Commentary: Ophthalmic manifestations of homocystinuria

Homocystinuria is an autosomal recessively inherited defect in the transsulfuration pathway (type-I) or methylation pathway (types II and III). The authors should be congratulated for an excellent review article on ocular manifestations of homocystinuria published in the current issue of the *Indian Journal of Ophthalmology*.[1] The internationally reported incidence of homocystinuria varies between 1 in 50,000 and 1 in 200,000.[1,2] Normally, homocysteine is an intracellular intermediate and is not detectable in plasma or urine. However, when the reconversion of homocysteine to methionine or cysteine is blocked, it accumulates extracellularly and results in homocystinuria.[3]

Infants with this disorder are normal at birth. Clinical manifestations during infancy are nonspecific and may include failure to thrive and developmental delay. The diagnosis is usually made when subluxation of the ocular crystalline lens occurs. This causes severe lens-induced myopia and iridiodonesis. Progressive mental retardation is common. Affected individuals with homocystinuria manifest skeletal abnormalities resembling those of Marfan syndrome. Children usually have fair complexions, blue eyes, and a peculiar malar flush. Thromboembolic episodes involving both large and small vessels, especially those of the brain, are common and may occur at any age. The diagnosis is based on elevated homocysteine in serum and urine. The urine nitroprusside test may be falsely negative in mildly affected adult patients. The sensitivity of this test can be improved by methionine loading.

Ocular findings of homocystinuria are also nicely summarized in the review article by Rahman *et al*.[1] and other articles.[4-8] As per published reports, approximately 40% of 5-year-old patients with untreated homocystinuria have crystalline lens subluxation, and almost all patients have it by the age of 25 years. The zonules are absent, as compared with the stretched zonules in Marfan syndrome. The crystalline lenses move down and nasally in 50% of patients, posteriorly in 20%, and anteriorly in 10%. A pupillary block occurs in some patients with anterior crystalline lens subluxation and leads to an increase in intraocular pressure (IOP) and corneal decompensation may occur from crystalline lens-corneal endothelial contact.

Dietary and therapeutic aspects

A low methionine and high cysteine diet help in maintaining intellectual development in cases of homocystinuria. The introduction of dietary therapy is worthwhile at any age but may be costly for the Indian patient, as the commercially produced low methionine and high cysteine formulas may not be readily available. Therefore, team efforts (by pediatrician, nutritionist, ophthalmologist, and counselor) may be helpful to manage these children, and most of the time, one has to plan a special diet for patients, using locally available foods. These diets aim to provide 25–45 mg/kg/d of methionine in infants and 8–10 mg/kg/d of methionine in teenagers. Plasma levels of methionine are to be maintained between 0.03 and 0.1 mmol/L and cystine levels between 0.037 and 0.085 mmol/L.[9]

Supplementation with pyridoxine (50 to 1000 mg/day) results in a clinical and biochemical improvement in 50% of patients with homocystinuria. Vitamin B_6 nonresponders may benefit from a diet low in methionine and supplementation with cystine. Early detection and treatment using dietary restriction and vitamin supplementation in an Irish study of 14 patients by Burke *et al*.[5] resulted in the prevention of ectopia lentis after a mean follow-up of 8.2 years, compared with a 70% dislocation rate in untreated patients with a similar

follow-up period. Ectopia lentis developed and progressed in five patients diagnosed later in life, despite satisfactory biochemical control.

One of the largest management series of homocystinuria was reported from a study of 45 patients from Saudi Arabia.[4] A total of 84 ophthalmic surgical procedures were performed on 40 patients: 82 were done with general anesthesia and two with local anesthesia. Medical therapy was attempted initially in all patients with crystalline lens dislocation and was the sole therapy used for five patients. A total of 14 of the 45 patients (31%) were receiving dietary treatment at the time of presentation and 29 (64%) were mentally retarded. There were two surgical complications and one postoperative complication. Crystalline lens dislocation into the anterior chamber was the most frequent indication for the surgery (50%), followed by pupillary-block glaucoma (12%). Prophylactic Nd:YAG laser peripheral iridectomy was not successful in preventing crystalline lens dislocation into the anterior chamber in five patients. Anesthetic precautions, such as stockings to prevent deep venous thrombosis (DVT), preoperative hydration, or aspirin, were taken in 85% of cases. Other common ophthalmic complications included optic atrophy (23%), iris atrophy (21%), anterior staphylomas (13%), lenticular opacities (9%), and corneal opacities (9%). The authors of this series concluded that with the appropriate anesthetic precautions and modern microsurgical techniques, the risks associated with the surgical management of ocular complications of homocystinuria are reduced.

If the crystalline lens is in the anterior chamber, dilation of the pupil and gentle pressure over the cornea can lead to the repositioning of the crystalline lens behind the pupil. Patients are then administered 2% pilocarpine eye drop, and an Nd:YAG laser peripheral iridotomy is performed to prevent pupillary-block glaucoma. In the case of recurrent dislocations of the crystalline into the anterior chamber, a lensectomy should be performed. A primary lensectomy can also be performed. Prophylaxis of thromboembolic phenomena should be considered whenever these patients need general anesthesia. This should include a few weeks of supplementation with vitamin B_6 before surgery, good intravenous hydration before and during surgery, and dipyridamole or acetylsalicylic acid daily before and after surgery is performed.

Prenatal diagnosis and reducing the disease burden

Homocystinuria is a distressing disorder as it leads to mental retardation and visual impairment. There is a 25% risk of recurrence in each pregnancy. Prenatal diagnosis is possible by measuring cystathionine synthetase activity in cultured cells from chorionic villus biopsy at 10–12 weeks or amniocentesis at 15–18 weeks of gestation.[10] Therefore, early diagnosis is not only important for preventing visual and mental handicaps in the proband but also for preventing the birth of another affected child. This may eventually help in reducing the burden of this disease in the community.

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