Rare disease

First reported cases of gyrate atrophy of the choroid from Nepal

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Summary

Two sisters previously diagnosed as having retinitis pigmentosa presented with complaints of frequent change of glasses. On ocular examination, the fundus showed the appearance of confluent arcuate equatorial full thickness lesions of the choroid and retina, sparing some of the large choroidal vessels, and separated from one another by thin margins of pigment, in both the sisters. Serum analysis was done for ornithine levels, which showed hyperornithinaemia (741 and 462 $\mu\text{mol/l}$ in the elder and younger sister, respectively) consistent with gyrate atrophy (GA) of the choroid. Both the sisters were prescribed vitamin B₆ and a restricted protein diet to which they responded very well. This case highlights the importance of correct diagnosis and prompt management in diagnosed cases. These are the first reported cases of GA of choroid from Nepal.

BACKGROUND

Our case emphasises the need for correct diagnosis, family screening and early treatment in gyrate atrophy (GA) of the choroid as it slows down the progression of retinal degeneration and prevents complications of the disease. These are the first reported cases of GA of the choroid from Nepal.

CASE PRESENTATION

An 18-year-old girl (patient 1) presented to Dr N D Joshi Eye Department for a second opinion regarding the diagnosis of retinitis pigmentosa. She complained of frequent change of glasses for the past year. She was also diagnosed as having petit mal epilepsy, which was proven on EEG, and her CT

Figure 1 Fundus photograph of both the patients. (A,B) Right and left eye of patient 1. The arrows denote macular sparing with severe chorioretinal atrophic changes in the peripheral fundus. (C,D) Right and left eye of patient 2. The arrows denote confluent arcuate equatorial full-thickness lesions of the choroid and retina separated from one another by thin margins of pigment.

Figure 2 Automated perimetry of both patients. (A,B) Perimetry of left and right eye of patient 1. (C,D) Perimetry of left and right eye of patient 2. Both show constricted visual fields in both eyes.

scan was within normal limits (WNL). She had been taking sodium valproate and pentids for the past year. Her 15-year-old sister (patient 2) was subsequently examined. On ocular examination, best corrected visual acuity (BCVA) of patient 1 in the right eye (RE) was 20/60 with -9.25 D sph/ -1.0 D cyl at 180° and in the left eye (LE) was 20/60 with -8.0 D sph/ -1.5 D cyl at 170° . BCVA of patient 2 in the RE was 20/60 with -3.5 D sph/ -0.5 D cyl at 180° and in the LE 20/80 with -3.0 D sph/ -1.0 D cyl at 180° . External eye examination was WNL in both patients. Slit lamp examination revealed early posterior subcapsular cataract in each eye (OU) in both patients. Applanation tonometry revealed normal intraocular pressure (IOP) in both patients. Fundus examination after dilatation of the pupils OU in both the patients showed the appearance of confluent arcuate equatorial full-thickness lesions of the choroid and retina, sparing some of the larger choroidal vessels, and separated from

one another by thin margins of pigment (figure 1). Colour vision was WNL in both patients.

INVESTIGATIONS

Humphrey visual fields (central 30° -2 threshold test) showed constricted fields OU in both patients (figure 2). Blood samples of both the sisters were sent to the Department of Genetic Medicine, Sir Ganga Ram Hospital, New Delhi, for analysis from and then sent to Kurume University Pataou, Japan, for confirmation. The results for patient 1 and 2 showed significant increase in ornithine levels in the serum. The normal ornithine levels in the serum samples are 28 – 110 $\mu\text{mol/l}$. In patient 1 it was 741 $\mu\text{mol/l}$ (control 12 – 206) and in patient 2 it was 462 $\mu\text{mol/l}$ (control 12 – 206). There were no decreased levels of plasma creatine and creatinine; therefore, ruling out phosphocreatine deficiency. There was no associated hypoplasinaemia, hypoglutamic

acidaemia, hypoglutaminaemia and hypoammonaemia found in the patients. The pedigree of the patients showed an autosomal recessive inheritance pattern. The nephew of the sisters also had diminution of vision in both eyes and on ocular examination showed similar myopic astigmatism and ophthalmological changes; thus, confirming an autosomal recessive pattern.

DIFFERENTIAL DIAGNOSIS

Atypical retinitis pigmentosa

The diagnosis of GA can easily be made with certainty if the five most prominent features are present. These are typical gyrate retinal and choroidal lesions, early posterior subcapsular cataract, high myopia with marked astigmatism, hyperornithinaemia and autosomal recessive inheritance pattern.

Paving stone degeneration

Paving stone degeneration is usually found in the inferior quadrants peripherally, whereas GA is not segmental and involves all 360° of the fundus.¹

Extremely high myopia

Patients without GA with extremely high myopia (usually more than −15 D) may occasionally have posterior polar, peripapillary or peripheral clusters of round, full-thickness, chorioretinal atrophic lesions, often causing significant reduction in visual acuity. However, this is not the pattern of the lesions seen in GA.²

TREATMENT

The normalisation of ornithine levels as a primary therapeutic objective secondarily normalises all other metabolic parameters. This is done by administration of pharmacological doses of pyridoxine as GA is caused by a B₆-dependent enzyme. Treatment protocols have indicated doses ranging from 15–750 mg/day. The second approach is by arginine-reduced diet, which can be titrated to achieve desired plasma ornithine levels (0.5 g protein/kg/day). Both the patients were treated with restricted protein diet (25 g/day) and pyridoxine 40 mg four times a day and responded well to treatment.

OUTCOME AND FOLLOW-UP

The patients were followed up for 5 years and they showed no significant increase in retinal lesions but had developed significant posterior subcapsular cataract in both eyes over time. One of the patients with abnormal EEG significantly improved with treatment and presently does not require anticonvulsants.

DISCUSSION

This case emphasises the importance of correct diagnosis, family screening and early treatment in GA of the choroid as it slows down the progression of retinal degeneration and prevents complications of the disease. Human hereditary deficiency of ornithine aminotransferase activity is transmitted as an autosomal recessive trait,³ and results in a 10-fold to 20-fold increased level of plasma ornithine and is shown to be associated with GA.⁴ The initial complaint of decreasing visual acuity and night vision is followed by the

appearance of sharply demarcated, circular areas of chorioretinal atrophy with hyperpigmented margins in the mid periphery of the fundus. This appears through the first three decades of life and leads to blindness in the fourth to seventh decades. Myopia, posterior subcapsular cataracts and vitreous opacities may also be present.⁵ GA is a genetic disorder with increased frequency in the Finnish population with an incidence of one case per 50 000 individuals in Finland.⁵ Valle and Simell in a review in 2001 revealed that among over 150 biochemically documented cases of GA, about one-third of them were from Finland and only 7 of them (less than 5%) had been responsive to treatment with vitamin B₆ dietary supplementation.⁶ We report rare cases of GA, in which the patient's high level of serum ornithine was responsive to treatment with a vitamin B₆ dietary supplement. Weleber and Kennaway in a clinical trial of vitamin B₆ for GA reported that three out of seven patients responded to oral B₆ supplementation with over 50% reduction of serum ornithine.⁷ Among approximately 70 Finnish GA cases reported to date, none has been responsive to vitamin B₆.⁸ Of the remaining studies reported worldwide (from USA, Canada, Japan, Italy, Germany, The Netherlands and Israel) only seven have been reported to have responded to vitamin B₆ treatment.⁹

McCulloch and Marliss demonstrated that ornithine was being released from many organ systems and suggested multisystem involvement.¹⁰ Takki first reported that abnormal EEG recordings and borderline low intellectual function were common in GA.¹¹ One of our patients also had abnormal EEG with no muscle wasting; thus, favouring multisystem involvement in GA of the choroid. Long-term treatment with certain anticonvulsants (phenytoin, succinimide) cause reduced plasma levels of pyridoxine,¹² but our patient was on sodium valproate which itself does not cause pyridoxine deficiency. Our patients fulfil the diagnostic criteria of GA of the choroid, which include: typical gyrate retinal and choroidal lesions, early cataract, high myopia with marked astigmatism, hyperornithinaemia and autosomal recessive inheritance pattern.

The visual fields coincide fairly well with the remaining area of healthy appearing retina (about 15–50°) with an enlarged blind spot corresponding to the peripapillary lesion if present. Our patients showed constricted visual fields in both their eyes. GA of the choroid has been reported in patients around the world of different ethnic origin.^{13 14} Our patients belong to a Thakali community (one of the ethnic groups in Nepal). The proposed treatment for GA is to correct one or more metabolic alterations like hyperornithinaemia, creatine deficiency, lysine deficiency and P5C/proline deficiency. The administration of pharmacological doses of pyridoxine in a disorder caused by decreased activity of a B₆-dependent enzyme is an established procedure.¹⁵ The advantage of pyridoxine supplementation is that it is an easy treatment and, consequently, patient compliance is good. In addition, Weleber and co-workers reported that B₆-responsive patients typically have a milder course of disease compared to B₆ non-responsive patient in terms of visual function as well as less extensive lesions.¹⁶ By controlling the arginine intake in the diet, a desired plasma ornithine level can be achieved. One protocol called for 0.5 g protein/kg/day with 0.3–0.5 g Essential Amino Acids (EAA)/kg/day.¹⁷ The major reported

risk in arginine-restriction treatment is that if the arginine restriction is carried to excess, both arginine and ornithine levels may become depleted with resultant impairment of urea cycle function and consequent hyperammonaemia.¹⁸ Both our patients responded well to pyridoxine intake and tolerated a restricted protein diet. Correction of lysine deficiency, creatine deficiency and proline deficiency is also recommended but clinical results of such treatment over the long-term are needed.

Learning points

- ▶ Early diagnosis and treatment of GA of the choroid prevents the visual and life-threatening complications of disease.
- ▶ Confusion in diagnosis is primarily due to the rarity of the disease. Correct clinical diagnosis with confirmation by biochemical investigations of this rare disease should be done.
- ▶ Screening of the family members is important as GA of the choroid follows an autosomal recessive inheritance pattern.

Competing interests None.

Patient consent Obtained.

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