Sight-Threatening Phenylketonuric Encephalopathy in a Young Adult, Reversed by Diet

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Abstract Phenylketonuria (PKU) leads to severe neurological disorders in childhood, shunned by the diet. The long-term prognosis after diet diversification at adolescence is uncertain. We report a case of cortical blindness in a young patient regressive 1 month after the diet was resumed.

Mr M., 25 years old, had PKU detected at birth. He maintained good serum levels of Phenylalanine (Phe) (120–300 $\mu\text{mol/L}$) during childhood and got a normal intellectual development. During adolescence he diversified his diet but maintained low meat and fish intake; Phe was $\sim 1,200 \mu\text{mol/L}$ with no symptoms. In 2009, the patient stopped the low-Phe amino acid substitutes due to weariness. On June 27, 2011, he consulted for a decrease of visual acuity

progressing for 6 months. Ophthalmologic examination found that visual acuity was 2/10 in two eyes associated to a central visual field defect. The visual evoked potentials were altered. MRI showed bilateral and symmetric occipital FLAIR hyperintensities. On admission in the Nutritional Unit on June 29, 2011, blood pressure was 120/70 mmHg, there was no other neurological abnormality. Phe was at 1,512 $\mu\text{mol/L}$, and not responsive to BH4. He was then treated with a very low-Phe diet with an amino acid substitute, and he obtained Phe between 120 and 300 $\mu\text{mol/L}$. Visual acuity was suddenly restored on August 1, 2011, with a dramatic attenuation of the MRI hyperintensities.

Our observation shows that the withdrawal of the diet and substitutes exposes to serious neurological complications in adults that may reverse with a fast nutritional support.

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A 25-year-old man was referred to the ophthalmic department in June 2011 for a progressive painless bilateral visual loss of few months' duration. After correction, visual acuity was 20/200 in both eyes. Slit lamp and fundus examinations were normal, no optic nerve atrophy was observed. The visual field examination showed a large bilateral central scotoma and pattern reversal visual evoked potentials were flat in the different spatial frequencies. The diagnosis of cortical blindness was evoked, confirmed by Cerebral Magnetic Resonance Imaging which disclosed symmetric high signal intensity on T2-weighted images in the periventricular white matter and cortico-subcortical occipital lobes (Fig. 1a).

As his only past medical history was phenylketonuria (PKU), the patient was quickly transferred to the nutrition department on June 29, 2011. PKU had been diagnosed at birth, immediately treated by diet, and phenylalanine levels

Fig. 1 MRI T2 weighted images (a) MRI on admission. High signal intensity of white matter in occipital lobes and periventricular areas. (b) MRI after 5 weeks of optimal diet. Signals were decreased

(Phe) were within target levels (120–300 $\mu\text{mol/L}$) during childhood. During adolescence dietary compliance was less good, although he still consumed Phe-free substitutes. Phe levels increased to $\sim 1,200$ $\mu\text{mol/L}$ with no appearance of symptoms. He stopped the Phe-free substitutes during the summer of 2009.

On admission, Phe was 1,512 $\mu\text{mol/L}$. He was then treated with a low-Phe diet (300 mg/day) and amino acid substitutes; Phe were monitored daily by Guthrie tests. After 1 week, Phe reached a plateau at 400 $\mu\text{mol/L}$ and the patient reported a slight visual improvement. The diet was strengthened (Phe 240 mg/day), the target Phe level (<300 $\mu\text{mol/L}$) was obtained on July 25, 2011, and the patient was discharged. A few days later, on waking he realized his sight had returned.

On August 01, 2011, the visual acuity was 20/20 in both eyes. Visual field examination showed normalization in his right eye, with a persistent central scotoma in his left eye.

Pattern reversal visual evoked potentials improved as P-100 reappeared in large size patterns. On MRI examination, the white matter abnormalities in the occipital lobes were drastically reduced (Fig. 1b).

We report the first case of a young patient who lost vision after withdrawing from the low-Phe diet, and regained it by change in diet. Screening by Guthrie test and a prompt phenylalanine-free diet can prevent the dramatic neurological consequences of PKU in childhood (Blau et al. 2010 Oct 23). In many cases, the patients stop adherence to a strict diet during adolescence, and do well. However, in adults, poorly controlled PKU can be complicated by seizures or cognitive defects and white matter injury (Thompson et al. 1990 Sep 8). Two cases of cortical blindness have been reported. The first patient also had spastic tetraplegia and seizures; he died during follow-up (Korneguth et al. 1992 Nov 1). The second also had impaired gait and spasticity (Ishimaru et al. 1993). None of

these symptoms reversed as in our patient. The main mechanism of the neurological deterioration in untreated PKU in childhood is the reduction in cerebral protein synthesis, particularly myelin protein, due to low transport of Large Neutral Amino Acids (LNAA), as Phe has the most affinity for LNAA type 1 Transporter (LAT-1). High Phe level is also responsible of an impaired cholesterol synthesis (one of the primary constituents of myelin lipid) by activity reduction of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-controlling enzyme of cholesterol synthesis. The disease causes a neurotransmitter reduction (dopamine and catecholamines by competition between brain Phe and Tyrosine for hydroxylation by tyrosine hydroxylase and serotonin by unclear mechanisms). In adults treated during childhood like our patient, mechanism of white matter pathology is principally a cytotoxic edema partially due to a worse activity of Na-K ATPase in PKU. (Anderson and Leuzzi 2010) Consequence of this is the swelling of myelin sheaths. This would affect relaxation times and restrict diffusivity on MRI (Vermathen et al. 2007).

These mechanisms are potentially reversible with Phe restriction (de Groot et al. 2010) which we instigated

promptly in our case. Our patient's history argues for maintenance of a strict diet to control PKU in adults.

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