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Case Report

# Gyrate Atrophy of the Choroid and Retina Diagnosed by Ornithine-δ-aminotransferase Gene Analysis: A Case Report

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A pair of 19-year-old female identical twins was referred to our hospital with progressive visual loss. They exhibited bilateral chorioretinal atrophy involving the midperiphery on fundoscopy and fluorescein angiography. Bilateral visual field constriction was noted on dynamic Goldmann perimetry, and a markedly impaired response was observed on both photopic and scotopic electroretinograms. Cystoid macular edema was identified in both eyes on optical coherence tomography. Plasma levels of ornithine were elevated. Based on these observations, the patients were diagnosed with gyrate atrophy of the choroid and retina. The clinical diagnosis was confirmed by mutation analysis of the ornithine-δ-aminotransferase (OAT) gene. Patients were treated with a pyridoxine supplement (300 mg/day) and an arginine-restricted diet to lower plasma levels of ornithine, which were successfully reduced without progression of chorioretinal atrophy for 15 months. Our report describes the first case of gyrate atrophy in the Korean population diagnosed by OAT gene analysis and treated with vitamin B6 dietary supplementation.

**Key Words:** Gene mutation, Gyrate atrophy, Hyperornithinemia, Ornithine-δ-aminotransferase deficiency, Pyridoxine

Gyrate atrophy (GA) of the fundus is a rare autosomal recessive disease characterized by deficiency of ornithine-δ-aminotransferase (OAT). OAT deficiency causes hyperornithinemia, which results in progressive chorioretinal atrophy [1]. To date, dozens of mutations in the OAT gene locus have been identified [2-4], and thus OAT gene analysis is helpful for diagnosing patients with suspected GA. To the best of our knowledge, this is the first report of GA in the Korean population diagnosed by OAT genetic analysis.

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## Case Report

A pair of 19-year-old female identical twins presented with complaints of gradual visual loss and progressive night vision deterioration occurring over the past several years. The older twin's best-corrected visual acuity (BCVA) was 20 / 32 in both eyes. The refractive error was -17.75 diopter (D) in the right eye and -17.25 D in the left eye. She had bilateral posterior subcapsular cataracts. On examination, her fundus exhibited bilateral severe chorioretinal atrophy involving the midperiphery (Fig. 1A and 1B). Fundus fluorescein angiography revealed leakage at the margin of chorioretinal atrophy and dye accumulation in the maculae of both eyes (Fig. 1C and 1D). Disclosed cystoid macular edema was evident in both eyes on optical coherence tomography (Fig. 1E and 1F). Dynamic Goldmann perimetry demonstrated visual field constriction in both eyes, and a full-field electroretinogram showed markedly impaired photopic and scotopic responses. On plasma

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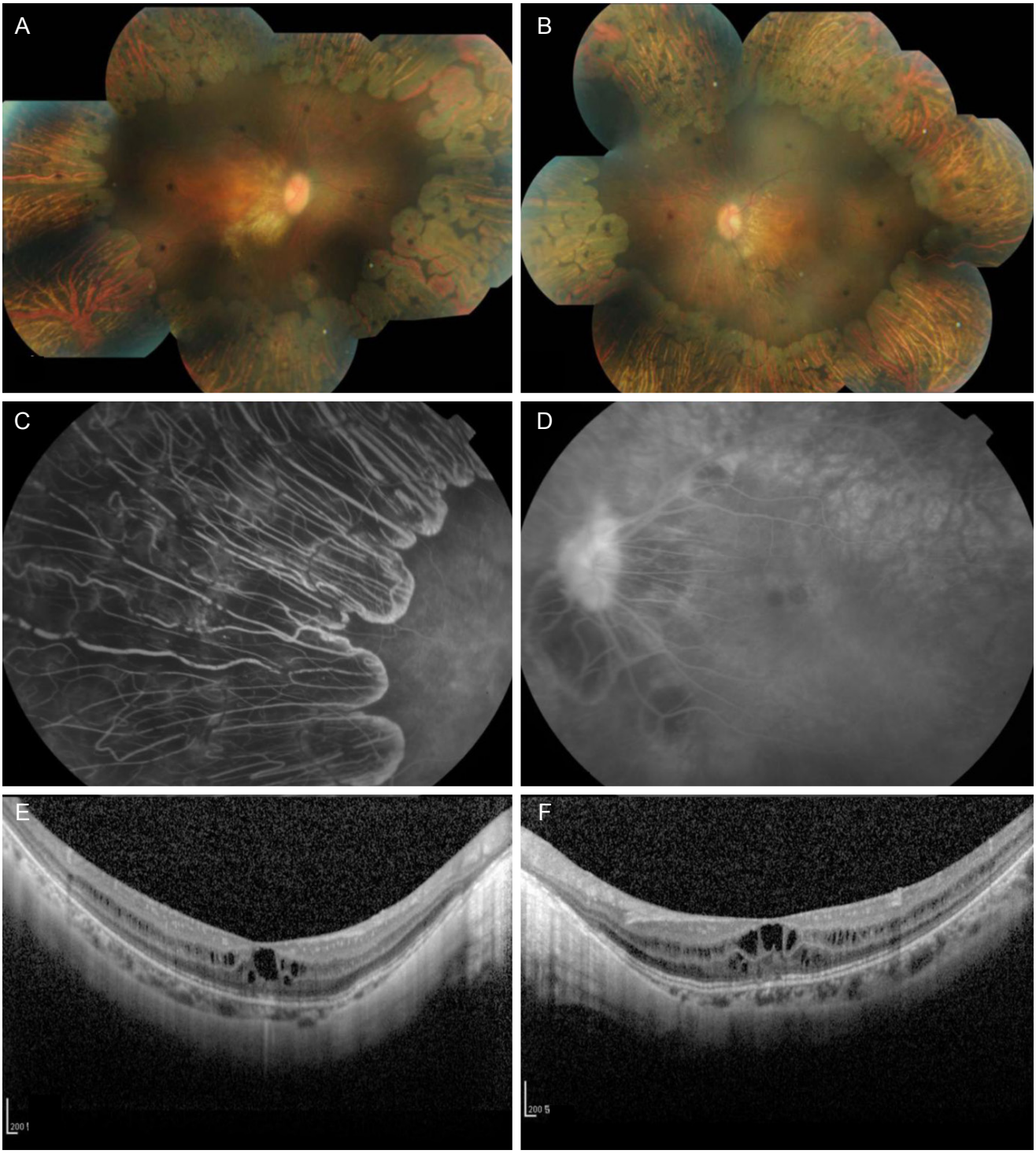


**Fig. 1.** Panoramic fundus photography, fluorescein angiography, and optical coherence tomography images in both eyes of the older twin. (A,B) The images show coalescent, scalloped chorioretinal atrophy with well-circumscribed, hyperpigmented margins in the midperiphery of the retina and chorioretinal atrophy of the peripapillary area. (C) Fundus fluorescein angiography in the peripheral retina of the right eye exhibiting slight leakage at the margin of chorioretinal atrophy and hyperfluorescence within the atrophic lesion. (D) Fundus fluorescein angiography of the left eye showing minimal leakage and dye accumulation in the macula. (E,F) Optical coherence tomography in both eyes showing a thickened macula simulating cystoid macular edema.

amino acid analysis, she had markedly elevated plasma levels of ornithine (783 μmol/L; normal range, 48 to 195 μmol/L). Screening for inherited metabolic disorder by tandem mass spectrometry (MS/MS) revealed plasma ornithine levels of 380 μmol/L (cutoff, 290 μmol/L).

The younger twin's BCVA was 20 / 25 in the right eye and 20 / 32 in the left eye. The refractive error was -17.0 D in the right eye and -16.0 D in the left eye. Her fundoscopy, fluorescein angiography, optical coherence tomography, Goldmann perimetry and full-field electroretinogram findings were similar to those of her older twin. Accordingly, her plasma levels of ornithine on amino acids analysis and MS/MS were 831 μmol/L and 424 μmol/L, respectively.

The clinical diagnosis of both patients was consistent with OAT deficiency and GA of the choroid and retina. OAT gene analysis resulted in the detection of two mutations in both patients: c.425G>A, a known mutation, and c.199+11_199+16dupAATTAA, a previously unclassified mutation. Both patients were treated with vitamin B6 (pyridoxine) 300 mg daily and an arginine-restricted diet. After three months of treatment, plasma ornithine levels as measured by MS/MS were 254 μmol/L in the older twin and 365 μmol/L in the younger twin. Their visual acuities in each eye were preserved with no progression of chorioretinal atrophy on fundoscopy after 15 months, and the plasma ornithine levels were controlled at 386 μmol/L and 408 μmol/L, respectively.

## Discussion

Patients with GA initially complain of decreasing visual acuity and loss of night vision [1]. Eventually, loss of central vision occurs in the fourth to fifth decades [5]. The fundus in patients with GA exhibits circular, well demarcated chorioretinal atrophy with hyperpigmented margins in the midperiphery [1]. Patients with GA may also have myopia and posterior subcapsular cataracts [1]. Usually the fundus finding of scalloped chorioretinal atrophy in the midperiphery is sufficiently characteristic to determine GA. Advanced choroideremia with generalized atrophy of the retinal pigment epithelium and choriocapillaris may be confused. Choroideremia is an X-linked disorder and the macula may be involved earlier than GA. The other differential diagnosis includes diffuse choriocapillaris atrophy, generalized choroidal dystrophy and central areolar choroidal dystrophy. Plasma ornithine levels help to confirm GA. GA is a genetic disorder caused by OAT deficiency that results in markedly elevated levels of ornithine in plasma and other body fluids [5]. The exact mechanism of chorioretinal atrophy due to hyperornithinemia is not known, although a low-arginine diet and vitamin B6 supplementation may decrease plasma ornithine levels and reduce the progression of GA [6]. However, the long-term effects of this treatment approach have not been completely evaluated.

More than 60 different mutations in the OAT gene locus have been identified [2-4]. In this report, two gene mutations were detected by OAT gene mutation analysis in both patients. Genomic DNA was extracted from the peripheral blood leukocytes of both patients by using the Wizard Genomic DNA Purification Kit according to the manufacturer's instructions (Promega, Madison, WI, USA). All exons of the OAT gene were amplified by polymerase chain reaction (PCR) on a thermal cycler (Applied Biosystems, Foster City, CA, USA) with primer pairs designed by the authors. Direct sequencing was performed with the BigDye Terminator Cycle Sequencing Ready Reaction kit on an ABI Prism 3130 Genetic Analyzer (Applied Biosystems). The sequences were analyzed using the Sequencher program (Gene Codes Corp., Ann Arbor, MI, USA) and were compared to the reference sequences. The numbering of nucleotide positions was done according to the ACADM cDNA sequence, and the GenBank accession number was NM 000274.3. Sequence variation was described according to the recommendations of the Human Genome Variation Society (http://www.hgvs.org/mutnomen). These were c.425G>A, a known mutation, as well as c.199+11_199+16dup AATTAA, a previously unclassified mutation. Further evaluation including a large controlled study or family study is necessary to confirm whether c.199+11_199+16dupAATTAA is an actual mutation rather than a polymorphism. Reverse transcriptase PCR (RT-PCR) analysis may be helpful in clarifying this issue; however, the likelihood that c.199+11_199+ 16dupAATTAA is a mutation is quite high considering the autosomal recessive pattern of inheritance of the OAT gene.

Patients with GA generally present with decreased night vision and high myopia during their adolescence, and early diagnosis in these patients allows for early treatment. Indeed, OAT gene studies in children with a high degree of myopia, especially in cases in which there is a complaint of

nyctalopia, would be helpful for early identification. To the best of our knowledge, this is the first report of GA in the Korean population diagnosed by OAT genetic analysis and treated with vitamin B6 dietary supplementation.

## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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