Gyrate Atrophy of the Choroid and Retina

Further Experience With Long-term Reduction of Ornithine Levels in Children

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Objective: To determine whether the long-term reduction of plasma ornithine levels by way of an arginine-restricted diet in patients with gyrate atrophy will slow the progression of this chorioretinal degeneration.

Design: Natural history study of 2 pairs of siblings with gyrate atrophy treated with an arginine-restricted diet.

Main Outcome Measures: Fundus photography and electrophysical and psychophysical retinal function tests.

Results: After 16 to 17 years of receiving an arginine-restricted diet, the younger sibling in each pair, who was prescribed the diet at an earlier age than the older sibling, demonstrated a slower progression of lesions compared with the older sibling.

Conclusions: If started at an early age, long-term substantial reduction of plasma ornithine levels may appreciably slow the progression of the chorioretinal lesions and, to a lesser extent, the progressive loss of retinal function in patients with gyrate atrophy.

Gyrate atrophy (GA) of the choroid and retina is a rare, autosomal recessive, chorioretinal dystrophy. The initial symptoms are myopia and reduction of peripheral vision and in some patients, reduction of night vision in the first decade of life. Correspondingly, sharply demarcated circular patches of chorioretinal atrophy appear in the peripheral retina. With increasing age, these lesions increase in size and number, eventually coalescing and involving the entire posterior pole. Loss of visual function accompanies the chorioretinal degeneration, with decreased visual acuity or severe visual field constriction occurring in the fourth to seventh decade. Almost all patients demonstrate impaired peripheral vision by age 10 years.

The primary defect causing GA is a deficiency of the enzyme ornithine-δ-aminotransferase (OAT), which results in markedly elevated levels (10- to 15-fold) of ornithine in plasma and other body fluids.

Multiple efforts to treat GA have resulted in conflicting reports, in part due to the difficulties in evaluating therapies for a rare, slowly progressive genetic disorder. The patients often vary in their genotype at the disease gene locus, their genetic background, and their compliance with and age at the time of institution of treatment. These variables, together with the small number of patients, make objective evaluation of therapeutic trials difficult.

In 1991, we described the effects of long-term reduction of ornithine levels on the progression of the chorioretinal degeneration in GA. To minimize the variables mentioned above, we concentrated on sibling pairs. Siblings with autosomal recessive disorders like GA have identical genotypes at the disease gene locus and, on average, half of all of their genes are identical by descent. Thus, to the extent that genetic factors influence phenotypic variation, affected siblings can be expected to be more similar than unrelated patients, ie, intrafamilial variability should be less than interfamilial variability. Our comparison of phenotypic severity in 6 GA sibling pairs confirmed this expectation.

In the current study, we focused on the 2 youngest sibling pairs. The retina of the younger sibling in each pair (<10 years old) was largely normal appearing and functioning at the time the treatment was instituted.

We present the long-term follow-up of these subjects. At the time of this report, the sibling pairs had been receiving the diet for 16 to 17 years. Our results further support the conclusion that long-
PATIENTS AND METHODS

PATIENTS

Two sibling pairs with GA were studied. The younger sibling in each pair was younger than 10 years at entry into the study. The 2 sisters in pedigree GA 008 are Americans of German/Iranian ancestry. The brother and sister in pedigree GA 021 are Lebanese.

THE OPHTHALMIC EXAMINATION

The 4 patients underwent at least yearly complete ophthalmic examinations. Best-corrected visual acuity was determined using the standard Early Treatment Diabetic Retinopathy Study chart. Slitlamp biomicroscopy, funduscopic examination, and fundus photography were performed at each visit. Visual fields were tested with manual kinetic perimetry (Goldmann perimeter; Haag Streit, Bern, Switzerland) and automated static perimetry (Humphrey Field Analyzer, program 30-2; Zeiss Instruments, Jena, Germany). A global visual field score was obtained by summing the sensitivity values of the 76 points tested by this program. Dark adaptation was measured with a Goldmann-Weekers adaptometer (Haag Streit, Bern), modified to use the von Bekesy threshold tracking method. Patients underwent light adaptation for 5 minutes with a Ganzfeld background with a luminance of 2700 cd/m². The luminance threshold was then measured for a minimum of 30 minutes during dark adaptation, using a central 11°-diameter circular stimulus with a 0.6-Hz flicker rate. Final thresholds below a luminance of -4.24 log cd/m² were considered normal; this value was the upper limit of a tolerance interval estimated using a control sample of 20 subjects with normal dark adaptation. This tolerance interval was calculated to include 95% of the population with 95% confidence.

Color vision was evaluated using the Hardy-Rand-Rittler plates (American Optical Co, Buffalo, NY), the Farnsworth panel D-15 (Luneau, Ophthalmologie, Paris, France), and the Lanthein desaturated panel D-15 (Luneau, Ophthalmologie, Paris). When age permitted, the Farnsworth Munsell 100 Hue test was used and the scores were compared with the scores for normal subjects reported by Verriest et al. Electroretinography (ERG) was performed as described previously following the recommendation of the International Society for Clinical Electrophysiology of Vision. In brief, ERGs were elicited after 30 minutes of dark adaptation by dim and bright white stimuli (rod-mediated ERG and maximal retinal responses). After 10 minutes of light adaptation, ERGs elicited by 0.3-Hz and 30-Hz white stimuli were recorded (cone and flicker response). The electro-oculogram was recorded using the standard technique of the International Society for Clinical Electrophysiology of Vision. All ERG and electro-oculographic recordings were obtained using the same recording system (Universal Testing and Analysis System, model E-2000; LKC Technologies, Gaithersburg, Md) and the same type of bipolar electrode (Burian-Allen lens; Hansen Instruments, Iowa City, Iowa), although different lenses were used. Fluorescein angiography was performed when possible owing to age and cooperation.

To quantify the rate of change of the main outcome variables (static perimetry and ERG), the half-life of the outcome variable, ie, the number of years required for the field score or ERG amplitude to decline to 50% of its value, was used. Half-lives were calculated by fitting the data points with the model: \( V_t = V_0 \times e^{-(k/t)} \), where \( t \) represents time (in years); \( V_t \), the magnitude of the outcome variable at \( t \); and \( k \), half-life (in years). This method also provides an unbiased approach to deal with the test-retest variability of our results.

The study was approved by the National Eye Institute (Bethesda, Md) clinical institute review board and the Johns Hopkins Joint Committee on Clinical Investigation (Baltimore, Md). The patients were admitted to the study after obtaining parental consent or patient consent if aged 18 years or older.

RESULTS

Our initial evaluations of each of the affected children were reported previously and are summarized and updated as follows.

PATIENT GA008-1

This female patient, born in April 1977, was found to have GA at age 4 years 6 months, and was first evaluated in August 1983 at age 6 years, 4 months (Table). At that time, the diagnosis was confirmed and she was prescribed an arginine-restricted diet and followed at yearly intervals. Photographic montages of both retinas were constructed at each visit. The right and left retinas are shown for August 1983 (age 6 years 4 months) and most recently in August 2000 (age 23 years 4 months) (Figure 1) after adhering to the diet for 17 years. At the time of diagnosis, there were scattered chorioretinal atrophic lesions typical for GA. During the following 17 years, there were alterations in the pigmentation of some lesions and in general, an increase in size and number of atrophic lesions. The right and left retinas in August 2000 reflect the progression of the chorioretinal atrophic lesions. These fundus changes were paralleled by a gradual decline in sensitivity in the central 30° visual field and in the amplitude of the ERG maximal response (Figure 2). The half-lives of these variables were 24.6 and 20.1 years, respectively; they were both abnormal in our initial evaluation. In contrast, the final threshold of dark adaptation as assessed with a central 11° target remained in the normal range. The Lens Opacities Classification System II at age 23 years revealed that there was only a trace posterior subcapsular opacity bilaterally, although she had been receiving an arginine-restricted diet for the entire 17 years. Her compliance had been poor and her plasma ornithine concentration had been consistently elevated (mean±SD, 4.9 ± 1.7 mg/dL; 370 ± 129 μmol/L) [normal, 120 ± 65 μmol/L]). Measurements were obtained at intervals of about 6 months.
The sister of patient GA008-1, born in October 1980, was first examined at age 2 years 10 months (Table 1). With confirmation of the diagnosis of GA, she was prescribed an arginine-restricted diet in December 1982 at age 2 years 10 months. Right and left retinas were first successfully photographed in August 1986 (age 5 years 10 months) (Figure 3) and yearly thereafter. The last montage was obtained in August 2000 at age 19 years 10 months (Figure 3). In 1986, there was diffuse mottling of the retinal pigment epithelium (RPE) in the mid and far periphery but with no evidence of atrophic lesions. This was in sharp contrast to her older sister who, at age 6 years 10 months, already had extensive chorioretinal atrophy typical of GA. By August 2000, a fine dusting of pigment was noted peripherally in both eyes. In addition, a discrete atrophic lesion was noted at the 2-o’clock position in the right eye and at the 3-o’clock position in the left eye. The final threshold of dark adaptation, as assessed with a central 11° target, remained normal. However, a moderate gradual decline in sensitivity in the cen-

*Ornithine-Δ-aminotransferase missense alleles are designated by using the single-letter abbreviations for amino acids. The first letter and number indicate the normal residue and codon number, respectively. The second letter indicates the replacement residue, eg, C93F is a phenylalanine substitution for cysteine at codon 93. The relevant single-letter amino acid abbreviations for the alleles presented are: C, cysteine; F, phenylalanine; H, histidine; L, leucine; M, methionine; N, asparagine; P, proline; and Y, tyrosine. These molecular results are from Brody et al. Ellipses indicate not applicable.

**Figure 1.** Photographic montages of the eyes of patient GA 008-1. Right eye (A) and left eye (B) at age 6 years 4 months, and right eye (C) and left eye (D) at age 23 years 4 months. Comparison of top and bottom shows progression in both size and number of atrophic lesions after receiving an arginine-restricted diet for 17 years.

**PATIENT GA008-2**

The sister of patient GA008-1, born in October 1980, was first examined at age 2 years 10 months (Table 1). With confirmation of the diagnosis of GA, she was prescribed an arginine-restricted diet in December 1982 at age 2 years 10 months. Right and left retinas were first successfully photographed in August 1986 (age 5 years 10 months) (Figure 3) and yearly thereafter. The last montage was obtained in August 2000 at age 19 years 10 months (Figure 3). In 1986, there was diffuse mottling of the retinal pigment epithelium (RPE) in the mid and far periphery but with no evidence of atrophic lesions. This was in sharp contrast to her older sister who, at age 6 years 10 months, already had extensive chorioretinal atrophy typical of GA. By August 2000, a fine dusting of pigment was noted peripherally in both eyes. In addition, a discrete atrophic lesion was noted at the 2-o’clock position in the right eye and at the 3-o’clock position in the left eye. The final threshold of dark adaptation, as assessed with a central 11° target, remained normal. However, a moderate gradual decline in sensitivity in the cen-

**Table 1.**

<table>
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<tr>
<th>Variable</th>
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<th>GA008-2</th>
<th>GA021-1</th>
<th>GA021-2</th>
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<td>F</td>
<td>M</td>
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<td>11 mo</td>
<td>8 y 11 mo</td>
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<td>2 y 10 mo</td>
<td>9 y 4 mo</td>
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<td>17</td>
<td>16</td>
<td>16</td>
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<tr>
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<td>13 y 8 mo</td>
<td>...</td>
<td>9 y 5 mo</td>
</tr>
<tr>
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<td>C93F/P241L</td>
<td>M1I/M1I</td>
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Central 30° visual field was observed, associated with an even milder reduction in amplitude of the ERG maximal response (Figure 4). The half-lives of these variables were 35.3 and 150.9 years, respectively. At age 19 years, the Lens Opacities Classification System II revealed that there was only a trace posterior subcapsular opacity bilaterally. The mean±SD plasma ornithine level was 3.4 ± 1.0 mg/dL (256±76 µmol/L), with measurements obtained at roughly 6-month intervals. Her values have been consistently lower than those of her older sibling.

PATIENT GA021-1

This female patient, born in October 1975, was found to have GA at age 8 years 9 months, and was first evaluated at age 8 years 11 months, at which time the diagnosis of GA was confirmed. The arginine-restricted diet was begun at age 9 years 4 months, by which time the ERG maximal response was already considerably reduced. Photographic montages of the right and left retinas are shown for October 1984 (age 9 years) and September 2000 (age 24 years 11 months) (Figure 5). At the commencement of the diet, the retinas showed chorioretinal atrophy typical for GA. During the ensuing 16 years of follow-up, there was mild progression and coalescence of a few lesions while others became more pigmented with apparent reduction in size. However, both static and kinetic perimetry demonstrated progressive loss of the visual field (Figure 6); the half-life of her visual field score was 14.9 years. Dark adaptation showed a gradual elevation of final threshold. The amplitude of the ERG maximal response declined from 1990 to 1992 and has since remained stable (Figure 6); the half-life of her ERG amplitude was 20.0 years. She first showed early posterior subcapsular opacities bilaterally at age 13 years. By age 25 years, these opacities had progressed to P2 on the Lens Opacities Classification System.

Figure 2. Patient 008-1. Graph of central 30° field sensitivity measured with static perimetry (decibels, open circles) and electroretinogram (ERG) maximal response amplitude (microvolts, solid circles) as a function of time. The line passing through the data points is an exponential curve.

Figure 3. Photographic montages of the eyes of patient GA 008-2. Right eye (A) and left eye (B) at age 5 years 10 months, and right eye (C) and left eye (D) at age 19 years 10 months. There is a solitary atrophy lesion in each eye (arrow) at age 19 years 10 months, after the patient had been receiving the diet for 17 years (beginning at age 2 years 10 months). The small depigmented area (left) at the 3-o’clock position may be an additional early atrophic lesion. The apparent lesion at the 11-o’clock position does not indicate atrophy but is a discrete area of depigmentation. This minimal involvement should be compared with the multiple lesions in her sibling, patient GA-008-1, at age 6 years 4 months (Figure 1, A and B).
II. These changes have occurred despite excellent control of plasma ornithine levels (mean ± SD, 1.9 ± 0.8 mg/dL [144 ± 62 µmol/L]).

PATIENT GA021-2

The brother of patient GA021-1, born in April 1982, was diagnosed as having GA in July 1984 at the age of 2 years 3 months. He was first seen at age 2 years 6 months. Following confirmation of the diagnosis of GA, he began an arginine-restricted diet at age 2 years 8 months. Photographic montages of the right and left retinas were prepared in October 1986 at age 4 years 9 months (Figure 7). There was diffuse mottling of the RPE in the middle and far periphery with multiple, small, discrete depigmented spots but no areas of atrophy. The ERG amplitude was decreased. By September 2000, at age 18 years 6 months (Figure 7), the appearance of the retinas had changed, with mottling of the pigment epithelium and a moderate increase in selected areas of pigmentation. During the 16 years he received the diet, he had not developed atrophic lesions but had shown further deposition of pigment, mainly lacy in appearance but with 2 clumps (Figure 7). During the follow-up period, the final threshold of dark adaptation remained normal and the decline in sensitivity of the central 30° visual field was minimal. The half-life of his visual field score was 120.6 years (Figure 8). However, a gradual reduction in amplitude of the ERG maximal response had occurred (Figure 8); the half-life of his ERG amplitude was 9.63 years, shorter than that seen in his sister. By age 19 years, there was no evidence of any lens opacity. The mean ± SD plasma ornithine level was 1.6 ± 0.8 (123 ± 64 µmol/L).

COMMENT

Siblings with GA have the same OAT genotype and tend to follow a similar course of chorioretinal degeneration. In this study, we first asked how the retinas of 2 siblings would differ at the same age if the younger sibling had begun the...
diet at an earlier age than the older sibling. This would provide early data on the effects of a reduction in plasma ornithine levels on retinal degeneration. The second question asked how retinal degeneration would progress in a younger sibling who had been receiving the diet for 16 to 17 years and who had not yet shown any retinal lesions compared with the older sibling, who already had typical chorioretinal degeneration. This would tell us whether the diet might be more effective in early cases without retinal lesions compared with later cases with well-established retinal lesions. The third question we asked was whether the functional status of the retina, as measured by routine psychophysical and electrophysiological techniques, could be preserved over time in both siblings, especially in the younger, with absent or minimal retinal changes.

At the time of our previous report, both sibling pairs had been receiving the diet for 7 to 8 years and each younger sibling had reached the age of the older sibling at the time of the older sibling’s diagnosis. For both sibling pairs, the younger had not yet developed any atrophic lesions and had only diffuse mottling of the RPE with some small, discrete depigmented spots in the periphery. The appearance of the earliest lesions in the RPE is consistent with the observations of Kuwabara et al17 in rats and monkeys receiving intravitreal injections of l-ornithine, and with the more recent results of Wang et al,18,19 who produced an OAT-deficient mouse by gene targeting and found that the RPE cells were the site of the earliest pathologic changes.

After 16 to 17 years of receiving the diet, the appearance of the retinas in the younger siblings was quite remarkable. Patient GA008-2, who had been receiving the diet for 17 years with excellent reduction of ornithine levels, had only a fine dusting of pigment noted peripherally in both eyes, somewhat reminiscent of the early changes...
in retinitis pigmentosa. There was only 1 discrete atrophic lesion in each eye. The phenotype of patient GA021-2, who had been receiving the diet for 16 years with excellent reduction in ornithine levels, also showed diffuse mottling of the RPE in the mid and far periphery. Deposition of pigment was found, usually lacy in appearance but occasionally in clumps and without atrophic lesions. Again, this retinal appearance suggests early retinitis pigmentosa. Further consideration of our first question suggests that a different phenotype of retinal changes, more akin to retinitis pigmentosa than GA, resulted from prolonged and successful reduction of plasma ornithine levels, with the RPE cells showing the major pathologic changes. This was probably in process before the diet was instituted.

With respect to the second question, it was apparent that the younger of the 2 sibling pairs, in whom the retinas appeared considerably less affected at the start of the diet, appeared to progress more slowly and toward a different fundus phenotype. The older of the sibling pairs, both of whom had well-established typical-appearing retinal lesions of GA, continued to experience progression and coalescence of a few chorioretinal lesions while receiving the diet. Whether the course of GA reflected the variable nature of the disease or a decrease in plasma ornithine levels (GA021-1 having a larger decrease than GA008-1 but both having the fundus lesions progressing about the same) could not be determined at the time. Thus, the younger siblings appeared to have had a notable slowing of the fundus change. This result is consistent with those found in the murine study of OAT deficiency produced by gene-targeting in which an arginine-restricted diet with reduction of plasma ornithine levels, also showed diffuse mottling of the RPE and RPE cells showing the major pathologic changes. This was probably in process before the diet was instituted.

The third question is the most important. Even in a retina with no atrophic lesions and only diffuse mottling of the RPE (patient GA021-2), ERG amplitude at the time of initial diagnosis, while the patient was receiving general anesthesia, was reduced. It is unlikely that ERG amplitude was reduced at birth (as is thought to be the case in retinitis pigmentosa) given that fetal umbilical cord blood ornithine concentration had been measured in 1 patient and found to be normal. Furthermore, Wang et al reported that ERG amplitudes in mice with GA were found to be normal at age 2 months and did not show a clear decrease until the animals were 6 months old. It is clear that during the 16- to 17-year follow-up in our study, a small but slowly progressing measurable decrease in functional status occurred in the younger member of each sibling pair. These changes were seen in either ERG amplitude or visual field sensitivity, while psychophysical measurements of central visual function, such as visual acuity, color vision, and dark adaptation remained normal. In the 2 older siblings, the rates of change of ERG amplitude and central 30° visual field sensitivity were similar. In patient GA008-2, a mild decline in visual field sensitivity was seen despite the stable ERG maximal response amplitude. However, flicker response amplitude (data not shown) evidenced a decline comparable with that of the central visual field. We speculate that the stability of the maximal response amplitude may be due to preservation of rod-mediated function since the rod response (data not shown) did not show a declining trend similar to that seen for the flicker response. In contrast, in patient GA021-2, the reduction in maximal response amplitude was more conspicuous than the minimal change in visual field sensitivity in the central 30° visual field. This was probably because static perimetry only reflects the function of the posterior pole of the retina (central 30°) while the ERG also reflects the function of the peripheral retina. The time course of the ERG amplitude of patient GA021-2 was the only instance in which the rate of change was greater in the younger than in the older sibling. This decline in ERG amplitude suggests that, despite the absence of typical chorioretinal atrophic lesions, a moderate reduction in RPE/photoreceptor function had occurred, which is possibly reflected by the changes in peripheral fundus pigmentation seen in this patient. Since the OAT-deficient mice fed an arginine-restricted diet from age 6 weeks had a normal ERG over a 12-month period, it is possible that the retinal function could have been preserved if the arginine-restricted diet was instituted at an earlier age and had been more effective in maintaining ornithine levels in the normal range.

Three of the 4 patients included in this study (GA008-1, GA008-2, and GA021-2) showed final dark adaptation thresholds in the normal range. This may be because dark adaptation was measured with a large test target in a single test locus centered on the fovea. Therefore, this finding does not rule out a patchy distribution of functional loss that could have been detected using a smaller target in multiple test loci. It does, however, suggest that these 3 patients have rod-mediated function, at least in some areas of their central retinas, which allows them to detect very dim stimuli. In accord, patients did not report difficulties seeing at night or in dim illumination.

In summary, commencing an arginine-deficient diet to reduce plasma ornithine levels at an early age before any chorioretinal changes have occurred would seem to slow the development of retinal lesions and to result in a different phenotype similar to early retinitis pigmentosa. However, there is still a progressive, relatively small loss in some aspects of retinal function despite excellent dietary compliance as seen in patient GA021-2. Continued follow-up of these patients may provide further insights into the development of new and improved methods of treatment. This suggests that other factors, such

Figure 8. Patient 021-2. Graph of central 30° field sensitivity measured with static perimetry (decibels, open circles) and electroretinogram (ERG) maximal response amplitude (microvolts, solid circles) as a function of time. The line passing through the data points is an exponential curve.
as genetic heterogeneity, local requirements for OAT activity in retinal cells, or other modifying genes may also play a role in the pathophysiology of GA.

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REFERENCES


