Lenticular Subluxation in a Patient with Homocystinuria Undetected by Neonatal Screening

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A case of homocystinuria with lenticular subluxation was misdiagnosed as Marfan syndrome since the patient had no apparent mental impairment and had had a negative neonatal screen for homocystinuria. The delayed diagnosis of homocystinuria was due to a negative prior neonatal screen which was checked when he was a breastfed healthy newborn. In the absence of an autosomal dominant family history, and because of prior poor school performance, amino acid analysis and mutational analysis of the cystathionine β-synthase gene were performed, which revealed the presence of homocystinuria. Low methionine diet with vitamin B6, folic acid, betaine, dipyridamole and aspirin was prescribed for emergency ophthalmologic surgery to prevent thromboembolic events. Fortunately, the operation was completed uneventfully. The patient has been followed-up for 4 years without any significant complaints under diet and medical control. Since homocystinuria is easily missed in neonatal screening programs, it should be suspected in patients who present with lenticular subluxation, even after a negative neonatal screen. [*J Chin Med Assoc* 2007; 70(12):562–564]

Key Words: homocystinuria, lenticular subluxation, Marfan syndrome

Introduction

The clinical characteristics that distinguish Marfan syndrome (MFS) from cystathionine β-synthase (CBS) deficiency or homocystinuria include anomalies of the cardiovascular system (mitral valve prolapse, aortic root dilation), an autosomal dominant inheritance pattern, and absence of mental retardation. MFS potentially leads to aortic dissection and rupture, these being the major causes of death.[1] However, there are exceptions, such that patients with MFS may develop major ocular manifestations much earlier than cardiovascular disease manifestations. Furthermore, approximately 20% of MFS cases are the product of *de novo* mutations, precluding the identification of an inherited pattern.[2] Conversely, up to 20% of patients with late-treated homocystinuria have a normal IQ score.[3]

The 1 in 5,000 to 1 in 10,000 prevalence of MFS is considerably higher than the 1 in 300,000 prevalence of homocystinuria in most populations. Furthermore, after the introduction of neonatal screening for homocystinuria, the incidence of lenticular subluxation among patients with homocystinuria has markedly decreased. Therefore, ophthalmologists might be unfamiliar with the care of patients who present with homocystinuria, and might not readily distinguish homocystinuria from MFS, particularly when there is a history of a negative neonatal screen for homocystinuria. However, an accurate preoperative diagnosis of homocystinuria is of major importance, since perioperative therapeutic measures are needed to prevent thromboembolic events.

Case Report

This 14-year-old boy was the youngest child in a consanguineous family. A tall and slim general appearance,

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elongated limbs with arachnodactyly, pectus excavatum and severe myopia had been present since early childhood. After suffering from an acute episode of blurred vision and pain in the left eye 2 years earlier, he underwent intracapsular lenticular extraction at a local teaching hospital where lens dislocation and acute glaucoma had been detected. Since he had a history of negative neonatal screen for homocystinuria, a diagnosis of MFS was made and further investigations were not undertaken.

The patient presented to our hospital 2 years later for evaluation of lenticular subluxation in the right eye (Figure 1) which resulted in severe pain. In the absence of an autosomal dominant family history, and because of prior poor school performance, amino acid analysis and mutational analysis of the cystathionine β-synthase gene were recommended. Serum methionine and free homocysteine concentrations were 772 mmol/L and 47.9 mmol/L, respectively (normal, 13–40 mmol/L and <12.5 mmol/L, respectively), and the mutational analysis of the cystathionine β-synthase gene confirmed a homozygous mutation for D47E (Figure 2).

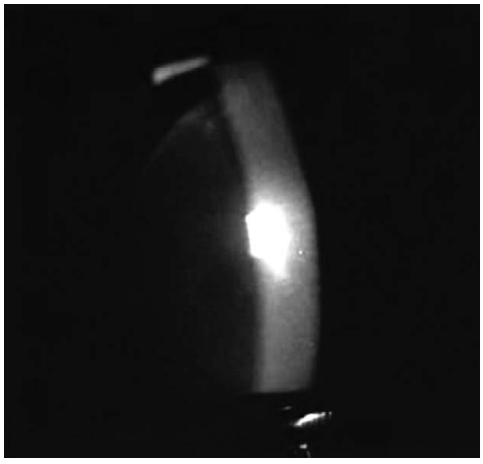

Figure 1. Lenticular subluxation in the right eye.

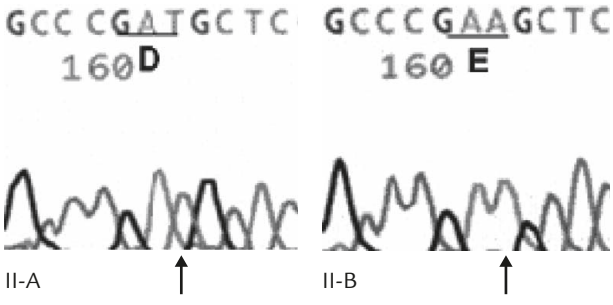

Figure 2. DNA sequencing results from a normal individual (II-A) and from the patient (II-B). The nucleotide change from T to A in exon 1 at position g.4259 (arrow) and the predicted codon change (D → E) are also shown.

A low methionine diet (Hominex-2) and regimen of vitamin B6 (300 mg/day), folic acid, betaine, dipyridamole and aspirin were prescribed in preparation for emergency ophthalmologic surgery. After 1 week of treatment, serum methionine and free homocysteine concentrations had returned to normal (38.3 mmol/L and 0 mmol/L, respectively) and uncomplicated intracapsular lens extraction was performed under general anesthesia. Five days after the operation, the patient was discharged in a stable condition without wound infection or thromboembolic episode. Under dietary control with low methionine and adjuvant medicine including folic acid and betaine, a follow-up series of amino acid analyses revealed normal serum methionine level and homocysteine concentrations. Over 4 years of follow-up, the patient has become more active and talkative without progressive mental retardation. There has also been no thromboembolic event.

Discussion

Because of the instability of homocysteine, methionine has been chosen as a marker for homocystinuria screening. However, methionine is not a reliable marker of cystathionine β-synthase deficiency in neonatal screening since in the newborn, it might not accumulate in sufficient amounts. There is an estimated 20% false-negative rate in homocystinuria neonatal screening.[4] Early discharge from hospital, low protein intake from breast feeding, high upper normal concentration of blood methionine, and pyridoxine responsiveness have been identified as factors contributing to inaccurate neonatal screening.

Thromboembolic episode, 1 of the most life-threatening complications of homocystinuria, involves various vessels, including those of the brain. Serious consequences of a thromboembolic episode include paralysis, severe hypertension and optic atrophy. The thromboembolic risk increases during and after surgical procedures such as the operation our patient underwent for lens subluxation. Recognition of the true diagnosis of homocystinuria, rather than MFS, played a crucial role in preventing life-threatening complications in our patient. Since the general appearance of the 2 diseases is similar, with the common characteristic of displacement of the lens of the eye, physicians need to differentiate between them very carefully.

The prevalence of cystathionine β-synthase deficiency has recently been re-evaluated via hotspot mutation screening in Denmark and Norway.[5,6] The prevalence estimated via the frequencies of hotspot mutations was surprisingly higher (1 in 20,000 in Denmark and

1 in 6,400 in Norway) than previously estimated (~1 in 300,000) in both populations, indicating much higher false-negative rates than expected in homocystinuria screening programs based on methionine measurements. Therefore, homocystinuria should be suspected in patients who present with lens subluxation, even after a negative neonatal screen.

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