GYRATE ATROPHY-LIKE PHENOTYPE WITH NORMAL PLASMA ORNITHINE

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Purpose: To describe the clinical characteristics of a chorioretinal disease with a gyrate atrophy-like phenotype and normal plasma ornithine.

Methods: One family with three men who had progressive chorioretinal disease and three additional patients with simplex cases were examined clinically and with standard electroretinography, electrooculography, and dark adaptometry.

Results: In the family, a 70-year-old man and his two sons (39 and 41 years of age) were affected. On ophthalmoscopy, sharply demarcated peripheral patches of retinal pigment epithelium and choroidal atrophy were seen to progress to the posterior pole in the father's eye. In three unrelated men (62, 70, and 80 years of age), chorioretinal atrophy was present in the mid- and far periphery. Visual acuity was normal in the two youngest of all six patients; however, electroretinogram and electrooculogram waves were reduced. Advanced visual field defects and visual acuity loss occurred in the four older patients. Electroretinogram and electrooculogram were reduced, and the dark adaptation thresholds were elevated. In all patients, serum ornithine levels were normal. Ornithine-delta-aminotransferase activity in cultured skin fibroblasts and the apparent Michaelis constant (Km) for ornithine and $\alpha$-ketoglutarate were within the normal range in all patients.

Conclusions: A gyrate atrophy-like phenotype can result from causes other than deficient ornithine-delta-aminotransferase. Its occurrence in three male members in two generations in one family suggests an autosomal dominant inheritance in at least some such patients.

RETINA 17:403–413, 1997

Gyrate atrophy is an autosomal recessive chorioretinal dystrophy.1–13 Most patients with this disorder have high myopia, and posterior subcapsular cataracts are common. The chorioretinal atrophy starts in the midperiphery and proceeds to the periphery and toward the posterior pole. Later, the dystrophic areas become confluent. There is a corresponding progressive constriction of visual fields. For these patients, severe visual acuity loss usually occurs in the fifth or sixth decade of life. Patients affected with gyrate atrophy show various mutations in the gene encoding the enzyme ornithine-delta-aminotransferase (OAT).14–22 These mutations lead to markedly elevated serum levels of ornithine. The diagnosis of gyrate atrophy can be established by the examination of serum ornithine levels or OAT enzyme activity in cultured skin fibroblasts of affected patients and carriers.4,23–31 Since the detection of hyperornithinemia in patients

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The study was partially funded by a grant from The Foundation Fighting Blindness, Baltimore, Maryland, by Research to Prevent Blindness (R. G. Weleber & N. G. Kennaaway), New York, New York, and by a grant from the Deutsche Forschungsgemeinschaft (Ke442/7-1, U. Kellner).

The authors have no proprietary interest in the materials or ideas described in this article.

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with gyrate atrophy in 1973,23 the term "gyrate atrophy" has been reserved for choroidal dystrophies that show hyperornithinemia.

Gyrate atrophy can be differentiated from choroideremia and diffuse choriocapillaris atrophy based on clinical and biochemical findings and the inheritance pattern.32–36 Isolated, sporadic cases with ophthalmoscopic findings resembling gyrate atrophy and with normal serum ornithine levels have been described.37–43 Before the association between gyrate atrophy and hyperornithinemia was detected, individuals from two families who had chorioretinal dystrophy and autosomal dominant inheritance were diagnosed as having gyrate atrophy.33,44

We observed one family with apparent autosomal dominant inheritance and three unrelated patients with a chorioretinal dystrophy resembling gyrate atrophy. All patients had normal serum ornithine levels. The purpose of this study is to describe the clinical and electrophysiologic findings in patients with this infrequently reported chorioretinal disease.

We studied six affected patients from three different eye departments. Electrophysiologic recordings were obtained according to the standard protocol for clinical electroretinography and clinical electrooculography.45,46 Details of the recording techniques have been published previously for each laboratory.47–50

Case Reports

Family M

Four patients from Family M, including three affected men, were examined by one of the authors of this study (U.K.). The pedigree is shown in Figure 1. One patient (IV/4) was examined thoroughly in our department. His father (III/3) and brother (IV/3) were unavailable for examination in our department. Therefore, fundus examination and the drawing of blood samples were done at their home. The 6-year-old son (V/1) of patient IV/4 had normal visual acuity and fundoscopic appearance.

The paternal grandmother (II/2) of patient III/3 became blind at approximately 50 years of age, but further details were not available. Both parents (II/1 and II/2) of patient III/3 died before the age of 45 years. The mother (III/4) of patients IV/3 and IV/4 had no difficulties with her vision; however, an examination was not possible. There was no positive family history for eye disease in the family of the mother (III/4). None of the other family members shown in the pedigree had known ocular problems; however, detailed ophthalmologic examination was not performed. The three affected men representing two generations and the woman who was probably affected suggest the presence of an autosomal dominant inheritance in Family M. In the second generation, no affected patient is known; however, the male family member II/1 may have died before clinical signs were present.

Patient IV/4. The male propositus of the family had been diagnosed with retinitis pigmentosa when he was 18 years old. At that time, no subjective signs of ocular problems were present. The examination was performed because of the known disease in his father. His visual acuity was 20/20 in both eyes. Ophthalmoscopy showed a normal posterior pole and optic disc. Pigment epithelial changes were detected nasal to the disc and in the periphery. The vessels were described as normal. Goldmann visual fields were normal in both eyes (Figure 2). Electroretinography (ERG) and electrooculography (EOG) were recorded with unspecified techniques. The ERG results were described as slightly abnormal, and the EOG results revealed a severely reduced light rise.

This patient was examined by the authors (U.K. and M.H.F.) when he was 39 years old. At that time he had noted visual field defects. His general medical history was unremarkable, and he did not receive any medication. His visual acuity was unchanged. The refractive error was +2.25–2.25 × 11° in the right eye and +2.25–1.75 × 172° in the left. The anterior segments and the ocular pressures were normal. On ophthalmoscopy, patches of severe retinal pigment epithelial and choroidal atrophy in the mid- and far periphery were seen (Figure 3). These patches had become confluent in several areas. The borders between atrophic areas of the choroid and those that appeared to be normal were sharply delineated. For both eyes, there was a circular area of atrophy surrounding the optic disc, which temporally extended to approximately half the distance between the optic disc and fovea. The atrophic area around the disc was connected to the peripheral atrophy via a bridge of atrophic choroid and retinal pigment epithelium in the lower nasal quadrant. There was no hyperpigmentation or pigment clumping. Fluorescein and indocyanine angiography showed severe loss of choroidal vasculature with no leakage (Figure 3).

On visual field testing, concentric narrowing was detected on both eyes, and absolute paracentral scotomas (target V/4) were seen in connection with the blind spot (Figure 2). Results of color vision testing showed minor errors without typical axis in the desaturated Panel D-15 test. Results of tests using a Nagel anomaloscope were normal. Results of dark adaptation testing using a Goldmann-Wekers adaptometer with a target size of 11 degrees in the diameter in the upper field 10 degrees from the fovea showed normal cone and rod thresholds and a normal cone–rod break. Standard ERG recording showed a reduction of rod-mediated responses to approximately 15% and a reduction of cone-mediated responses to approximately 25% of the normal median; both were for responses mediated by photoreceptors (a-waves) and responses mediated by middle and inner retinal neurons (b-waves; Figure 4). Implicit times (the time from beginning of the light flash to the maximum of either the a- or b-wave in the ERG) were normal under dark and light adapted conditions. Standard EOG recording showed a reduced light rise
Fig. 2. Visual field defects in family M, patients III/3 and IV/4. A, Visual field of the left eye in patient IV/4 at 23 years of age. B, Visual field of the left eye in patient IV/4 at 39 years of age. C, Visual field of the left eye in patient III/3 at 51 years of age. D, Visual field of the left eye in patient III/3 at 62 years of age.

in both eyes (right eye, 1.28; left eye, 1.37; normal, > 1.60). The serum ornithine level was normal (122 µmol/L), as were the serum levels for other amino acids.

Patient IV/3. This 41-year-old healthy man had not noted his visual problems until his most recent examination. His visual acuity and visual fields were normal; however, those records were not available. The anterior segments were normal. Ophthalmoscopy showed chorioretinal atrophy similar to that in his brother, but it had not progressed as far centrally.

Patient III/3. In this 70-year-old male patient, we performed a funduscopic examination and serum examinations. The other clinical data are based on the notes of different ophthalmologists who examined this patient over the past 20 years. His general medical history was unremarkable, and he had no systemic disease that might have affected eye function. He did not receive any medication regularly.

Difficulties with visual function were noted when he was approximately 40 years old. At the age of 50 years, his visual acuity was 20/20 in both eyes. Visual fields showed concentric narrowing to approximately 15 degrees for the III/4 target of the Goldmann perimeter. He underwent cataract surgery with lens implantation in both eyes at age 63. Nd-YAG laser capsulotomy was performed 3 years later on the left eye. At the age of 64 years, his visual acuity was 20/40 in the right eye and 20/200 in the left. Six years later, his visual acuity was 20/60 in the right eye and 20/100 in the left. Visual fields tested with a Goldmann perimeter showed a remaining central island of 3 degrees for the III/4 target (Figure 2).

Fundus findings obtained by previous examiners showed retinal degeneration, but no detailed description was given. At the age of 70 years, the bare sclera was visible with a general loss of retinal pigment epithelium and choroidal vessels except for the foveal area. The optic disc was pale, and the retinal vessels were attenuated. There was no pigment clumping (Figure 3).
Electroretinography responses in the patient tested at different institutions were undetectable when he was 52 and 62 years of age; however, the stimulus characteristics were not specified. The serum ornithine level was normal (125 μmol/L), as were the serum levels for other amino acids.

**Simplex Cases**

Three additional patients (cases 1–3) were observed in the United States. Some of their data have been published previously. These patients were unrelated to those described.

**Case 1.** An 80-year-old man was diagnosed with gyrate atrophy during a routine eye examination. For several decades, he had noted difficulty in adjusting to dim illumination. Over the past several years he experienced progressive difficulty reading. His visual acuity was 20/40 –1 in the right eye with +1.0–1.25 × 100° and 20/60 in the left eye with −1.00–1.00 × 90°. Confrontation visual fields were constricted. External ocular examination results, ocular motility, applanation intraocular pressures, and pupillary responses were normal. Biomicroscopy revealed moderate nuclear sclerotic cataracts bilaterally. Fundus examination disclosed extensive, subtotal, peripheral, and peripapillary chorioretinal atrophy; macular depigmentation; a mild decrease in caliber of the retinal vessels; and sparse, fine, bone-spicule-like pigmentation in the areas of peripheral chorioretinal atrophy (Figure 5).

When evaluated 1 year later, the patient’s right eye had gained one diopter of myopia, but his visual acuity and other examination results were otherwise unchanged. Goldmann perimetric visual fields demonstrated enlarged blind spots, absolute constriction of the peripheral isopters, and depression of the retinal sensitivity of the central field (Figure 6). A tritan color-vision defect was evident with the Panel D-15 and the Farnsworth 100-Hue test (Luneau Ophthalmologie, Chartres, France). Results of dark adaptometry tested with a Goldmann-Weekers adaptometer with a target size of 11 degrees in diameter in the upper field 10
Fig. 4. Electoretinography recordings of patient IV/4 (right) and a normal control subject (left). The upper three traces show recordings at dark adaptation (DA, calibration: 200 μV and 20 ms); rod response, mixed rod–cone response, and oscillatory potentials. The lower two traces show recordings at light adaptation (LA), cone response (calibration: 100 μV and 20 ms), and 30-Hz flicker (calibration: 100 μV and 50 ms).

degrees from the fovea showed elevated cone thresholds (0.8 and 1.3 log units above the mean for the right eye and the left eye, respectively) and rod thresholds (1.0 and 1.5 log units above the mean for the right eye and the left eye, respectively) bilaterally. Electroretinogram a- and b-waves were severely subnormal for cone- and rod-mediated responses. Cone and rod implicit times were prolonged (Figure 7). Electrooculography light-to-dark ratios were subnormal in each eye (right eye, 1.26; left eye, 1.16; normal, > 1.35).

The fasting serum ornithine level was normal (116 μmol/L; normal, 30–120 μmol/L). The glutamine (947 μmol/L; normal, 410–690 μmol/L) and alanine (764 μmol/L; normal, 210–660 μmol/L) levels were elevated in one sample but normal on repeat testing. The arginine level (135 μmol/L) was at the upper limit of the normal range (20–130 μmol/L). All other amino acid levels were normal. Ornithine-delta-aminotransferase activity in cultured skin fibroblasts was also normal, and the apparent Km for ornithine and α-ketoglutarate was within the normal range.

Case 2. This 70-year-old man reported slowly progressive, lifelong limited side vision, but did not produce noticeable disability until the age of 65 years. Since the age of 30 years he noted progressively worse night vision. At age 63 his visual acuity measured 20/60 in the right eye and 20/40 in the left, attributed mostly to the presence of moderate cataracts in each eye. Several ophthalmologists believed that he might have an atypical form of retinitis pigmentosa. A non-Ganzfeld ERG obtained when the patient was 64 years old demonstrated markedly subnormal photopic and scotopic responses. Before age 67 the patient drove a car, but he drove at night only when he had no other option. His only medication was aspirin for osteoarthritis, which he had taken since his third decade of life.

At 70 years of age his best corrected visual acuity, wearing +2.25–2.50 × 87° in the right eye and +2.25–1.25 × 97° in the left, was 20/200 in the right eye and 20/100 in the left. Moderately advanced nuclear sclerotic cataracts were present bilaterally; from the results of laser interferometry, visual acuity potentials of 20/40 in the right eye and 20/75 in the left were predicted. Fundus examination showed extensive peripheral chorioretinal atrophy bilaterally. Goldmann perimetry displayed enlarged blind spots, severe constriction of peripheral visual fields, and depression of the central retinal sensitivity bilaterally. Major crossing errors with no discernible axis were made with the Panel D-15; the patient refused to complete the 100-Hue test, claiming no visible difference in the color of the chips upon which to perform the match. Results of dark adaptometry tested with a Goldmann-Weekers adapter with a target size of 11 degrees in the diameter in the upper field 10 degrees from the fovea disclosed marked elevation of the cone threshold (2.0 log units above the mean in both eyes), no discernible cone–rod break, and marked elevation of the final rod dark adaptation threshold (2.8 and 3.5 log units above the mean in the right eye and left eye, respectively). Ganzfeld ERGs (Figure 7) revealed a profound loss of dark-adapted rod, dark-adapted cone, and light-adapted cone mediated amplitudes for a- and b-waves. Rod-cone mediated b-wave implicit times were prolonged. Essentially no light-induced rise of the resting potential was seen on the EOG (light-to-dark ratios of 1.00 in both eyes).

Fig. 5. Funduscopic appearance of simplex case 1 (81 years of age). A, Montage of fundus images of the left eye. B, Montage of the corresponding fluorescein angiogram.
At the age of 72 years, an intracapsular cataract extraction was performed on the right eye; a sample of aqueous humor was removed at the time of surgery and analyzed to determine amino acid levels. Postoperative visual acuity with aphakic correction was 20/70.

The levels of fasting serum ornithine (130 μmol/L) and arginine (139 μmol/L) were at the upper limit of the normal range. The level of ornithine in the aqueous humor was 42 μmol/L (normal mean, 63; range, 38–84). Ornithine-delta-aminotransferase activity in cultured skin fibroblasts was also normal, and the apparent Km for ornithine and α-ketoglutarate was within the normal range.

Case 3. A 62-year-old man, first examined at the University of Illinois in December 1980 (G.A.F.), reported mild photosensitivity and decreased distance and near vision that had lasted 2 years. He denied having problems with color or night vision. His medications included methyl dopa 250 mg bid and hydrochlorothiazide 50 mg daily; both were to control systemic hypertension. One year earlier, he had undergone successful quadruple vessel coronary artery bypass surgery. Seven years earlier, an aortic aneurysm had been repaired with a dacron graft. There was no history of diabetes, neurologic disease, peptic ulcer disease, or renal disease. Family history showed no members with night blindness or any blinding disease. No other family members were available for examination.

Manifest refraction with +1.00 sphere in both eyes improved vision to 20/30 –2 in the right eye and to 20/30 +2 in the left. With a +1.50 add for near, the patient was able to read four-point size print. Although both anterior segments were unremarkable, trace cells in the right vitreous and +1 cells in the left vitreous were detected on slit-lamp examination. Dilated fundus examination showed typical findings of gyrate atrophy. There were extensive, atrophic, scalloped lesions circumferential within the midperipheral retina of each eye. The optic disc and retinal vessels appeared normal (Figure 8).

Fluorescein angiography showed characteristic atrophy of the retina and choroid in the sharply defined scalloped regions. Some of the large choroidal vessels were spared. The posterior pole of the retina showed very subtle, granular pigment epithelial window defects. Fluorescein stained the intact choriocapillaris at the border of the degenerative areas.

Goldmann visual fields showed marked peripheral constriction (Figure 9). Color vision with the Farnsworth-Munsell 100 Hue test showed a mild blue-yellow defect. Dark adapted thresholds were obtained with a Goldmann-Weekers dark adaptometer using a 2-degree test stimulus. Rod thresholds tested at 15 degrees superior and inferior to the fovea were at the upper limits of the normal range. At 30 degrees superior and inferior to the fovea, rod thresholds were elevated by 1 log unit, whereas at 45 degrees thresholds were elevated by 2 log units above the upper limit of the normal range.

Electroretinography showed undetectable cone responses to a single-flash stimulus and 30-Hz flicker cone responses that were reduced to 85% below the normal value. The dark-adapted, rod-dominant response showed a b-wave amplitude that was only 10% of the normal response. Isolated rod function to a single-flash, blue stimulus was undetectable.

Independent analysis of the patient’s serum and urine by three separate laboratories showed normal ornithine levels (120 μmol/L) and normal levels for other amino acids. Ornithine ketoacid aminotransferase activity was normal.

Discussion

The differential diagnosis of inherited, progressive, generalized, choroidal dystrophies includes three entities: diffuse choriocapillaris atrophy, choroideremia, and gyrate atrophy.33–36 Diffuse choriocapillaris atrophy is a rare disorder with autosomal dominant inheritance.35 Choriocapillaris atrophy and pigment clumping originate at the posterior pole and result in early visual loss. The disease slowly progresses to an end stage with large choroidal vessels visible as thin, white cords.

Choroideremia is an X-linked, recessive, choroidal dystrophy that begins in the periphery and progresses to the posterior pole.32,51 It is characterized by a scalloped loss of retinal pigment epithelium and choriocapillaris. Night blindness occurs at an
Fig. 7. Electroretinography (ERG) recordings of patients with simplex cases 1 and 2 compared with that of a normal control subject. The intensity settings for the Grass stimulator are to the left for the scotopic blue and red stimuli. The numbers to the left of the white-light waveforms indicate the integrated light intensity in log foot-lambert seconds. To act as an indicator of the vertical scale, the stimulus spikes for the 30-Hz flicker, photopic, and scotopic waveforms have been set at 10 μV, 25 μV, and 50 μV for patients 1 and 2 and 75 μV, 75 μV, and 100 μV for the normal ERG. Note that the 30-Hz flicker response without background is prolonged for both patients.

eary stage, and severely constricted visual fields and visual loss are present in the patient’s fifth decade of life. Choroideremia is caused by a deficiency of Rab geranylgeranyl transferase. The gene is located at Xq21.5253

The patients in this study have a slowly pro-
gressive choroidal dystrophy, which most resembles gyrate atrophy. With this disorder, the chorioretinal atrophy begins in the periphery and progresses more centrally with increasing age. This is in contrast to findings in patients with diffuse choriocapillaris atrophy, which originates at the posterior pole. The margins of the patches of chorioretinal atrophy are often sharply delineated in the early stages, and pigment clumping is rare. The most advanced form of the disease, which was present in patient III/3 (Family M), resembled a late stage of gyrate atrophy or choroideremia. None of our patients had hyperornithinemia, which excludes gyrate atrophy as a diagnosis. Moreover, the inheritance pattern in the family suggests an autosomal dominant trait, which would exclude autosomal recessive gyrate atrophy and X-linked choroideremia.

On ophthalmoscopy, the findings in these patients resembled gyrate atrophy, but in other ophthalmologic aspects there were differences. High myopia was not present in our patients. There was no early cataract formation, and cataract surgery was only performed in patients older than 63 years of age. The onset of subjective signs and the stage of legal blindness occurred later in life than they would in patients with gyrate atrophy. Functional loss as measured with ERG was milder in these patients than in patients with gyrate atrophy.

It is difficult to define whether the disease process was the same in the family and the simplex cases. In none of the simplex cases was the family history suggestive of other affected individuals, but information on other family members was

Fig. 8. Funduscopic appearance of simplex case 3 (62 years of age). A, Posterior pole of the left eye. B, Choroidal atrophy below the optic disc of the left eye.
lacking. There was no consanguinity. The existence of a new mutation for an autosomal dominant disorder or the possibility that other family members were affected but not recognized cannot be excluded. There was no indication that the peripheral changes were secondary to inflammation or uveitis. However, the functional loss was apparently more advanced in the older patient in family M than in the patients of similar age with the simplex cases of the disease. Only the 70-
year-old patient in family M had a nonrecordable ERG.
Biochemically, our patients are quite distinct from those with gyrate atrophy. Serum ornithine levels and OAT activity in cultured skin fibroblasts were normal. Further, the apparent Km for ornithine and α-ketoglutarate was normal in the two patients in whom it was measured, eliminating the possibility that these patients had a variant OAT with deficient activity at low concentrations of substrates. It is important to distinguish the disorder in the patients described here from gyrate atrophy, because the latter is amenable to treatment in some cases, either by the administration of pyridoxine to vitamin B6-responsive patients or by dietary restriction of arginine to non-B6-responsive patients.5-11,54-61
Other cases of gyrate atrophy phenotype without hyperornithinemia have been described. In four families, consanguineous marriages led to ophthalmoscopic findings similar to gyrate atrophy but associated with other defects, e.g., muscular dystrophy and mental retardation, iminoglycinuria and iris atrophy, nystagmus and strabismus, and congenital amaurosis.37-41 In another family without consanguinity, choroidal dystrophy developed in two men, one of whom had spontaneous lens subluxation in both eyes.37,38
There are only a few cases that parallel the findings in the simplex cases observed in this study. Bargum42 observed a 67-year-old female patient with late-onset choroidal dystrophy and normal serum levels of ornithine. There was no family history of eye disease. The patient’s six brothers and their children were examined and had normal ophthalmologic findings. Barcaroli et al43 described three patients with choroidal dystrophy similar to gyrate atrophy who had normal serum ornithine levels and were emmetropic or hyperopic. In some cases of advanced retinitis pigmentosa, peripheral patches of choroidal atrophy may be seen, but the other ophthalmoscopic features of advanced retinitis pigmentosa enable a correct diagnosis to be made.11
Three families with members with autosomal dominant gyrate atrophy-like choroidal dystrophy have been described. Raitta et al45 observed a patient in whom spinocerebellar ataxia was an additional finding. Marchesani and Sautter46 described a pedigree with several affected members in three generations; however, besides the pedigree and a fundus drawing, no further information was given. Krill and Archer47 examined one female and two male siblings and their affected mother. In their family, the area of choroidal dystrophy was variable, but the fovea was involved in a late stage of the disease. These two families are the only ones that showed dominant inheritance and that are similar to the family in the present report.
Although defects in the OAT gene are associated with gyrate atrophy, the precise pathogenesis of the choroidal dystrophy has not yet been defined, and different theories are under discussion.13 There are two possible explanations for the development of these choroidal dystrophies. First, there may be one single and yet undefined disease process that is common to our patients and patients with gyrate atrophy. A second explanation is that different disease processes may lead to a similar chorioretinal degeneration. The difference in severity of functional loss in patients with gyrate atrophy, family M, and the simplex cases suggests that different disease processes with a similar ophthalmoscopic picture are more likely. A recently described mouse model of gyrate atrophy may be helpful for the further analysis of the pathogenesis of these choroidal dystrophies.63

**Key words:** choroid, electrooculogram, electroretinogram, gyrate atrophy, retinal degeneration.

**References**


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