Assessment of Visual Function in Patients With Gyrate Atrophy Who Are Considered Candidates for Gene Replacement

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Objective: To assess the course of change of visual function outcome variables in 5 patients with gyrate atrophy before a gene replacement therapy clinical trial.

Methods: The outcome variables selected were visual field sensitivity and electroretinogram amplitude. The course of change of these outcome variables was determined by calculation of their half-lives.

Results: In the 4 to 6 years during which each patient was followed up for this study, median visual field half-lives were 17.0 years (static perimetry) and 11.4 years (kinetic perimetry). Median electroretinogram half-lives were 16.0 years (maximal response) and 10.7 years (flicker response).

Conclusions: The course of the decline of visual function outcome variables is frequently slow. Thus, a long-term clinical trial would be required to assess the efficacy of the intervention in the preservation of visual function.

Gyrate atrophy (GA) is a chorioretinal dystrophy characterized by progressive development of atrophic areas in the choroid and retina. The molecular basis of GA is a mutation of the ornithine-delta-aminotransferase (OAT) gene, and its biochemical hallmark is hyperornithinemia. Results in humans and in a mouse model of GA indicate that reduction of ornithine plasma concentration slows or prevents further retinal degeneration. One potential approach to achieve this aim is to create an ornithine “sink,” by introducing the OAT gene into a cell population, and thereby reduce ornithine concentration.

Between November 3, 1993, and April 10, 1994, skin keratinocytes of 5 patients diagnosed as having GA were harvested by performing a 2 × 1-cm elliptical skin biopsy with the use of local anesthesia. The purpose of this procedure was to determine whether the normal OAT gene could be introduced into these cells, which could then be returned to the donor’s skin to act as a sink. Laboratory studies to determine the feasibility of introducing the gene were performed, and ongoing research will determine the viability of the modified cells before a possible skin transplantation.

In preparation for a clinical trial, and while these studies were being carried out, the patients’ visual function was followed up during the intervening 4 to 6 years by measuring, among other variables, their visual acuity, visual field (VF), and electroretinogram (ERG). Herein, we report the changes in visual function during this 4- to 6-year period.

Table 1 presents data on the 5 patients, including the date of biopsy, the date of the last visit, and visual acuity on these 2 dates. The second and third columns of this table identify the specific OAT gene alleles present in each patient. Cataract surgery was performed on patient 3 in the left eye and the right eye in 1988 and 1989, respectively. Patient 5 underwent cataract surgery on the left eye in 1989.

In 3 patients (patients 1, 3, and 4), there was a good agreement between the severity of ophthalmoscopic findings and the abnormality of visual function variables. However, in the remaining 2 patients, the severity of visual loss exceeded the degree predictable by fundus appearance. Therefore, visual function variables, rather than ophthalmoscopic findings, were used to quantify progression.
PATIENTS AND METHODS

All patients included in this study gave informed consent after the research project had been approved by the National Eye Institute, Bethesda, Md, institutional review board.

The 2 main outcome variables used to assess visual function were VF sensitivity and ERG amplitude. Although other aspects of visual function were measured in our patients, outcome variables that reflect central visual function (visual acuity, dark adaptation, and color vision) were not analyzed in this study, because they may remain stable despite progressive loss of peripheral retinal function. Central 30° VFs were measured with a Humphrey Field Analyzer (Humphrey Instruments, San Leandro, Calif), using the threshold 30-2 program with a full threshold strategy. A global VF score was obtained using the summation of sensitivity values in the 76 points tested by this program. Kinetic perimetry was performed with a Goldmann perimeter, and the area of a representative isopter was measured.3 The isopter obtained with stimulus V4e was used in patients 1, 4, and 5. In patients 2 and 3, the isopter obtained with stimulus V4e was used because of their marked VF contraction. Electroretinograms were recorded following the standard procedure recommended by the International Society for Clinical Electrophysiology of Vision.6 The amplitude of maximal retinal responses (mixed rod- and cone-mediated responses elicited by the standard flash after dark adaptation) and of flicker responses (cone-mediated responses elicited by the standard flash at a 30-Hz rate after light adaptation) was measured in 4 of the 5 patients. In patient 2, low ERG amplitude precluded the use of the standardized ERG, so the amplitude of flicker ERGs elicited using the micro-ERG technique7 was used instead.

With all techniques, the half-life of the outcome variable, ie, the number of years required for VF score or ERG amplitude to decline to 50% of its value, was used to follow the course of the chorioretinal dystrophy. Half-lives of visual function outcome variables were calculated by fitting the data points with the model

\[ V_t = V_0 \cdot 2^{-(k/t)} \]

where \( t \) represents time (in years); \( V_t \), the magnitude of the outcome variable at time \( t \); \( V_0 \), initial magnitude; and \( k \), half-life (in years). The period examined was from the biopsy date to the last visit.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Allele 1</th>
<th>Allele 2</th>
<th>Birth Date</th>
<th>Date of First Visit</th>
<th>Date of Biopsy</th>
<th>VA* at Biopsy</th>
<th>Date of Last Visit</th>
<th>VA at Last Visit</th>
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</thead>
<tbody>
<tr>
<td>GA004†</td>
<td>Y245C</td>
<td>Y245C</td>
<td>7/22/50</td>
<td>4/2/79</td>
<td>4/10/94</td>
<td>20/25</td>
<td>4/21/99</td>
<td>20/32</td>
</tr>
<tr>
<td>GA060</td>
<td>E318fs(-1)</td>
<td>E318fs(-1)</td>
<td>5/9/57</td>
<td>9/5/88</td>
<td>11/3/93</td>
<td>20/200 + 1</td>
<td>7/19/99</td>
<td>20/200 – 2</td>
</tr>
<tr>
<td>GA007-1‡</td>
<td>M1I</td>
<td>M1I</td>
<td>6/1/51</td>
<td>2/27/83</td>
<td>1/10/94</td>
<td>20/32 + 2</td>
<td>1/25/99</td>
<td>20/200 – 1</td>
</tr>
<tr>
<td>GA072-1†</td>
<td>Y55H</td>
<td>Y55H</td>
<td>1/17/34</td>
<td>2/1/87</td>
<td>1/3/94</td>
<td>20/200</td>
<td>6/9/98</td>
<td>20/400</td>
</tr>
</tbody>
</table>

*VA indicates visual acuity; CF, counting fingers.
†From Brody et al.8
‡From Kaiser-Kupfer et al.2

Table 2 lists the half-lives of all visual function variables in all 5 patients. The median VF half-life was 17.0 years for static perimetry and 11.4 years for kinetic perimetry. The median ERG amplitude half-life was 16.0 years for the maximal response and 10.7 years for the flicker response. An example of the course of a single visual function variable (ERG maximal retinal response amplitude) in patient 4 is depicted in the Figure. This figure shows that the exponential model adequately described the course of the decline in magnitude of this variable.

In 2 patients (patients 1 and 4), the VF and ERG outcome variables had similar half-lives. In patient 2, no ERG amplitude decay could be detected in the left eye (his most severely affected eye). This was probably because the severity of the dystrophy had effected a decline in ERG amplitude beyond a value that could be reliably assessed, even with the sensitive technique used for this purpose. In patient 3, no decay in central VF sensitivity could be observed in the left eye. Similarly, in patient 5, maximal response amplitude did not show a measurable decay in the right eye. In both patients, a slow decay of this outcome variable was observed in the fellow eye. This apparent interocular difference was probably because of the slow decline in magnitude of the variable being measured, so that the observation time was short relative to its half-life. Patient 5 was the only patient in this sample with a ring scotoma. Therefore, the central 30° static perimetry measurement identified only the central island of vision, while kinetic perimetry and both ERG measurements reflected the function of the much larger peripheral VF.

Little information exists about the natural history of visual function variables (visual acuity, VF, and ERG) as a function of age in GA. An article9 describing the heterogeneity of a group of 29 Finnish patients with GA concludes that the natural history is variable. The experience gathered in our laboratory gives further evidence of this heterogeneity.10
The earliest detectable outcome of a gene replacement clinical trial for GA would be a modification in plasma ornithine concentration. However, the primary therapeutic objective of such a clinical trial is the preservation of visual function. Therefore, outcome measures that assess the intervention’s effect on visual function are more relevant. Because the atrophic lesions of GA first appear in the peripheral retina, diagnostic techniques that measure overall retinal function, such as perimetry or electroretinography results, are more appropriate than methods that only assess central retinal function. The use of the half-life of a given visual function variable as an estimator allows comparisons between patients with different degrees of visual loss and comparisons between different outcome variables.

The decline in visual function outcome variables in these 5 patients with GA, although relentless, is slow: the median half-life of the outcome variables assessed exceeded 10 years. In this small sample, it was not possible to relate decay in visual function to median level of plasma ornithine. Given the slow course of the deterioration in visual function, a long-term clinical trial will be required to determine the efficacy of any intervention technique, including gene replacement therapy. The selection of those patients who demonstrate a more rapid course of disease progression, ie, with a shorter half-life of the outcome variables, would reduce the time required to assess the effect of an intervention. Before an intervention, a knowledge of the rate of decay of visual function is essential to assess its efficacy.

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REFERENCES


Table 2. Half-Life (in Years) of Visual Function Outcome Variables

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Static Perimetry</th>
<th>Kinetic Perimetry</th>
<th>Maximal Response</th>
<th>Flicker Response</th>
<th>Median Plasma Ornithine, μmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OD</td>
<td>OS</td>
<td>OD</td>
<td>OS</td>
<td></td>
</tr>
<tr>
<td>GA004*</td>
<td>17.0</td>
<td>16.9</td>
<td>11.3</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>GA060</td>
<td>16.3</td>
<td>16.6</td>
<td>13.8</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>GA007-1†‡</td>
<td>47.3</td>
<td>No decay</td>
<td>5.4</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>GA072-2†‡</td>
<td>2.3</td>
<td>13.9</td>
<td>2.3</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>GA072-2†‡</td>
<td>89.5</td>
<td>6.4</td>
<td>4.4</td>
<td>7.4</td>
<td></td>
</tr>
</tbody>
</table>

*From Kaiser-Kupfer et al.2
†From Brody et al.8
‡Low electroretinogram amplitude precluded the use of the standardized electroretinogram.

Electroretinogram maximal retinal response amplitude in patient 4 as a function of time after biopsy. Circles indicate data for the right eye; triangles, left eye. The lines passing through the data points correspond to the model described in the text. The half-life of this variable was 5.4 years for the right eye and 10.3 years for the left eye.