Unusual Case of Phenylketonuria With Atypical Brain Magnetic Resonance Imaging Findings

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Abstract
Phenylketonuria is a treatable inborn error of amino acid metabolism caused by deficiency of the enzyme phenylalanine hydroxylase, responsible for converting phenylalanine to tyrosine. We report a 10-month-old boy with psychomotor regression and infantile spasms. He was diagnosed with classic phenylketonuria and West syndrome. Treatment was initiated with phenylalanine-restricted diet and vigabatrin. After 5 months of treatment, he persists with developmental delay, severe hypotonia, swallowing disorder, and drug-resistant epilepsy. Brain magnetic resonance imaging showed the typical abnormalities in supratentorial white matter and exceptional infratentorial and basal ganglia compromise. Severity of white matter abnormalities and neurologic symptoms correlates with blood levels of phenylalanine. Infratentorial changes occur in severe cases. Other mechanisms could take part in cases like this with atypical neuroimaging abnormalities of the basal ganglia.

Keywords
phenylketonuria, West syndrome, epilepsy

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Phenylketonuria is an inborn error of amino acid metabolism caused by the deficiency of the hepatic enzyme phenylalanine hydroxylase, responsible for converting phenylalanine to tyrosine.1,2 Phenylalanine hydroxylase gene (PAH) is located on the chromosome 12q23.2,3 and more than 500 different mutations have been described.2 For its normal function, it requires the cofactor tetrahydrobiopterin, molecular oxygen and iron.2 Loss of phenylalanine hydroxylase function results in increased concentrations of blood phenylalanine with resultant neurotoxicity when left untreated. Depending on the residual enzyme activity, the hyperphenylalaninemia and thus phenotype of the patient is different. Normal phenylalanine concentration is between 50 and 110 μmol/L. Phenylketonuria is classified by hyperphenylalaninemia severity into classic phenylketonuria (>1200 mmol/L), mild phenylketonuria (600-1200 mmol/L), and moderate hyperphenylalaninemia (120-600 μmol/L).4 Phenylketonuria prevalence varies from 1/70 000 live births in Japan to 1/4000 in Turkey.2 From a clinical point of view, phenylketonuria patients develop intellectual impairment, microcephaly, epilepsy, autism, motor deficits, developmental problems, conduct disorders, and psychiatric symptoms.2,3 Treatment consists of phenylalanine-restricted diet using special formulas free of this amino acid and enriched with tyrosine.1,3 Early onset of treatment can prevent permanent brain damage1 and neuropsychological complications.2 To achieve this, the condition should be diagnosed during the first weeks of life in asymptomatic newborns.1 Guthrie and Susi6 developed the newborn screening for phenylketonuria in 1963.

West syndrome is an intractable epileptic syndrome that is age dependent. The association between West syndrome and phenylketonuria is well known. As a consequence of the wide implementation of newborn screening for phenylketonuria, this association has decreased.

In phenylketonuric patients, magnetic resonance imaging (MRI) typically shows abnormal signal in periventricular and deep cerebral white matter, and in rare cases, abnormalities...
in corpus callosum, brainstem, and cerebellum. To our knowledge, there are no descriptions in the literature of basal ganglia compromise in classic phenylketonuria.

We present a case of classic phenylketonuria with severe clinical presentation, atypical images on brain MRI, and poor outcome.

**Case Report**

We describe a 10-month-old boy with unremarkable family, pregnancy, and delivery history. His parents are not consanguineous. Newborn screening for hyperphenylalaninemia was reported as normal (<150 μmol/L). In the neonatal period, he was diagnosed with ventricular septal defect and patent ductus arteriosus. His psychomotor development appeared normal during the first months of life. At the age of 8 months, he developed psychomotor regression, with loss of head control, eye tracking, social smile, and grabbing objects. He was eventually diagnosed with infantile spasms. On admission he was irritable, had axial hypotonia, occipitofrontal circumference of 45.5 cm (50th percentile), his limb muscle tone and strength were normal, and had normal tendon reflexes. Funduscopic examination was normal. No abnormalities were found on serum acid-base balance, electrolytes, glucose, ketonemia, ketonuria, and renal function. Cerebrospinal fluid assay was normal, including lactic acid; neurotransmitters were not analyzed. An electroencephalogram was performed, showing hypsarrhythmia. Brain MRI showed bilateral and symmetric abnormal signal, hypointense in T1 and hyperintense in T2 and fluid-attenuated inversion recovery with restriction in diffusion-weighted imaging, on periventricular and deep cerebral white matter, globus pallidus (A), and cerebellum and brainstem (Figures 1 and 2). Flash visual evoked potentials were abnormal bilaterally with increased latencies.

Blood phenylalanine concentration was 1260 μmol/L. Neonatal screening was reviewed and showed that phenylalanine had been high on neonatal screen. Tetrahydrobiopterin cofactor metabolism was assessed on dried blood spot and tetrahydrobiopterin deficiency was excluded. Biopterin was 0.69 nmol/g Hb (reference 0.15-1.68) and neopterin 0.53 nmol/g Hb (reference 0.35-4.62). Dihydropteridine reductase function was 1.3 mU/mg Hb (reference 1.8-3.8).

He was diagnosed with classic phenylketonuria and West syndrome. Treatment was initiated with phenylalanine-restricted diet and vigabatrin. Infantile spasms and tonic, clonic, and myoclonic multifocal seizures continue despite different antiepileptic drug schedules. He has received combinations of several drugs including vigabatrin, adrenocorticotropic hormone, phenobarbital, valproic acid, benzodiazepines and prednisolone. After 5 months of evolution he persists with developmental delay, severe hypotonia and swallowing disorder. The last electroencephalogram shows background slowing and multifocal spikes. After starting treatment, blood phenylalanine concentration remained below 360 μmol/L (average 174 μmol/L).

The mother’s blood phenylalanine is in normal range. The patient was not screened for other genetic or metabolic conditions such as ARX, MECP2, CDKL5 or mitochondrial diseases.

**Discussion**

We present a boy with phenylketonuria, West syndrome, and atypical brain MRI findings. About 1% to 2% of all hyperphenylalaninemia cases are due to mutations in enzymes involved in tetrahydrobiopterin biosynthesis and regeneration. In our case, tetrahydrobiopterin metabolism deficiency was excluded.
Dihydropteridine reductase function is slightly lowered, but it is not suggestive for a defect in the regeneration of tetrahydrobiopterin.

Regarding brain MRI, the particularity of this case is the severity and topography of the lesions, with basal ganglia, cerebellum, and brainstem involvement. In treated and untreated phenylketonuric patients, usually MRI shows abnormal signals on periventricular and deep cerebral white matter, hyperintense in T2 and in diffusion-weighted imaging and slightly hypointense in T1 located in occipital, parietal, frontal and temporal lobes, exceptionally in brainstem and cerebellum.3,7 Diffusion-weighted imaging is more sensitive than T2 for evaluation of white matter abnormalities.7 It is known that severity of white matter abnormalities and neurologic symptoms correlates with blood levels of phenylalanine8-10 and they usually improve when phenylalanine concentration is reduced in a period no less than 2 months.11 In untreated patients, white matter is impaired with hypomyelination and gliosis, probably because of toxicity of hyperphenylalaninemia on oligodendroglia.8 Hypomyelination occurs in areas of postnatal myelination such as optic tract, corpus callosum, and subcortical and periventricular white matter, whereas areas of prenatal myelination such as brainstem and internal capsule are resistant to the toxic effect of hyperphenylalaninemia.8 Even in patients diagnosed with phenylketonuria early in life and treated immediately, white matter pathology appears.8 In our case, abnormalities were found at cerebellum, brainstem, and basal ganglia in addition to the typical white matter lesions. In infants, infratentorial abnormalities have been rarely described.10 They are associated with severity of supratentorial abnormalities and higher concentrations of phenylalanine, occurring in severe cases.3 Good metabolic control from the newborn period has been described as the most important predictor of MRI grade.3 It has been reported that children with mesencephalic abnormalities have moderate to severe intellectual impairment.10 It is also known that patients with West syndrome have more severe white matter abnormalities10 as in our case. In this infant, the MRI also showed basal ganglia abnormalities that, to our knowledge, has not been described in children with classic phenylketonuria.

Good outcome in phenylketonuria depends on long-term metabolic control of hyperphenylalaninemia.2-3 Our patient had a poor outcome, even though phenylalanine concentration remains under target concentrations: 360 μmol/L.2 We think that there is more than 1 reason for this outcome: the late diagnosis, the fact that he developed West syndrome, and the difficulty in controlling epilepsy.

With respect to epilepsy, up to 12.3% of phenylketonuria patients develop West syndrome,10 which is more frequent than in the general pediatric population (1:5000).12 More often infantile spasms are observed before phenylketonuria diagnosis.10 It has been reported that when treatment is started in the first 3 months of age no patient developed West syndrome, whereas 10.9% suffered it when treatment was initiated between 4 and 12 months of age.10 Early phenylketonuria diagnosis and treatment prevents West syndrome, and when they develop it, once treatment is initiated, most patients stop having seizures.10

Newborn screening for hyperphenylalaninemia was started in Uruguay in 2007 using tandem-mass spectrometry, with newborn coverage of 99.5%. Normal values are considered 150 μmol/L or less (cut-off level). The incidence of phenylketonuria in Uruguay is 1/11 595 live births.13 In the present case, the screening was misinterpreted as normal. Although newborn screening can have false-positive results, false-negative cases have also been described.15 Possible causes for false-negative results are neglect requisites for taking blood samples and laboratory errors.15 To avoid this, criteria for conducting the screening must be followed strictly.
In summary, we present the case of an infant with classic phenylketonuria diagnosed at 10 months of age when he developed West syndrome, with atypical MRI findings and poor outcome despite maintaining adequate blood phenylalanine levels. The understanding of the genetic basis and pathophysiology of phenylketonuria have increased substantially in recent years, but there might be specific unknown mechanisms for hyperphenylalaninemia induced damage to the brain responsible for the atypical neuroimaging findings that we observed in our case. Phenylketonuria is an active area of research, and cases like this highlight the importance of investigations trying to link clinical and biochemical phenotype and neuroimaging findings with yet possible unidentified pathophysiology mechanisms and genetic data.

Author Contributions
CM, GG, CV, VP, AC, and AL worked up the case. CM, GG, CV, and VP participated in writing the first draft of the manuscript. CM, GG, AC, AL, and NB participated in the review and critique of the manuscript. NB helped in the exclusion of tetrahydrobiopterin deficiency by assessing tetrahydrobiopterin cofactor metabolism. All authors have contributed to, read, and agreed to the content of the manuscript.

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Ethical Approval
The study was not reviewed by any ethics committee. It is a clinical case and it doesn’t have any data that can identify the patient; patient’s photos, name, and patient’s name in the MRI was erased.

References