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Classic Homocystinuria Revealed by a Stroke

Amar NB[1]*, Kabbaj K[1], Ourrai A[2], Hassani A[2] and Abilkassem R[2]

[1]Department of Pediatrics, Children's Hospital of Rabat, Morocco
[2]Department of Pediatrics, Military Hospital Mohamed V of Rabat, Morocco

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***Corresponding Author:**
Dr. BEN AMAR Naji,
Department of Pediatrics, Children's Hospital of Rabat, Morocco

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1. Abstract

Homocystinuria, by cystathionine beta-synthetase deficiency (CAS), is an autosomal recessive anomaly of sulfured amino acids catabolism. The gravity of the disease depends on ocular and thromboembolic involvements prevented by early diagnosis for life méthionin devoid diet and betaïne intake. We report a 6-year-old girl presenting Homocystinuria, by CAS deficiency, declared by stroke which caused visual aftereffects and epilepsy. We try to describe disease clinicals, biologicals, therapeutical and outcomes features. We emphasize interest to evoke Homocystinuria disease when ischemic stroke in childhood and early diagnosis.

2. Keywords: Homocystinuria; Stroke; Blindness; Epilepsy; Prevention

3. Introduction

Classical homocystinuria is an autosomal recessive disorder caused by a deficiency in cystathionine beta synthetase (CAS), which is involved in the catabolism of sulfur-containing amino acids, particularly methionine. The gene responsible for CAS synthesis is located on chromosome 21. The condition is transmitted autosomal recessively. Prenatal diagnosis is possible by measuring CAS in amniocyte and chorionic villus cultures. Clinical manifestations

are due to the accumulation of homocysteine in vascular, cerebral and connective tissue, with a phenotype similar to Marfan syn- drome. We report the case of a 6-year-old girl with homocystinuria discovered during a stroke. We describe the clinical, biological, therapeutic and evolutionary features of the disease, stressing the importance of evoking the disease in the event of ischemic stroke in children, and of early diagnosis.

4. Observation

A 6-year-old child from a non-consanguineous couple, with no particular history of illness and previously in good health, consulted the pediatric emergency department for intense headaches predominantly on the right, which did not improve with the usual analgesic treatment, occurring in a context of apyrexia. The fol- lowing day, she complained of bilateral blindness. Cardiovascular examination was unremarkable. An emergency cerebral CT scan revealed multiple parenchymal lesions with an ischemic appear- ance. Cerebral angio-MRI revealed no cerebral vascular malfor- mation. The patient was started on low-molecular-weight heparin by subcutaneous injection, combined with intravenous analgesics. Headaches disappeared after a week, but vision was only partially improved. Plasma amino acid chromatography revealed high ho- mocysteine levels at 180 µmol/l (normal value: <10 µmol/l) and

double sulfides (cysteine-homocysteine) associated with high methionine levels at 93 µmol/l and low cysteine levels at 10 µmol/l. Plasma homocysteine levels remained elevated after administration of vitamin B6, suggesting homocystinuria due to CAS deficiency. Currently, the child is treated with a non-strict hypoprotein diet low in methionine, with vitamin B6, B12 and folates. She still has epilepsy, but no new vascular manifestations after 5 years. The patient is currently followed up in consultation with biannual monitoring of plasma total homocysteine levels.

5. Discussion

Homocystinuria is the 2nd most common metabolic encephalopathy after phenylketonuria, with an incidence varying between 1/60000 and 1/500000 [1]. Homocysteine, a non-protein amino acid, results from the demethylation of methionine. It is then transsulfurated to cystathionine by CAS and then to cysteine or restored to methionine by remethylation by Betaine Homocysteine Methyltransferase (BHMT) [2]. The increase in homocysteine in plasma can therefore be due either to a defect in the transsulfuration pathway via CAS deficiency (the most frequent enzyme deficiency), which is the cause of classic homocystinuria with autosomal recessive inheritance (chromosome 21) [3], or to a remethylation defect (Figure 1).

Classical homocystinuria is characterized by ligamento-skeletal involvement (marfanoid syndrome, scoliosis, genu-valgum, osteoporosis, ligament hyperlaxity), ocular involvement (lens subluxation, myopia, cataract), mental retardation and sometimes psychiatric disorders [4]. These different symptoms may be associated in highly variable ways. It evolves as a chronic intoxication with heterogeneous clinical expression, which explains the often-late diagnosis. In fact, there is a vitamin B6-sensitive phenotype, in which diagnosis is delayed (moderate phenotype and later onset) and the duration of exposure to major hyperhomocysteinemia is longer [5,6] before the onset of the first vascular thrombosis than in vitamin B6-resistant patients [7,8].

Thrombotic complications (stroke, myocardial infarction, venous thrombosis) arise when plasma homocysteine levels rise significantly and rapidly (>50µmol/l) during severe decompensation (surgery or general anaesthesia). They affect a third of homocystinuric patients in the second or third decade. Mudd et al. report 25.1% thrombotic complications at age 30 in 624 untreated patients, including 51% venous thrombosis and 49% arterial thrombosis [9]. In our patient, the anamnestic, clinical and para-clin- ical data did not support a cardiac (congenital heart disease or acquired rheumatic heart disease), vascular (Moya-Moya disease or syndrome, arterial dissection) or infectious (varicella, menin- gitis, mycoplasma, enterovirus or parvovirus) origin. Thrombotic microangiopathy, sickle cell disease, thrombophilia, leukemia or autoimmune disease are unlikely, given the absence of a suggestive context. Furthermore, the absence of clinical manifestations prior to the stroke suggests that the rise in homocysteine to 18-fold occurred rapidly. Plasma homocysteine may be increased, but not to such high levels, in the absence of any enzyme deficiency, and in cases of vitamin B6, B12 and folate deficiency. It may also be increased in cases of hepatic or renal insufficiency, or when taking anti-folate or anti-B6 drugs. Diagnosis of homocystinuria is based on the presence of elevated levels of homocysteine in the blood (and urine), mixed cysteine-homocysteine disulfide and methionine on amino acid chromatography.

There are therefore 2 types of homocystinuria, depending on response to vitamin B6 treatment. Non-responders (CAS deficiency), such as our patient, require a lifelong methionine-free diet [10,11,12] and treatment with betaine (betaine citrate) to activate the secondary remethylation pathway [13]. Betaine is proposed at an average dose of 6-9 g/d orally [14]. For responding patients, treatment includes a combination of folic acid (5mg/d), vitamin B12 (1mg/IM per month) and vitamin B6 (200 mg/d). The aim of treatment is to correct the biochemical disorder and control the high level of total homocysteine in the blood as far as possible (homocysteine < 11µmol/l), and to prevent complications, particularly thrombo-embolic events [15]. It is important to screen siblings in order to start the diet before complications arise. In our case, we screened for latent homozygotes and heterozygotes likely to transmit the disease. This led to the detection of a homozygous form in the younger brother, who was immediately put on a diet and betaine. The prognosis of the disease also depends on ocular damage, in particular subluxation of the crystalline lens, which is present in over 90% of cases at the age of 16, in association with severe myopia. This requires prolonged ophthalmological follow-up.

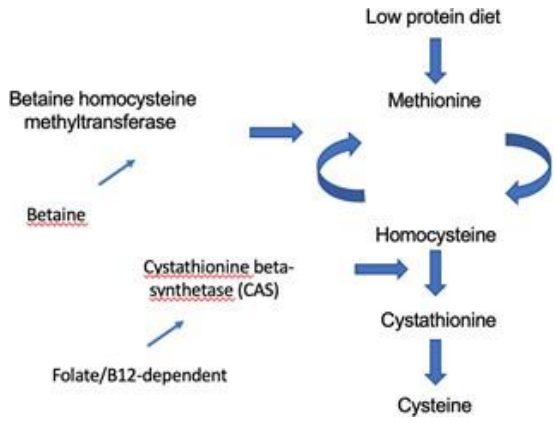

Figure 1: Methionine metabolism pathways

6. Conclusion

Homocystinuria due to CAS deficiency is a hereditary disease that should be suspected in the event of thromboembolic events in children and young adults. It requires regular biological monitoring of plasma homocysteine levels and lifelong treatment based on a specific diet combined with betaine intake. Patient and family education, as well as regular medical follow-up, help control compliance, and prevent and detect the early signs of thromboembolic events. Early detection of the disease in the siblings of homocystinuric patients is also important.

7. Conflict of Interest

The authors declare no conflicts of interest.

8. Authors' Contributions

All authors have read and approved the final version of the manuscript.

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