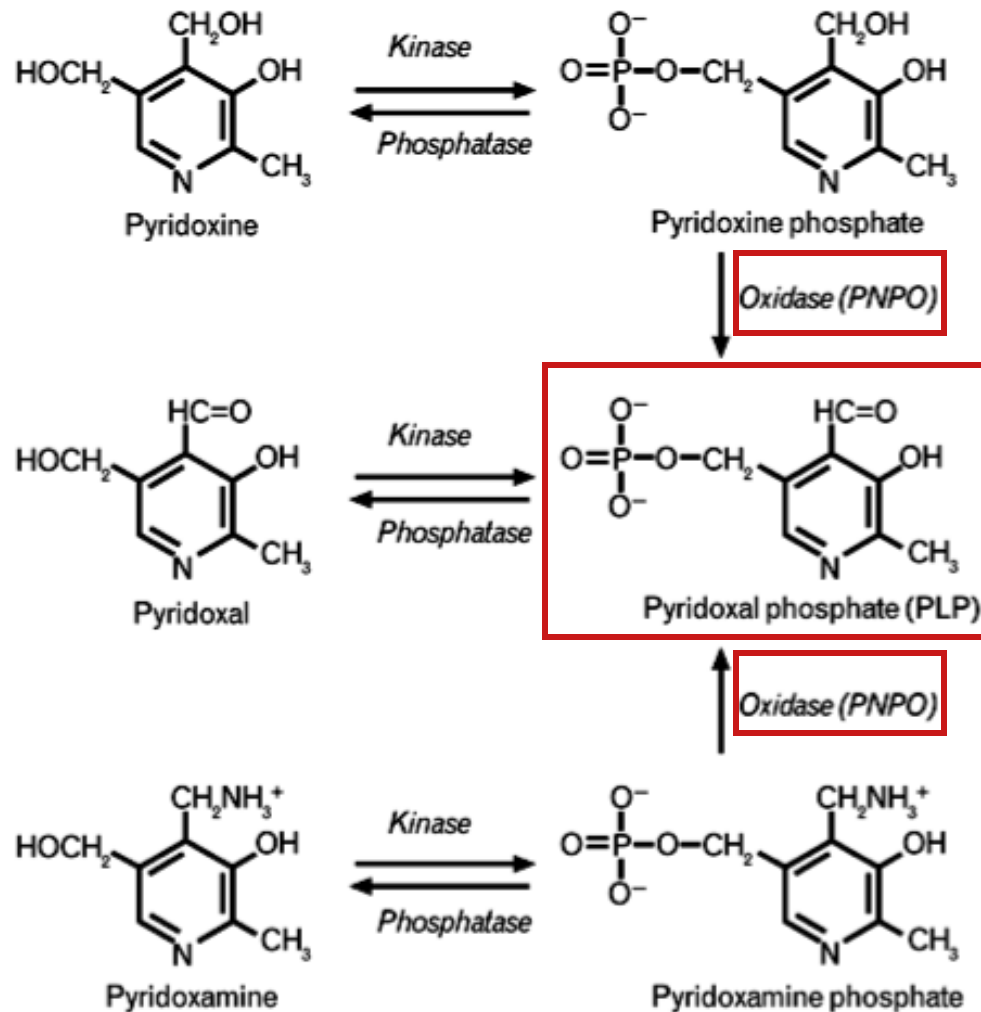
Developmental Outcome

- Only four of 24 individuals meeting classic diagnostic criteria had normal development
- They required special education, and therapies - physical, occupational, speech

PNPO Deficiency

- Several children had seizures responsive not to pyridoxine, but to pyridoxal 5'-phosphate
- This suggested a defect in pyridox(am)ine 5'-phosphate oxidase (PNPO)

Forms of Pyridoxine - Vitamin B6



Summary

- Pyridoxine dependency is a cause of IEE as well as later-onset seizures of diverse types
- The understanding of the biochemical pathway involved and the pathogenic mechanism now allows both for accurate diagnosis and for additional approaches to therapy and monitoring
 - limitation of lysine, following metabolites
- The response of some to folinic acid is not understood, this may be of benefit to some

Summary

- Even with early therapy developmental delay is common
- Clinical trials would benefit our understanding of this disorder
- PDE may be fatal without pyridoxine therapy
 - Evaluation for pyridoxine-dependent epilepsy in an infant or older child with seizures through urine, serum or CSF α -AASA is critical