Delayed diagnosis of homocystinuria presenting as bilateral congenital lens subluxation

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SUMMARY
Introduction Homocystinuria is an autosomal recessively inherited defect leading to hyperhomocysteinemia and associated with ocular manifestations, mainly myopia and ectopia lentis.

Case outline A 26-year-old male with secondary glaucoma due to bilateral lens subluxation was admitted to the Department of vitreoretinal surgery. Horizontal nystagmus, bilateral lens subluxation, and bilateral amblyopia were first discovered at the age of three years. Preoperative laboratory workup revealed elevated levels of homocysteine. Bilateral pars plana lensectomy and vitrectomy followed by a sulcus fixation of the intraocular lens (ALCON MA60 Acrysof IOL) were performed. The patient was prescribed folic acid, methionine, and pyridoxine, and was urged to maintain a methionine-low diet. After a bilateral lensectomy and sulcus fixation of the intraocular lens and a methionine restriction therapy combined with vitamin B6, B9, and B12 supplementation, his condition improved greatly.

Conclusion In this report of a rare case we emphasize the importance of examining differential diagnoses of lens subluxation, since early intervention can prevent serious complications.

Keywords: lens subluxation; homocystinuria; glaucoma

INTRODUCTION
Homocystinuria is an autosomal recessive defect in methionine metabolism leading to hyperhomocysteinemia. It is associated with mental retardation, seizures, marfanoid habitus, and ocular manifestations, mainly myopia and ectopia lentis (EL) [1]. It has an estimated incidence of 1:50,000–200,000, sufficiently high to consider it for screening in newborns [2, 3]. After the condition is suspected based on physical findings, personal and family history, a workup is done for confirmation, including measuring homocysteine levels in blood and urine. Treatment consists of pyridoxine, vitamin B12, folic acid, anticoagulation agents for stroke prevention, and low-methionine diet in drug-resistant cases [4].

Since treatment can reduce mortality and severity of complications, early diagnosis is crucial. Neonatal screening tests used for testing other similar metabolic disorders lack sensitivity in detecting homocystinuria. In most cases, the condition is confirmed after three years of age, presenting with lens subluxation [5]. We report a case of homocystinuria diagnosed in a 26-year-old, who had experienced ocular manifestations of the disease since early childhood.

CASE REPORT
A 26-year-old Caucasian male was referred to the Department of Vitreoretinal Surgery, Osijek Clinical Hospital Center. The reason of the referral was the need for surgical treatment of a subluxated lens that had caused secondary glaucoma. At the age of two, he underwent a left nephrectomy and subsequent chemotherapy due to Wilms tumor. At the age of three, he was diagnosed with horizontal nystagmus, bilateral subluxation of lenses, and bilateral amblyopia, and was scheduled for periodical exams. During high school education he experienced learning difficulties.

On admission, light hair, short stature (height of 162 cm, weight of 73 kg, BMI 27.8 kg/m²), and bradydactyly were noted. The biomicroscopic ophthalmic examination showed bilateral inferotemporal subluxation of the lenses protruding in the inferior part of the vitreum (Figure 1). Zonular fibers were partially visible. Myopic changes were found on the fundus. Vitreal liquefaction was present. Best corrected visual acuity was 0.4 LogMAR (Snellen acuity 6/15, decimal acuity 0.4) in the right eye and 0.7 LogMAR (Snellen acuity 6/30, decimal acuity 0.2) in the left eye.

Figure 1. Biomicroscopic finding of the right (A) and left (B) eye shows bilateral inferotemporal subluxation of the lenses protruding in the inferior part of the vitreum.
Applanation tonometry showed increased intraocular pressure (IOP; 33/31 mmHg).

The patient was referred to an internal medicine specialist. He underwent a physical examination and a complete ophthalmologic examination. Routine laboratory tests, including plasma homocysteine measurement, were ordered. Homocysteine level was 15 μmol/L.

Systemic signs and elevated homocysteine levels suggested homocystinuria as the most probable underlying condition. Blood dyscrasia, Fabry disease, and acidemias were ruled out, since there was no history of thromboembolic events and coagulation test results were normal. There was no family history of serious diseases, including homocystinemia.

He was administered timolol/dorzolamide, brimonidine, and latanoprost in order to relieve elevated intraocular pressure. Since secondary bilateral glaucoma was unresponsive to treatment, a bilateral pars plana lensectomy, and vitrectomy followed by a sulcus fixation of the intraocular lens (ALCON MA60 Acrysof IOL; Alcon Inc., Hünenberg, Switzerland) were performed.

Also, a therapeutic regimen was established consisting of folic acid (5 mg/day), cobalamin (1 mg/week), pyridoxine (900 mg/day), and a methionine-restricted diet.

Three months upon the initiation of therapy, homocysteine levels were reduced to 10 μmol/L. Ophthalmologic examination showed cIOL 0.1 LogMAR (Snellen acuity 6/7.5, decimal acuity 0.8) in the right eye, cIOL 0.3 LogMAR (Snellen acuity 6/12, decimal acuity 0.5) in the left eye, and normal values of IOP.

The timeline of events is shown in Figure 2.

**DISCUSSION**

Early detection and treatment are of paramount importance in homocystinuria patients. Timely interventions can reduce the number and severity of complications. Abnormally high and progressive myopia at a young age combined with systemic complications are signs of suspected homocystinuria. Nevertheless, significant delays in diagnosis happen [6].

EL occurs in around 80% of patients and it is the most common involvement in homocystinuria [7, 8]. About 70% of patients will develop EL by eight years of age, and 82% by the age of 10 [9].

Signs that might suggest EL include very high myopia, abnormally progressive myopia, myopia at a young age, or high myopia without a myopic fundus [6]. Later signs include decreased vision, monocular diplopia or pain secondary to pupillary glaucoma, and vascular signs [10].

Even though EL is one of the most prominent symptoms of homocystinuria, and 5% of all lens dislocations may be attributed to this metabolic condition, homocystinuria is often neglected in the differential diagnosis of...
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Spond well to vitamin B6 (B6-responsive homocystinuria) the therapeutic response [9]. About 50% of patients respond well to vitamin B6 (B6-responsive homocystinuria) supplements in high doses [10]. Vitamin B6-responsive patients have lower incidence, and later occurrence of complications [7, 11]. B6-non-responsive patients require a methionine-restricted diet with daily intakes of methionine not exceeding 40 mg/day [9]. An alternative therapeutic approach can be considered in these patients, which involves the use of methyl donors, betaine or its precursor choline, that reduce homocysteine levels by promoting its conversion to methionine [6, 10]. A combined therapy was prescribed in our patient.

Treatment from infancy with pyridoxine, folic acid, and betaine reduces cardiovascular risk by 80–90% [12]. To prevent thromboembolism, antiaggregant treatment with acetylsalicylic acid should also be considered in cases of immobilization or after surgery [8].

Because of the increased probability of thromboembolism, conservative treatment of EL is advised when possible [10, 13]. Lensectomy is performed in cases of secondary complications, such as progressive lens subluxation, cataract formation, lens instability, retinal detachment, or pupillary block glaucoma, as was the case in our patient [13, 14].

REFERENCES


Касна дијагноза хомоцистинурије приказана обостраном конгениталном сублуксацијом сочиња

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САЖЕТАК

Ектопија сочива сеће на хомоцистинурију, као и неколико других сећа на хомоцистинурију у случају ретковидношку. У наших ниво корене диференцијалне дијагнозе сублуксације сочиња, пошто ње могу ради и ње могу ради и тешића окружни сочиња. Урађена је обострана хомоцистинурија је аутозомно рецесивни наследни део који води у хиперхомоцистенемију и повезанство са окружним сочиња. Урађена је обострана хомоцистинурија је аутозомно рецесивни наследни део који води у хиперхомоцистенемију и повезанство са окружним сочиња. Урађена је обострана хомоцистинурија је аутозомно рецесивни наследни део који води у хиперхомоцистенемију и повезанство са окружним сочиња. Урађена је обострана хомоцистинурија је аутозомно рецесивни наследни део који води у хиперхомоцистенемију и повезанство са окружним сочиња.

Кључне речи: хомоцистинурија; сублуксација; сочиња; глауком

САЖЕТАК

Увод. Хомоцистинурија је аутозомно рецесивни наследни део који води у хиперхомоцистенемију и повезанство са окружним сочиња. Урађена је обострана хомоцистинурија је аутозомно рецесивни наследни део који води у хиперхомоцистенемију и повезанство са окружним сочиња. Урађена је обострана хомоцистинурија је аутозомно рецесивни наследни део који води у хиперхомоцистенемију и повезанство са окружним сочиња. Урађена је обострана хомоцистинурија је аутозомно рецесивни наследни део који води у хиперхомоцистенемију и повезанство са окружним сочиња.

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