Gyrate atrophy of the choroid and retina: a case report

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Gyrate atrophy is a rare metabolic disease characterized by hyperornithinemia, typical retinal and choroidal lesions, high myopia with marked astigmatism, early cataract formation, and autosomal recessive inheritance pattern. In this paper, we describe a 12-year-old boy presenting with high myopia and gyrate fundus lesions, in addition to 10-times elevated serum ornithine level.

Key words: gyrate atrophy, hyperornithinemia.

Gyrate atrophy (GA) is a rare, progressive metabolic choroidal and retinal degeneration resulting from deficiency of the pyridoxal phosphate-dependent mitochondrial matrix enzyme ornithine aminotransferase (OAT) mapped on chromosome 10q26. It is a very rare disease, in such manner that until 2001, only approximately 150 biochemically documented cases have been reported, with about one-third being from Finland[1]. GA is characterized by hyperornithinemia, typical retinal and choroidal lesions, high myopia with marked astigmatism, early cataract formation, and autosomal recessive inheritance pattern. Here, we report a biochemically confirmed case of GA[2].

Case Report

A 12-year-old boy presented with near-sightedness. Best corrected vision was 9/10 in both eyes with a refractive error of -4.00 (-1.50 at 20º) and -4.00 (-1.50 at 180º) on the right and left eyes, respectively. Biomicroscopic examination revealed normal anterior segment findings. Fundus examination revealed bilateral sharply defined, scalloped retina pigment epithelium (RPE) and choroidal atrophy areas in the midperipheral zone, resembling brain gyri (Figs. 1, 2). There was consanguinity between the parents, as first-degree cousins. Ocular findings in the parents, the elder brother, and five of the accessible close relatives were within normal limits. The medical history of our patient disclosed another brother who had mental retardation, nystagmus, astigmatism, and retinal dystrophy of unknown type and who died at the age of 5 years. Our patient's sister had a history of strabismus surgery and her refractive status was hypermetropic astigmatism. Her fundus examination revealed granular, pigmentary mottling in the midperiphery, with punctuate hypopigmentation and hyperpigmentation (Fig. 3). These findings were consistent with the appearance of "salt-and-pepper" retinopathy, but not typical for GA.

Although routine laboratory findings of our patient were within normal range, his plasma ornithine level was 747 nmol/ml, approximately 10 times the normal value (10-163 nmol/ml). Plasma ornithine level was 92.5 nmol/ml in his sister. Upon the diagnosis of GA, an arginine-free diet was recommended in addition to the oral creatine 1 g/day and pyridoxine 400 mg/day supplement. After six months of this treatment regimen, plasma ornithine level was measured as 370 nmol/ml with a 50% decrease from baseline, and ocular findings were found to have stabilized in the follow-up period.

Discussion

Ornithine is a dibasic amino acid that is not normally found in proteins. However, it plays an important role in the metabolism of urea, creatinine and polyamines and in the exchange

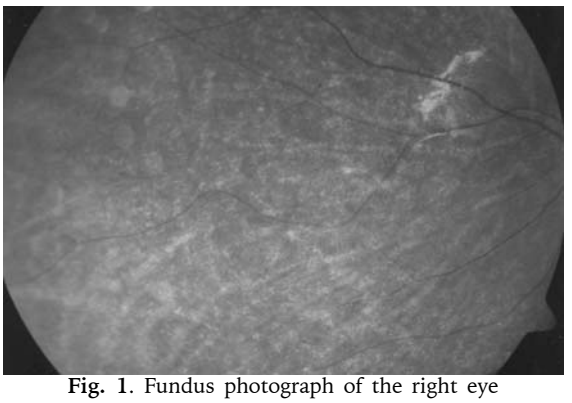

Fig. 1. Fundus photograph of the right eye demonstrating sharply defined, scalloped retina pigment epithelium and choroidal atrophy areas in the midperipheral zone.

of molecules between the urea and Krebs cycles. It is synthesized from arginine, and then participates in the synthesis of proline, glutamate and other alpha ketoglutarate-derived nonessential amino acids. Ornithine is reversibly transaminated with ketoglutarate to delta 1-pyrroline 5-carboxylic acid and glutamic acid by OAT. OAT is expressed in most tissues, including the kidney, small intestine, liver, and retina. OAT activity is reported to be high in the cell layer external to the photoreceptors in the retinal pigment epithelium.

The biochemical mechanism of the chorioretinal degeneration in GA is either the deficiency of essential products or toxicity of the accumulated excessive substrates. The proposed hypotheses for GA are hyperornithinemia, phosphocreatine deficiency, delta 1 pyrrolidine 5 carboxylate/ proline deficiency, and excess decarboxylation products (polyamines) [2]. In GA, gradual visual loss usually starts around the age of 10, and visual field constriction eventually ends in blindness in the fourth or fifth decade. Other systemic abnormalities in GA are borderline low intellectual activity, mild proximal muscle weakness, peculiar, sparse scalp hair with areas of alopecia, and bizarre elongated segmented mitochondria in liver biopsies.

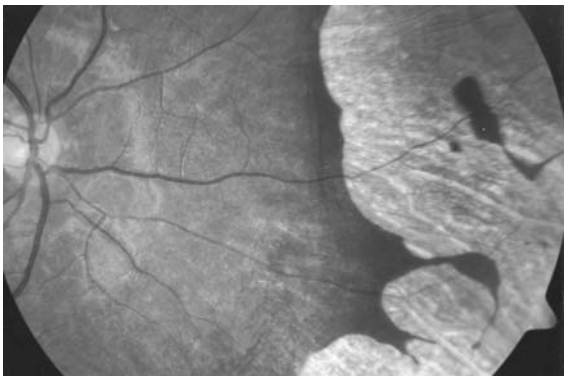

Fig 2. Fundus photograph of the left eye demonstrating sharply defined, scalloped retina pigment epithelium and choroidal atrophy areas in the midperipheral zone.

Our patient was 12 years old when he first presented with GA. On initial examination, his vision was fairly good with a moderate myopic astigmatism correction. He had the typical gyrate lesions on ophthalmoscopy and his ornithine level was approximately 10 times the normal value. However, the sister's findings were not consistent with GA. In addition to a normal ornithine level, she had a salt-and-pepper appearance instead of typical GA lesions. In a study of two sibling pairs with genetically confirmed GA, it was reported that the younger siblings had both mottling of RPE and small depigmented spots but no areas of atrophy, with ornithine levels slightly elevated in one and borderline in the other. Those younger siblings were also put on an arginine-free diet at an early age and substantially were found to have reduced ornithine levels and slow progression of the disease[3]. We performed a genetic analysis in the younger sibling of our patient to investigate whether her fundus lesions with salt-and-pepper appearance resembled an early phase of GA or whether they have a different origin; however, the results are pending.

In the treatment of GA, a low-protein diet, but sufficient for normal growth, is recommended. An arginine-free diet, if strictly obeyed, may decrease ornithine to normal levels but only 20% of patients are reported to tolerate this diet[4]. Lysine supplement may competitively inhibit the renal absorption of ornithine and arginine, and improve the effect of the arginine- free diet[5]. Since ornithine inhibits L-arginine-glycine aminotransferase enzyme in the synthesis of creatine, creatine supplement is also given in order to prevent muscle weakness but it does not improve ocular findings[6]. Pyridoxine hydrochloride (vitamin B6) is also recommended; however, only 5% of patients are responsive to vitamin B6. There is clinical heterogeneity in vitamin B6

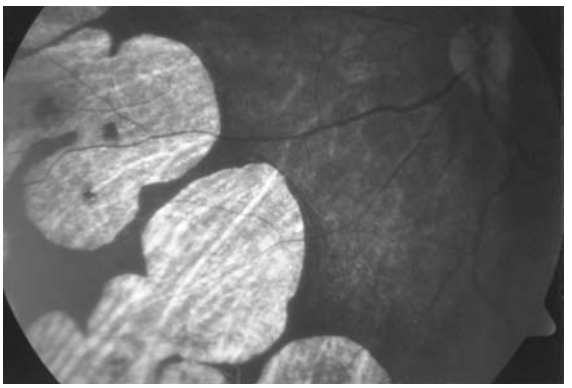

Fig. 3. Fundus photograph of our patient's sister with granular, pigmentary mottling in the midperipheral zone.

responsiveness, the amount of residual enzyme activity and severity of disease because of the variety of OAT mutations with a high degree of genetic heterogeneity in GA patients[7]. Enzyme replacement and gene therapy are the promising treatment possibilities for GA[8,9]. The plasma ornithine level of our patient showed an approximately 50% decrease after receiving a supplement of pyridoxine 400 mg/day and creatine 1 g/day accompanied with a low-protein diet.

In conclusion, since GA is one of the rare detainable retinal degenerations once diagnosed, both pediatricians and ophthalmologists should be aware of the importance of retinal examination, especially in high myopic children, and the value of routine fundus examination in refractive patients is revealed once again with this report.

REFERENCES

1. Valle D, Simell O, Scriver CR, Beaudet AL, Sly WS. The hyperornithinemias. In: Scriver CR, Beaudet AL, Sly WS (eds). The Metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill; 2001: 1875–1895.
2. Arshinoff SA, Leung K, Strube YN. Gyrate atrophy. In: William Tasman (ed). Duane's Clinical Ophthalmology. Philadelphia: Lippincott Williams & Wilkins; 2005.
3. Kaiser-Kupfer MI, Caruso RC, Valle D. Gyrate atrophy of the choroid and retina: further experience with long-term reduction of ornithine levels in children. Arch Ophthalmol 2002; 120: 146-153.
4. Valle D, Walser M, Brusilow S, Kaiser-Kupfer MI, Takki K. Gyrate atrophy of the choroid and retina: biochemical considerations and experience with an arginine restricted diet. Ophthalmology 1981; 88: 325-330.
5. Elpeleg ON, Korman SH. Sustained oral lysine supplementation in ornithine d-aminotransferase deficiency. J Inherit Metab Dis 2001; 24: 423-424.
6. 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: 1719-1727.
7. Hayasaka S, Saito T, Nakajima H. Gyrate atrophy with hyperornithinemia: different types of responsiveness to vitamin B6. Br J Ophthalmol 1982; 65: 478-483.
8. Weleber RG, Kennaway NG, Buist NR. Gyrate atrophy of the choroid and retina: approaches to therapy. Int Ophthalmol 1981; 4: 23.
9. Inana G, Totsuka S, Zintz C, et al. Molecular genetics of gyrate atrophy. Prog Clin Biol Res 1987; 247: 163.