

Cystoid macular edema resolution following arginine-restricted diet and vitamin B6 supplementation in a case of gyrate atrophy from Italy

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We report the outcome of 3 years of arginine-restricted diet and vitamin B6 supplementation in a boy who presented with gyrate atrophy of the choroid and retina and bilateral cystoid macular edema. The diagnosis of gyrate atrophy was made on the basis of clinical findings and increased plasma ornithine levels. Molecular genetic testing revealed a disease-causing homozygous mutation in the ornithine aminotransferase (*OAT*) gene. After 3 months of dietary modification and pyridoxine supplementation, visual acuity improved, and optical coherence tomography showed resolution of cystoid macular edema in both eyes. This anatomical and functional improvement was maintained during 3 years of follow-up.

Gyrate atrophy (GA) of the choroid and retina is an extremely rare progressive chorioretinal dystrophy inherited in an autosomal recessive manner and associated with significantly increased plasma ornithine levels due to a deficiency of the vitamin B6-dependent enzyme ornithine aminotransferase (OAT).¹ The clinical presentation and the severity of this condition vary widely, especially in terms of visual function²; however, circumferential chorioretinal atrophy in the peripheral retina along with nyctalopia, myopia, early cataract, and markedly reduced responses to nonrecordable electroretinography represent typical features of GA.² Cystoid macular edema (CME) detected by spectral domain optical coherence tomography (SD-OCT) is also a common finding along with a relatively thick fovea in early stages of disease.³

In patients with GA the arginine-restricted diet has been shown to effectively decrease the plasma ornithine levels and slow the long-term progression of chorioretinal lesions and deterioration of visual function.⁴ Some studies have shown decreased plasma ornithine levels after pyridoxine (vitamin B6) supplementation in patients with GA⁵; however, there is currently no definite evidence that pyridoxine supplementation affects the disease course and the visual function of patients with GA. Moreover, no proven treatment for CME

complicating GA is available. We report the 3-year outcome of arginine-restricted diet and vitamin B6 supplementation in a boy presenting with GA of the choroid and retina and bilateral CME.

Case Report

An 8-year-old boy was referred to San Raffaele Scientific Institute for evaluation of a possible retinal dystrophy. He complained of difficulty reading at school. He had a clinical history of failure to thrive, which was treated with somatotropin (growth hormone). Family history was unremarkable for retinal disease. On examination, best-corrected visual acuity was 20/40 with refraction of $-6.75 -2.50 \times 170$ in the right eye and 20/40 with refraction of $-6.50 -3.25 \times 180$ in the left eye. He had normal color vision in both eyes and no metamorphopsia. Fundus examination showed patches of circumferential chorioretinal atrophy in the peripheral retina of both eyes (Figure 1). SD-OCT revealed bilateral foveal-involving CME (Figure 2). Full-field electroretinography revealed abolished responses in both eyes.

A blood sample was obtained and serum ornithine level was 582 $\mu\text{mol/l}$ (normal level, 25.7–92.3 $\mu\text{mol/l}$), which was consistent with the diagnosis of GA. Molecular genetic testing identified a previously reported homozygous mutation in the *OAT* gene (c.1307T>A, c.1307T>A [p.Ile436Asn, p.Ile436Asn]; HGMD; <http://www.hgmd.cf.ac.uk>). An arginine-restricted diet with pyridoxine (vitamin B6; 500 mg daily) supplementation was started. Three months after initiation of treatment, serum ornithine levels did not decrease. However, best-corrected visual acuity improved to 20/25 in both eyes, and SD-OCT scans showed resolution of CME.

During 3 years' follow-up, serum ornithine levels were measured at regular intervals and were not found to decrease, despite the patient's reporting strict adherence to the arginine-restricted diet and pyridoxine supplementation.

The anatomical and functional improvement was maintained to 3 years' follow-up, during which SD-OCT imaging identified small fluctuations of residual intraretinal cysts with good foveal contour in both eyes (Figure 2).

Discussion

The widespread use of high-resolution OCT has enhanced recognition of CME and variable degree of intraretinal fluid in patients with GA.³ The pathogenesis of CME in macular dystrophies is still unclear. Retinal pigment epithelial dysfunction leading to disruption of the outer blood–retinal barrier and diffusion of fluid toward intraretinal spaces is likely to be the main mechanism of edema formation in GA.³

The current literature on the treatment of CME in GA is controversial. It is represented by small case series and limited by the lack of a randomized controlled study. Indeed, only a few cases of GA complicated by CME and initiated on arginine-restricted diet have been reported.⁶⁻⁹

Feldman and colleagues⁶ reported a 26-year-old woman with no changes in CME secondary to GA after 5 months of a low-protein diet. Katagiri and colleagues⁷ reported 2 Japanese brothers affected by GA who went from virtually no clinically significant CME on initial OCT scan to significant CME on the long-term follow-up OCT scan, despite early initiation of arginine-restricted diet. Similarly, Doguizi and colleagues⁸ reported no changes of macular edema after 2 years of arginine-restricted diet in a 9-year-old boy presenting with bilateral CME and GA. By contrast, Heller and colleagues⁹ recently found reversal of CME and visual acuity improvement in 2 unrelated Israeli patients with GA after low-protein intake and oral administration of pyridoxine (500 mg/die); however, the serum ornithine level decreased significantly in only one of these two patients.

Our case has several similarities to the cases reported by Heller and colleagues.⁹ Indeed, in these cases macular edema was bilateral and its reversal was already evident after

3 months of dietary modification and pyridoxine supplementation. Of note, in the present case, as in one of the cases reported by Heller and colleagues,⁹ the serum ornithine levels did not decrease greatly. Therefore, we hypothesize that in these cases the effect of the treatment on CME was independent of the serum ornithine levels. It remains unclear whether the oral pyridoxine alone or its combination with low-protein diet induced the resolution of CME in our case. Our case had the same homozygous missense mutation as previously reported in another Italian boy.¹⁰ Unfortunately the response to pyridoxine was not tested in the latter case.

Genetic differences in patients along with differences in dietary regimens and compliance to treatment may in part explain the heterogeneity of response to treatment in the current literature. Future studies of genotype–phenotype correlations may help to identify the subset of patients with GA-related CME who may benefit most from an arginine-restricted diet and pyridoxine supplementation.

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Legends

FIG 1. Fundus photograph of the right eye at presentation showing circumferential patches of chorioretinal atrophy in the mid peripheral retina.

FIG 2. Spectral-domain optical coherence tomography (SD-OCT) at presentation and 3 years after initiation of arginine-restricted diet and vitamin B6 supplementation. At presentation (A,B) SD-OCT scans show presence of cystoid macular edema (CME, *arrows*). After 3 years, SD-OCT scans show resolution of CME, with small residual intraretinal cysts in the right eye (C) and in the left eye (D), with recovery of the foveal contour in both eyes.