Case Report

Treatment-resistant papilledema in a boy with homocystinuria

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Keywords

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Abstract

We report an 8-year old boy with the diagnosis of pyridoxine non-responsive cystathione beta-synthase deficiency. At a routine ophthalmological examination bilateral papilledema was detected on fundoscopy. Urgent brain imaging showed the typical signs of elevated intracranial pressure and cerebral edema. Laboratory results revealed high plasma methionine levels, secondary to treatment with betaine and a catabolic state because of a low calorie intake. Methionine excess is usually reversible with discontinuation of betaine together with a methionine restricted diet. In our patient however, a ventriculoperitoneal shunt placement was required to lower intracranial pressure and resolve the bilateral papilledema.

Introduction

An 8-year old boy, diagnosed with autism spectrum disorder, was referred to our ophthalmology department because of a suboptimal visual acuity with his current spectacle correction. At presentation a suboptimal visual acuity of LogMar 0.35 was measured in the right eye and LogMar 0.45 in the left eye. Retinoscopy revealed myopic astigmatism of -4 (-3x180°) on the right and -2.5 (-1.75x10°) on the left eye. Biomicroscopic examination of the anterior segment revealed a bilateral lens subluxation. To exclude systemic disease associated with lens luxation, our patient was referred for metabolic screening. The biochemical investigations matched with the diagnosis of cystathione beta-synthase deficiency or classical homocystinuria. The plasma homocysteine and methionine concentration at diagnosis were respectively 120µmol/L (normal 7-15µmol/L) and 176µmol/L (normal 10-45µmol/L). Molecular genetic analysis confirmed the biochemical diagnosis. First-line treatment with pyridoxine (vitamin B6) was not successful in correcting the metabolic disturbances. Betaine was started in a low dose (100mg/kg/day), in combination with a moderate protein restriction of 2.4 g of natural protein per kg per day to reduce homocysteine and methionine levels. The plasma levels of methionine were routinely monitored after the introduction of Betaine. In the first six months after betaine introduction the plasma methionine concentration ranged between 834 µmol/L and 1004 µmol/L.

On routine ophthalmological examination, six months after the introduction of betaine, fundoscopy revealed bilateral papilledema (figure 1A). Early morning vomiting, an important neurological sign of increased intracranial pressure, was reported since one month with an increased frequency in the last week. Caloric intake in the last few weeks was low. Due to the autism of the child, headaches were not reported. The plasma methionine concentration was 1257 µmol/L (normal ≤45µmol/L) and urgent brain computed tomography showed crowding of the sulci and gyri with white matter edema, consistent with the diagnosis of elevated intracranial pressure (figure 2). In homocystinuria there is a well-known risk of thrombosis, but clinical or radiographically signs of a cerebral vein thrombosis were absent. A magnetic resonance venography to exclude a thrombosis, was not performed.

Betaine was discontinued and acetazolamide (dose 3x250mg) was started, but without significant improvement of the intracranial abnormalities or laboratory results after several days. A high calorie diet with more rigorous protein restriction was started to prevent a catabolic state that would aggravate the hypermethioninemia. Evacuating lumbar punctures to lower intracranial pressure, were not performed because of the cerebral edema. Unfortunately, ophthalmological follow-up on day 10 showed a bilateral decrease in visual acuity with persistent papilledema and beginning signs of optic disc pallor (figure 1B). Placement of a ventriculoperitoneal shunt to lower the intracranial pressure was decided. Hence, the bilateral papilledema resolved quickly. In the following months, there was no recurrence of the papilledema. Because of progressive astigmatism, bilateral lensectomy with intraocular lens implantation was performed. At a follow-up visit, two years after the acute episode of papilledema, the best-corrected visual acuity was LogMar 0.15 in the right eye and 0.05 in the left eye. Unfortunately the optic discs remained partially atrophic because of the episode of persistent intracranial hypertension (figure 1C).

Discussion

Classical homocystinuria, the most common type of homocystinuria, is an autosomal recessive disorder of the metabolism of homocysteine due to deficiency of cystathionine beta synthase. This leads to an accumulation of homocysteine and methionine, leading to adverse effects on the ocular, skeletal, cardiovascular and central nervous system (1). Early signs and symptoms of homocystinuria can be subtle in infants, leading to a diagnostic delay; visual problems can give a clue to the diagnosis of homocystinuria. The major ocular manifestation is a high and rapidly progressive myopia at young age. The presence of a suboptimal vision with full correction of myopia and astigmatism should suggest the presence of ectopia lentis. Less frequently reported ophthalmological findings are iridodonesis, glaucoma, optic atrophy, retinal detachment and central retinal artery occlusion. Systemic neurological findings include intellectual deficits, developmental delays, seizures and psychiatric disorders. Due to elevated levels of homocysteine, patients have an increased risk for premature atherosclerosis and venous thromboembolism (1). Early recognition and treatment of homocystinuria is important because symptoms at an early stage can be reversible (2). First-line treatment consists of high doses of vitamin B6 (pyridoxine). Insufficient lowering of homocysteine in pyridoxine-unresponsive patients requires the start of a methionine restricted diet in combination with betaine (trimethylglycine). Betaine lowers homocysteine levels by promoting the conversion of homocysteine to methionine (2).

The first case of cerebral edema in a patients with homocystinuria was

reported in 2002 in a 10-year old girl who recently was put on betaine therapy. After withdrawal of betaine and with a strict diet, the cerebral edema resolved (3). This timeline strongly suggests that betaine can be responsible for the elevated intracranial hypertension. Almost all reported cases of intracranial hypertension, including our case, started after introduction or dose raise of betaine. However, the incidence of brain edema in patients receiving betaine therapy is low and most patients tolerate betaine without apparent complications. The safe dose range of betaine is not yet established, but research suggests that the additional benefit of betaine dose above 150 mg/kg/day is low (4). Also, most cases of brain edema occur at levels above 150 mg/kg/day. Schwahn et al. reported only one case of intracranial hypertension when taking only 107 mg/kg/day of betaine, but in our patient the dose of betaine was also low (100 mg/kg/day)(5). In cases of excessive hypermethioninemia in patients taking a relative low dose of betaine, a bad adherence to the diet or a catabolic state due to a low calorie intake should be suspected.

Two hypothesis are currently proposed in literature to explain the development of brain edema in patients on betaine treatment. The first hypothesis suggests a direct effect of betaine on the brain. Betaine has been described as being an intracellular osmolyte and osmoregulator in the brain, which could lead to the accumulation of intracerebral fluid (6). There are few data regarding plasma and cerebrospinal fluid concentrations of betaine during an acute episode of brain edema. Devlin et al. reported a case with plasma levels of betaine of 98µmol/L (normal range for subjects without betaine intake of 18-73µmol/L) and cerebrospinal fluid levels of 6.6µmol/L (no normal range provided)(7). Schwahn et al. presented a case of cerebral edema in a patient with plasma betaine levels of 131µmol/L (5). Considering these available relatively low concentrations of betaine in plasma and in cerebrospinal fluid, they assumed the hypothesis of an accumulation of betaine was less likely. In contrast, the measured levels of methionine in plasma and cerebrospinal fluid were excessively increased when compared to normal levels (5). This finding could match with the second hypothesis, which states that the hypermethioninemia itself is responsible of the acute brain edema. Elevated methionine concentrations have a well-known toxic effect on cells of the brain (8). The intake of betaine only enhances the hypermethioninemia because of its working mechanism in converting homocysteine to methionine. This hypothesis is supported by reports of patients with cerebral edema and hypermethioninemia without intake of betaine. Mudd et al. described two healthy infants with methionine excess due to a high methionine intake who developed cerebral edema (9). Allen et al. reported a single patient not on betaine treatment in a group of 35 homocystinuria patients with hypermethioninemia and encephalopathy (10).

In patients with homocystinuria, plasma methionine levels should be monitored routinely. Schwahn et al. collected the methionine levels of all published case reports of acute encephalopathy. This revealed that the lowest plasma level of methionine at the time

Figure 1 : *Fundus photographs of the optic nerves. (*
A) Papilledema at presentation.
(B) Sectorial optic atrophy, day 10 after diagnosis of intracranial hypertension. The arrows delineate the optic nerve atrophic areas.
(C) Atrophic discs at the two year follow-up visit.

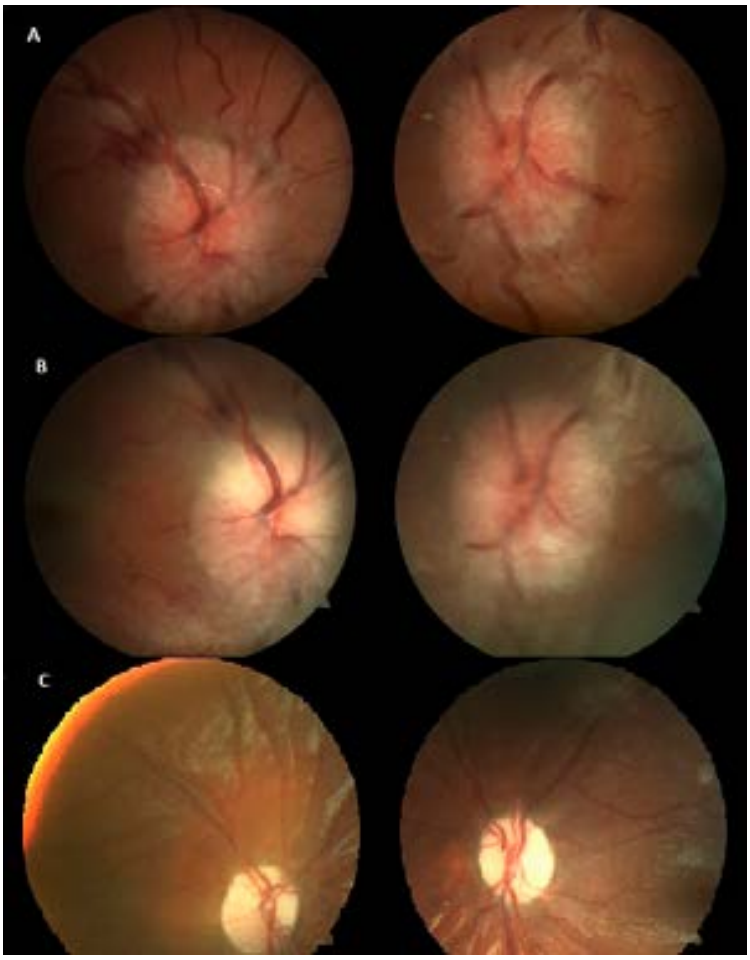
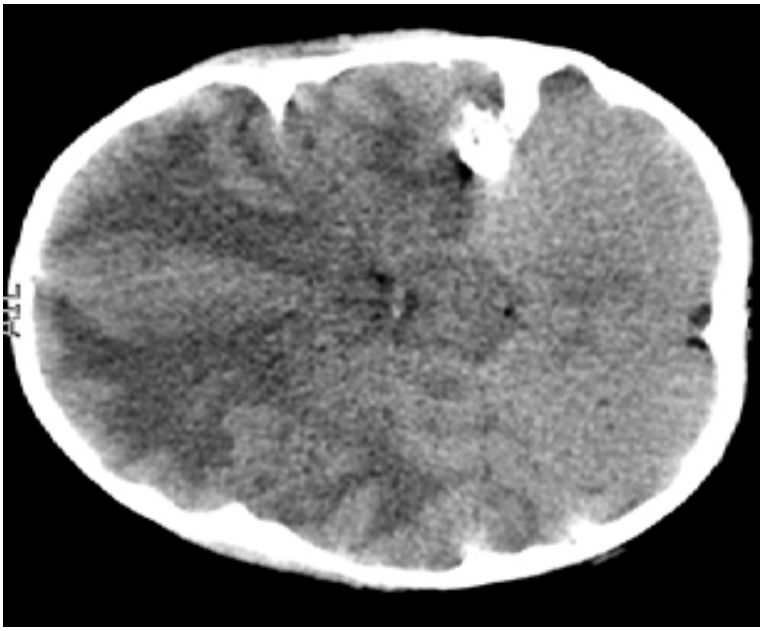


Figure 2 : *Diffuse white matter edema on brain CT.*



of elevated intracranial pressure was 559 µmol/L. They concluded that methionine levels below 500 µmol/L can be considered safe (5). Most cases of cerebral edema developed at levels close to or above 1000 µmol/L, analogous to our case.

The approach of hypermethioninemia in the context of signs or symptoms of intracranial hypertension varies in literature, but if methionine is prompt and successfully lowered, the prognosis is good. Ismayilova et al. reported a case of reversible white matter edema after tightening control of dietary methionine intake without reducing or stopping betaine treatment (11). Vatanavicharn et al. started enteral feeding in their case and continued betaine in a low dose (1 g/day)(12). In most cases however, treatment with betaine was stopped. Only in exceptionally cases, additional treatment was necessary to reduce intracranial pressure. Devlin et al. reported a case of acute hypertension, bradycardia and loss of consciousness due to the diffuse brain swelling. Bilateral frontotemporal decompressive craniotomies were performed (7). In our patient, the hypermethioninemia persisted 10 days after stopping betaine. Ophthalmological follow-up showed a bilateral decrease in visual acuity with persistent papilledema and beginning signs of optic disc pallor, leading to the decision to place a ventriculoperitoneal shunt to lower intracranial pressure.

Conclusion

We present a case of treatment-resistant papilledema associated with high methionine levels in a boy with cystathione beta-synthase deficiency on betaine treatment. The underlying pathophysiology of the cerebral edema and the susceptibility of some patients to this complication, is not clear. In patients receiving betaine, attention must be paid to signs and symptoms of intracranial hypertension. Ophthalmological follow-up is essential in the early detection and monitoring. Strict adherence to a methionine restricted diet and dose adjustment or discontinuation of betaine should be considered if methionine levels rise above 1000 µmol/L. In most cases of cerebral edema, the neurological symptoms disappear and the cerebral edema resolves. In selected cases, additional neurosurgical interventions are necessary to lower the intracranial pressure.

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