

Gyrate Atrophy of the Choroid: Two Cases

A C S W How,*^{MBBS}, A H C Koh,**^{MBBS, M Med (Ophth), FRCS (Edin)}

Abstract

Introduction: Gyrate atrophy of the choroid (GA) is a rare, inherited choroidal dystrophy that results in progressive deterioration in peripheral and night vision. This is the first documentation of GA in Singapore. **Clinical Picture:** This report illustrates 2 cases of a sibling pair from a consanguineous union, presenting with the classical clinical features and biochemical abnormality of this condition. **Treatment and Outcome:** One patient was treated with pyridoxine replacement and a low protein diet. However, his condition failed to improve. The other patient was left untreated. **Conclusion:** Treatment was ineffective for the first patient. As yet, there is no proven treatment of GA.

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Key words: Autosomal recessive, Chorioretinal atrophy, Hyperornithinemia, Nyctalopia, Retinal dystrophy

Introduction

Gyrate atrophy of the choroid (GA) is a rare choroidal dystrophy. It is an autosomal recessive disorder that results in progressive deterioration in peripheral and night vision. The main biochemical abnormality is hyperornithinemia 10 to 15-fold above normal, secondary to a deficiency in the enzyme ornithine-d-aminotransferase (OAT).¹ It is thus an inborn error of metabolism resulting in metabolic derangement in the retinal pigment epithelium. This report illustrates 2 cases of a sibling pair from a consanguineous union with this condition. GA has been widely reported in the Western countries as well as a few reported cases in Japan and India.²⁻⁴ To our knowledge, this is the first documentation of GA in Singapore and Southeast Asia. The clinical features, the biochemical abnormality, its inheritance and the treatment will be presented.

Case Report

The first patient is a young, healthy 24-year-old Malay male who presented with a 1-year history of poor night vision. He has a family history of consanguinity, as his parents are distant cousins. His best-corrected visual acuity was 6/36 in both eyes.

Slit lamp examination of the anterior segment of the eye was unremarkable. The lens was clear and the main abnormality was found on fundal examination. Epiretinal membranes were noted over the macula in both eyes (Fig. 1a). There were sharply demarcated confluent areas of chorioretinal atrophy in a typical scalloped fashion in the

mid-periphery of both fundi with vascular attenuation (Fig. 1b). Manifest refraction showed high myopia of -7 spherical diopters in the right eye and -8 spherical diopters in the left eye.

Blood investigations revealed plasma ornithine levels to be 1046 $\mu\text{mol/L}$ (11 times the upper limit of normal). He was put on pyridoxine replacement 1000 U/day as well as a low protein diet. A review 9 months later showed a mild improvement in the ornithine levels (925 $\mu\text{mol/L}$). No progression of the chorioretinal atrophy was seen over a 3-year period. He subsequently defaulted follow-up.

The second patient is the 19-year-old sister of the first patient. She was diagnosed when the family members of the first patient were screened for GA. She was asymptomatic and her best-corrected visual acuity was 6/6 in both eyes. Similar to her brother, she had myopia of -6 spherical dioptres in the right eye and -5.5 spherical dioptres in the left eye. In contrast to her brother, her lesions were less extensive, with the maculae unaffected (Fig. 2a). Fundal examination showed the classical scalloped areas of chorioretinal atrophy of GA in the periphery (Fig. 2b). Plasma ornithine levels were up 10-fold to 850 $\mu\text{mol/L}$. She was not treated and also subsequently defaulted follow-up.

Discussion

Gyrate atrophy of the choroid is a rare condition and the number of reported cases around the world has not been more than a few hundred. In most of these cases, the

* Resident

** Consultant, Vitreo-retina Service
Singapore National Eye Centre

Address for Reprints: Dr Adrian Koh, Singapore National Eye Centre, 11 Third Hospital Avenue, Singapore 168751.

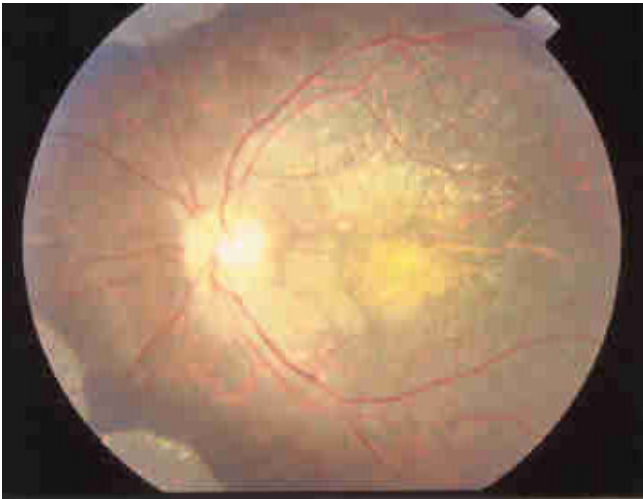


Fig. 1a. Left macula of the first patient.

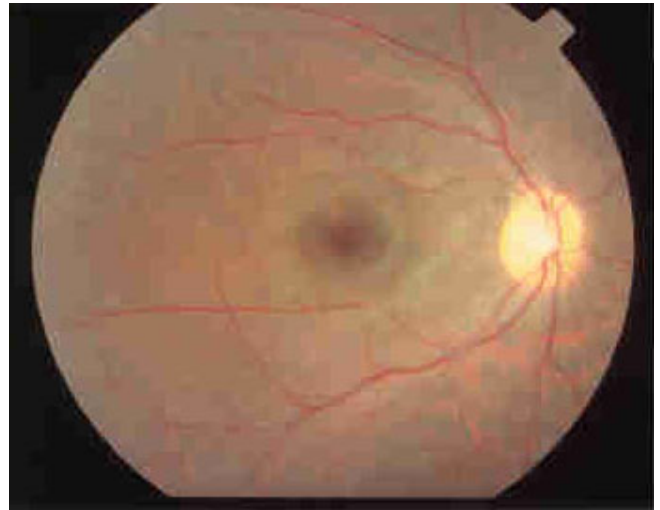


Fig. 2a. Right macula of the second patient.

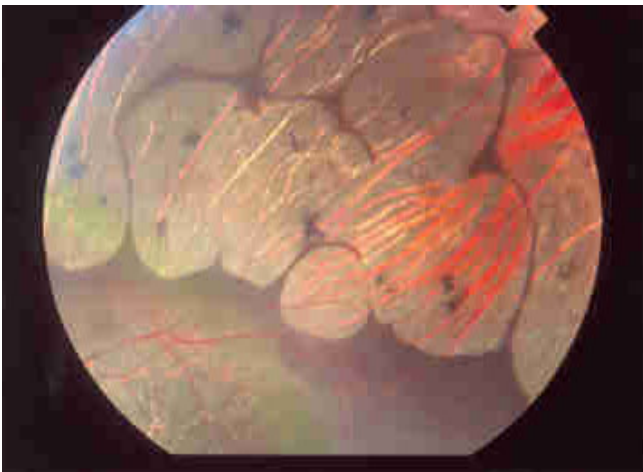


Fig. 1b. Left superior retina of the first patient.

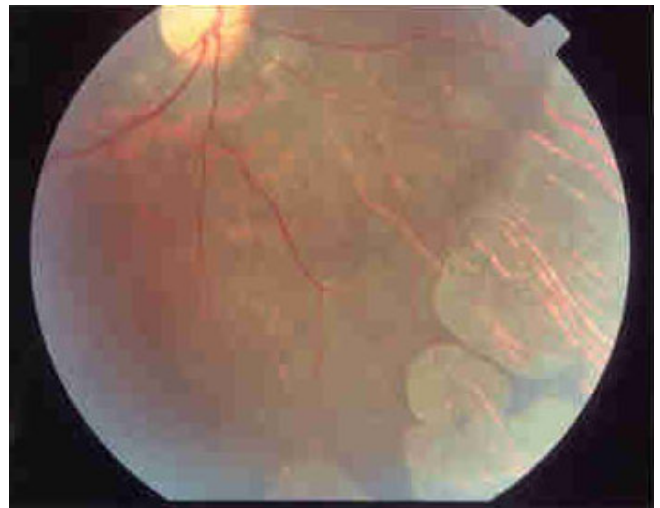


Fig. 2b. Right inferior retina of the second patient.

patients reside in Finland. This is postulated to be due to the genetic composition in a relatively isolated country. GA is caused by a mutation in the OAT gene, which has been mapped to locus 10q26.⁵ Our two case subjects are children from a consanguineous union, consistent with its autosomal recessive inheritance. Their parents, who are both Indian Muslims, are cousins.

The case report demonstrates classical clinical as well as biochemical features of GA. The fundal examination is typical of GA and the patients illustrate the spectrum of disease in a younger and older patient. The second patient has a less severe form of the disease as compared to her brother. GA patients usually present with night blindness in late childhood, as in the first patient. High myopia is also a common association, as in both patients.³ Posterior subcapsular cataracts develop in the late twenties. As yet, both our patients did not manifest lens opacities.

The natural course of the disease is slow and with increasing age, the areas of chorioretinal atrophy enlarge and eventually involve the posterior pole, resulting in constriction of peripheral visual field and nyctalopia to visual loss by the fourth to seventh decade. Some studies have shown a more rapid progression in younger patients.^{6,7} Although both our patients are relatively young, rapid progression of the disease has not been seen in the first patient. Currently the first patient has maintained borderline low vision due to the changes at the macula. Macular abnormalities such as pigmentary dystrophy and atrophy have been described in other reports.⁶⁻⁸ Takki and Milton⁷ found macular changes present in 30% of the patients at the age of 20 years and 60% at the age of 30 years. The macula in the second patient was normal.

OAT is a pyridoxal phosphate-dependent mitochondria

matrix enzyme that is expressed in the kidney, small intestine, liver and retina. However, its metabolic functions are not well understood. This, in addition to the small numbers of patients with GA and its slow and variable rate of progression, makes the development of effective therapy of GA difficult. As yet, there have been a few proposed treatments, which aim to correct the biochemical abnormalities in GA. One such treatment is pyridoxine supplementation. This effectively reduces the plasma ornithine levels in patients who have OAT alleles with mutations affecting the pyridoxine binding site of the enzyme.⁹ However, the long-term consequences of pyridoxine are still unknown and as yet, this form of treatment has been unable to halt the progression of GA.¹⁰ There was no improvement in visual function despite therapy and lowering of serum ornithine levels in the first patient.

In patients with GA, ornithine is derived from arginine. Thus an arginine-restricted diet has been shown to reduce plasma ornithine levels. Several studies have shown conflicting results with regard to an arginine restricted diet and progression of GA.¹¹⁻¹⁴

The pathogenesis of GA has been postulated to be due to deficient creatine and creatine phosphate formation; however, creatine supplementation has not been shown to be able to slow the progression of GA.¹⁵

Conclusion

In conclusion, current treatment techniques have been unable to replace areas of chorioretinal atrophy with healthy retina. Treatment regimens can only hope to prevent further progression of the disease. Genetic analysis may help identify suitable candidates for successful pyridoxine treatment. Ultimately, gene therapy to correct the underlying genetic mutation may prove to be curative.

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REFERENCES

1. Simell O, Takki K. Raised plasma ornithine and gyrate atrophy of the choroid and retina. *Lancet* 1973; 1:1031-3.
2. Verma L, Murthy H, Tewari H K, Khosla P K. Gyrate atrophy of the choroid and retina. *Indian J Ophthalmol* 1989; 37:143-5.
3. Shenoi A L N, Christopher R. Hyperornithinemia associated with gyrate atrophy of the choroid and retina in a child with myopia. *Indian Pediatr* 2001; 38:914-8.
4. Takashi O, Hayasaka S, Kiyosawa M, Mizuno K, Saito T, Tada K, et al. Gyrate atrophy of choroid and retina complicated by vitreous hemorrhage. *Jpn J Ophthalmol* 1985; 29:170-6.
5. Barrett D J, Bateman J B, Sparkes R S, Mohandas T, Klisak I, Inana G. Chromosomal localization of human ornithine aminotransferase gene sequences to 10q26 and Xp11.2. *Invest Ophthalmol Vis Sci* 1987; 28:1037-42.
6. Berson E L, Schmidt S Y, Shih V E. Ocular and biochemical abnormalities in gyrate atrophy of the choroid and retina. *Ophthalmology* 1978; 85:1018-27.
7. Takki K, Milton R. The natural history of gyrate atrophy of the choroid and retina. *Ophthalmology* 1981; 88:292-301.
8. Deutman A F, Sengers R C A, Trybels J M F. Gyrate atrophy of the choroid and retina with reticular pigmentary dystrophy and ornithine-ketoacid-transaminase deficiency. *Intl Ophthalmol* 1978; 1:49-56.
9. Weleber R G, Kennaway N G. Clinical trial of vitamin B6 for gyrate atrophy of the choroid and retina. *Ophthalmology* 1981; 88:316-24.
10. Hayasaka S, Saito T, Nakajima H, Takahashi O, Mizuno K, Tada K. Clinical trials of vitamin B6 and proline supplementation for gyrate atrophy of the choroid and retina. *Br J Ophthalmol* 1985; 69:283-90.
11. Kaiser-Kupfer M I, Caruso R C, Valle D. Gyrate atrophy of the choroid and retina: further experience with long-term reduction of ornithine levels in children. *Arch Ophthalmol* 2002; 120:146-53.
12. Berson E L, Shih V E, Sullivan P L. Ocular findings in patients with gyrate atrophy on pyridoxine, low-protein, low-arginine diets. *Ophthalmology* 1981; 88:311-5.
13. McInnes R R, Arshinoff S A, Bell L, Marliss E B, McCulloch J C. Hyperornithinemia and gyrate atrophy of the retina: improvement of vision during treatment with a low-arginine diet. *Lancet* 1981; 1:513-6.
14. Wang T, Steel G, Milam A H, Valle D. Correction of ornithine accumulation prevents retinal degeneration in a mouse model of gyrate atrophy of the choroid and retina. *Proc Natl Acad Sci U S A* 2000; 97:1224-9.
15. Vannas-Sulonen K, Sipila I, Vannas A, Simell O, Rapola J. Gyrate atrophy of the choroid and retina. A five-year follow-up of creatine supplementation. *Ophthalmology* 1985; 92:1719-27.