CASE REPORT

Unique case of gyrate atrophy with a well-preserved electroretinogram (ERG)

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SUMMARY

Gyrate atrophy is a rare autosomal recessive disorder caused by a mutation in the ornithine- δ -amino transferase gene. We present an interesting case of a 33-year-old woman who presented with increasing myopia, nyctalopia and failing vision. Examination revealed posterior subcapsular cataracts, narrowed peripheral visual fields and scalloped atrophic peripheral chorioretinal lesions. Blood investigations showed a raised plasma ornithine level at 917 $\mu\text{mol/L}$ (normal range: 32–88 $\mu\text{mol/L}$) confirming the diagnosis of gyrate atrophy. The patient, despite not tolerating dietary treatment, had retained central vision over a follow-up period of 18 years. The electroretinogram, which normally diminishes with disease progression, was still nearly normal when last tested at 16 years follow-up. Genetic testing did not reveal any novel mutation that could account for this variation.

BACKGROUND

Gyrate atrophy (GA), first described by Fuchs in 1896, is a chorioretinal degeneration inherited in an autosomal recessive manner. A deficiency of the mitochondrial matrix enzyme ornithine- δ -amino transferase (OAT) caused by mutations in the OAT gene account for the 10-fold to 20-fold elevation in plasma ornithine level observed. OAT is a nuclear encoded, vitamin B6 requiring, mitochondrial enzyme that catalyses the interconversion of ornithine, glutamate and proline. It is the main catabolic enzyme of ornithine and a defect in OAT results in hyperornithinaemia. Two clinical subtypes of GA have been described based on response to vitamin B6. Patients responding to B6 have less severe disease and slower progression compared with those that do not. However, fewer than 10% of patients with GA reported in the literature are 'B6 responders'.¹

Patients usually present with decreasing visual acuity due to progressive myopia and nyctalopia. Presentation is most usually in childhood. Visual field constriction often follows. Ocular manifestations include characteristic sharply demarcated, scalloped areas of chorioretinal atrophy with hyperpigmented margins in the peripheral fundus. In addition to posterior subcapsular cataract formation, vitreous opacities and cystoid macular oedema occur. These usually appear in the first three decades of life and often lead to blindness in the fourth to seventh decades. The electroretinogram (ERG) is usually reported to be severely

abnormal, significantly reduced or extinguished. In most patients, the clinical appearance, phenotype and the raised plasma ornithine levels confirm the diagnosis. Genotyping is a confirmatory test. Ophthalmic phenotype heterogeneity exists in patients with the same mutation in the OAT gene, suggesting that both genetic and environmental factors are important.

We report a unique case of genetically confirmed GA with an unusually well-preserved ERG response, with minimal changes over prolonged follow-up with implications for future research.

CASE PRESENTATION

A healthy 33-year-old woman was referred in 1998 because of increasing myopia, nyctalopia and failing vision. There was no medical or family history of note. She worked as a support worker and did not drive. There were no reports of consanguinity in her family history. Her best-corrected visual acuity (BCVA) at presentation was 6/12 Snellen in right eye (OD) and 6/9 left (OS). Refraction was -10.75 D OD and -7.5 D OS. Mild bilateral posterior subcapsular cataracts were present. Funduscopy showed scallop-shaped chorioretinal atrophic lesions in the peripheral retina (figure 1). Bilateral peripheral concentric visual field constriction with normal central visual fields was present (figure 2).

INVESTIGATIONS

The plasma ornithine level was 917 $\mu\text{mol/L}$ (normal range: 32–88 $\mu\text{mol/L}$) on presentation in 1998. Full field ERGs were recorded on two different systems. In 1998, 2002, 2003 and 2008, she was tested on a MS25 system (Medelec, Woking, UK) following which we introduced an Espion E² system (Diagnosys LLC, Lowell, Massachusetts, USA) allowing full compliance with the International Society for Clinical Electrophysiology of Vision (ISCEV) standards. Up until 2003, skin electrodes were employed; more recent studies (2008 and 2014) employed silver/nylon corneal fibre electrodes (Department of Physics and Clinical Engineering, Royal Liverpool University Hospital, UK). The ERGs between 1998 and 2003 were normal. The electrooculogram (EOG) was already markedly reduced when first tested at the 2002 visit, with Arden ratio of 1.09 OD and 1.19 OS (normal values >1.8). It remained at this level subsequently, with values in 2014 of 0.98 OD and 1.02 OS. The 2008 ERG data showed normal light-adapted responses (figure 3A). The rod ERG (dark-adapted

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Figures 1 Ultra wide field images (OPTOS California, Optos Inc., MA, USA) of both eyes showing peripheral chorioretinal degeneration with scalloped distinct edges, typical of gyrate atrophy. The degeneration has exposed the underneath sclera and is macula sparing, explaining the good level of central vision.

0.1J blue) was slightly reduced but still within normal limits and the combined response (dark-adapted 1J) was normal. In 2014, ISCEV standard ERG showed slightly reduced light-adapted flash and flicker responses (figure 3B). The rod ERG (dark-adapted $0.01 \text{ cd} \cdot \text{s} \cdot \text{m}^{-2}$) was delayed and attenuated and the 3 and $10 \text{ cd} \cdot \text{s} \cdot \text{m}^{-2}$ dark-adapted responses were reduced to the same extent as the light-adapted ERG. Next-generation sequencing revealed two heterozygous OAT changes, c.627T>A p.(Tyr209Ter) and OAT c.1250C>T p.(Pro417Leu).

DIFFERENTIAL DIAGNOSIS

Choroideremia (CHM)

CHM is a X-linked recessive rod-cone retinal dystrophy caused by deletion in the *CHM* gene at Xq21.2. Patients present with

nyctalopia initially followed by progressive loss of peripheral vision with development of a ring scotoma in the fourth to fifth decade. It affects males. The female carriers may have mild mottled choriocapillaris and retinal pigment epithelium (RPE) changes with a typical fundus autofluorescence pattern. Plasma ornithine level is normal.

Retinitis pigmentosa (RP)

RP causes vision impairment due to progressive degeneration of rod cells followed by RPE and cone cells in the retina. Patients present with nyctalopia and loss of mid-peripheral visual fields. Funduscopy reveals characteristic bony spicular pigmentation, narrowed vessels and chalky pale optic disc. The plasma ornithine level is normal and the disease can be

Figure 2 Bilateral full-field 120 point suprachreshold test of right and left eye showing bilateral peripheral concentric visual field constriction with sparing of central vision taken in 2004.

Figure 3 Ganzfeld (full-field) electroretinograms (ERGs) recorded on two different systems in 2008 and 2014 using corneal thread electrodes. (A) 2008 Medlec MS25 system with 1J light-adapted flash and flicker responses showing normal results (c.f. a typical normal response in grey). Dark-adapted rod ERG (0.1J blue) are a little reduced but within normal limits and the combined response (1J) is normal. (B) 2014 Espion E² system. Grey traces are 95% CIs for a normative population. Light-adapted flash and flicker are slightly reduced (by about 12%–25%). The rod ERG (dark-adapted 0.01) is delayed and attenuated by 50%, probably showing progression since 2008, and the 3 and 10 cd-s-m⁻² dark-adapted responses are reduced in proportion to the light-adapted ERG.

autosomal dominant, recessive or X-linked, with the latter being the most severe.

TREATMENT

A 4-week trial of oral pyridoxine (vitamin B6) supplementation at 500 mg/day was undertaken on diagnosis in 1998 but no reduction in plasma ornithine levels or symptomatic improvements was found. She was then commenced on a low protein arginine-free diet with Dialamine (nutritional supplement containing 25 g of essential and non-essential amino acids, 65 g carbohydrates, 125 mg vitamin C and 1530 kJ energy per 100 g of powder) supplementation at 135 g/day, multivitamin supplementation and calcium carbonate 420 mg twice daily. The diet was not tolerated and was subsequently abandoned by the patient. Bilateral cataract extraction with posterior chamber intraocular lens implantation was undertaken in 2002 followed by yttrium aluminum garnet laser capsulotomy for posterior capsular opacification 6 months later.

OUTCOME AND FOLLOW-UP

After 18 years of follow-up, her most recent BCVA is 6/6 OD and 6/5 OS. The improvement in vision compared with initial presentation was due to lens replacement surgery. Her fundal appearance, visual fields and plasma ornithine levels (measured at 739 μ mol/L) were stable with follow-up electrodiagnostics performed in 2014 showing evidence of significant rod involvement. Spectral-domain ocular coherence tomography imaging has not shown any macular abnormality during follow-up. ERG results were normal up until 2014, when there was an approximately 25% reduction in most responses, except the rod ERG

(DA 0.01), which was attenuated by 50% and markedly delayed. Overall, though, her ERG remains remarkably well preserved.

DISCUSSION

A review of GA in 2001 by Takki *et al* reported that among 150 patients with biochemically documented GA, nearly a 1/3 of cases were from Finland, where the prevalence is one in 50 000.² In vitro studies have shown ornithine to exert a cytotoxic effect on RPE cells when transported intracellularly.³ The adverse effects of creatinine or pyroline-5-carboxylate deficiency are also thought to be causative factors.

The ERG mainly measures electrical responses from the photoreceptor cells and inner retina (mainly bipolar cells). In patients with GA, the ERG shows a reduced rod and cone response with rods affected earlier than cones. This scotopic pattern gradually converts to an absent or reduced ERG as the disease progresses, reflecting reduced retinal function.⁴ There have been reports of patient with advanced GA who have an abnormal but detectable ERG.^{4–6} Our patient has markedly reduced EOG with near-normal ERG throughout follow-up. Such long-term preservation of the ERG has not been reported to date.

Our case demonstrates that high ornithine levels do not necessarily correlate with disease severity or progression, highlighting the lack of genotype–phenotype correlation for OAT mutations in some patients. This observation raises the possibility of other factors independent of ornithine levels influencing the pathogenesis and phenotypic variation seen in the disease. Another reason for this variation could be that some mutations in the OAT gene result in diminished but not absent OAT enzyme activity. A functional study by Doimo *et al* demonstrated that despite all OAT mutations reviewed in the study showing markedly reduced enzymatic activity, there was varying degrees of enzymatic function seen in different autologous human OAT mutations.⁷

In vivo studies using a mouse model of GA has shown the earliest pathological changes to be in the RPE cells.⁸ These changes include swelling and loss of basal infoldings and apical processes of RPE cells, cellular swelling and flattening and engorgement due to phagocytosed outer segment membranes of photoreceptors. This mouse model may explain why the RPE changes (as demonstrated by the EOG) preceded ERG changes in our patient. Furthermore, the OAT gene is expressed at higher levels in the RPE and at lower levels in the photoreceptors.⁹ RPE damage could result from local OAT deficiency or from special sensitivity of the RPE to ornithine accumulation. Our patient's relatively well-preserved ERG over time mirrors her good visual acuity over many years. The genotyping undertaken confirmed

Patient's perspective

I have been living with this condition ever since childhood and so have adjusted to the limitations it places to my life. I am unable to see the sides of things and routinely knock into people and trip over items on the floor due to my poor peripheral vision. I am unable to leave the house alone come evening as it becomes really difficult for me to see in the dark. If I do, it is with my family for meals in the evening as I require quite a hand outside and places that are brightly lit are a big help. Despite my predicaments, I am grateful that I can still see pretty well otherwise, much helped by the cataract surgery performed at my local hospital. I guess having the disease from an early age has allowed me to develop my own way of coping with the problems that I face, as I have never known anything different or better.

the clinical diagnosis. It is possible that the patient may have patchy preservation of rod activity or increased cone activity overshadowing reduced rod responses due to remodelling of retinal circuitry. However, there is no model to test this hypothesis at present. We hope that reporting this case will stimulate interest in exploring such matters further.

Learning points

- ▶ Gyrate atrophy is a rare inherited chorioretinal dystrophy (autosomal recessive) with characteristic peripheral retinal changes.
- ▶ Gyrate atrophy in the fundus is due to hyperornithaemia secondary to an inborn error of metabolism.
- ▶ Myopia, nyctalopia, posterior subcapsular cataracts, macula oedema and loss of peripheral vision occur as part of the disease process.
- ▶ The electroretinogram (ERG) usually shows a reduced rod then cone response. An absent ERG may occur as the disease progresses.
- ▶ Treatment of gyrate atrophy is with a low arginine diet and vitamin B6 supplementation. However, few patients respond.

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Competing interests None declared.

Patient consent Obtained.

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