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Original article

Progressive neuropsychiatric manifestations of phenylketonuria in adulthood

Phénylcétonurie progressant à l'âge adulte : manifestations neurologiques et modalités évolutives

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ABSTRACT

Introduction. – Neuropsychiatric signs and MRI abnormalities can occur in patients with phenylketonuria in adulthood. We describe clinical and radiological features of phenylketonuric patients and we discuss the advantage of continuing diet in adulthood.
Method. – We report late onset neuropsychiatric symptoms of four phenylketonuric patients (33–45 years) diagnosed in infancy and report the case of a patient (33 years) diagnosed with phenylketonuria because of late onset neurological signs. We describe clinical and radiological features of these 5 patients, and their evolution under diet and propose a review of the literature.
Results. – The main neurological abnormalities in phenylketonuric patients diagnosed in infancy are: brisk reflexes, spastic paraparesis, psychiatric signs that appear 10.5 years after the diet arrest. A leukoencephalopathy was present in 93% of cases and 91.7% improve clinically after poor phenylalanine diet reintroduction. In 4 patients, neurological abnormalities (spastic paraparesis, dementia, Parkinsonism) led to the late diagnosis. Two of them had a leukoencephalopathy on brain MRI. Patients had high levels of phenylalanine (above 1500 μmol/L) when neuropsychiatric signs occurred. Improvement after diet suggests that hyperphenylalaninemia has a direct toxic effect on the brain.
Discussion/Conclusion. – The long-term follow-up of phenylketonuric patients is mandatory to depict and treat neurological complications in time. Diet reintroduction is efficacious in most cases.

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RÉSUMÉ

Introduction. – La phénylcétonurie peut entraîner à l'âge adulte des troubles neuropsychiatriques et des anomalies à l'IRM cérébrale. Nous décrivons l'évolution des manifestations cliniques et IRM de patients phénylcétonuriques.

Méthode. – Étude de cas et revue de la littérature. Nous rapportons les manifestations neuropsychiatriques tardives de 5 patients phénylcétonuriques et nous présentons une revue de la littérature.

Résultats. – Les symptômes neurologiques chez les phénylcétonuriques connus apparaissent en moyenne 10,5 ans après la suspension du régime. Une leucoencéphalopathie est présente dans 93 % des cas. Lors de l'apparition des troubles, les patients ont une hyperphénylalaninémie élevée. Après reprise du régime, une amélioration clinique est constatée dans 91,7 % des cas suggérant un effet toxique direct de la phénylalanine.

Discussion/Conclusion. – La surveillance de la phénylalaninémie à l'âge adulte permettrait d'éviter les complications neuropsychiatriques grâce à la reprise du régime.

1. Introduction

Phenylketonuria (PKU) is an autosomal recessive genetic disorder characterized by a deficiency in the hepatic enzyme phenylalanine hydroxylase (PAH). Incidence is about 1:10,000 in Europe [1]. The level of phenylalaninemia correlates with the prognosis, as patients with moderate hyperphenylananinemia (180–600 μmol/L) usually remain asymptomatic whereas untreated patients with classical PKU (Phe > 1200 mg/dL), will suffer from neurological or psychiatric disorders (mental retardation, behavioural problems, epilepsy, movement disorders, or spasticity) [2]. Postnatal screening diagnosis followed by early treatment with a Phe free diet results in a nearly normal cognitive development [2]. Treatment guidelines vary among countries. In France, it is recommended to maintain Phe between 120 and 300 μmol/L until 10–11 years of age then below 900 μmol/L until the end of school age and then below 1200 μmol/L in adulthood [3]. Many patients show white matter abnormalities on brain MRI. These abnormalities are not correlated to intellectual or neurological signs and can be reversible after reintroduction of the diet [4]. A very small proportion of adolescent and adult patients will develop frank neurological symptoms that may improve under dietary treatment [5]. In addition, very few publications reported the cases of adult patients that escaped neonatal screening and remained poorly symptomatic until neurological symptoms progressed in adulthood. Here, we took advantage of 5 personal cases and of a literature review to delineate the neuropsychiatric signs observed in adults with PKU.

2. Methods

Five patients were referred to the Adult Neurometabolic Unit, Hôpital de la Salpêtrière for adult-onset neurological or psychiatric symptoms in the context of PKU. A literature review was performed, using the Pubmed database and the authors own bibliography to gather previous published cases. Inclusion criteria were:

- articles published in French or English;
- patients with clear neurological or psychiatric syndromes, excluding patients with minor cognitive abnormalities only;
- age at onset of neuropsychiatric signs after 15 years old;
- neuropsychiatric signs not explained by other causes.

3. Description of our cases

3.1. *Patient 1*

A man, aged 32 years, was evaluated for a 2 years history of slowly progressive spastic paraparesis. He was diagnosed with PKU by neonatal screening and low Phe diet was introduced at 1 month (see Table 1 for a summary). Observance of the diet was reported to be non-optimal with poor metabolic control during infancy and childhood. He walked at 16 months and spoke at 2 years. He went in a specialised school, but he never learned to read or to write. He totally stopped the diet at 30 years. Clinical examination at 32 revealed a marked low limbs pyramidal syndrome with spastic gait. Brain MRI disclosed a leukoencephalopathy involving the posterior and periventricular white matter. A poor Phe diet was then introduced leading to disappearance of the spasticity and normalisation of the gait while brain MRI remained unchanged. Follow-up during the next years revealed that high Phe values above 900 μmol/L were associated with reappearance of the spastic gait and that strict Phe control below this range was associated with gait normalization.

3.2. *Patient 2*

This woman was aged 38 when she was evaluated for psychiatric symptoms. She was diagnosed with PKU at 10 days of age through neonatal screening. The patient was abandoned by her parents and lived in an institution until she was adopted at the age of 6 years. A low Phe diet was introduced from 1.5 months to 4.5 years old and interrupted thereafter. The metabolic control in infancy and childhood is difficult to evaluate but was probably bad, as Phe was measured once at 2650 μmol/L when she was 5 years old. Walking and speaking