Principles and Practice of Clinical Electrophysiology of Vision

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PART XV

Retinal Pigment Epithelial Disease

85

Gyrate Atrophy of Choroid and Retina

Richard G. Weleber

HISTORY OF THE DISEASE

Gyrate atrophy of the choroid and retina is one of scores of genetic dystrophies allied to retinitis pigmentosa. Although first described by Cutler in 1895[5] and by Fuchs in 1896,[8] interest in gyrate atrophy was sparked by the reports by Simmel and Takki in 1973[34] and Takki in 1974[39] of the finding of hyperornithinemia associated with this condition. Since then, the enzyme defect (ornithine aminotransferase [OAT]) has been detected,[31] the abnormal gene product characterized biochemically and enzymatically,[16, 18] the gene for the missing enzyme cloned,[13] and studies begun on a molecular level to uncover the mechanism of the loss of functional gene product. OAT is a pyridoxal phosphate–dependent enzyme, and pyridoxine-responsive and nonresponsive forms of the condition have been described. Over 100 patients have been reported worldwide. The largest group of patients are Finnish, none of whom are pyridoxine responsive. Heterogeneity exists for gyrate atrophy for both pyridoxine-responsive and -nonresponsive cases. For more extensive coverage the reader is referred to recent reviews.[41, 46]

The electroretinogram (ERG) is severely abnormal in most patients with gyrate atrophy, even in childhood (Figs 85–1 and 85–2).[4, 15, 39, 45] Stoppoloni et al.[38] reported an allegedly normal ERG in a 3-year, 9-month-old girl, but the technique was inadequately described, and the amplitudes for the patient and the normal ranges were not presented. Rinaldi et al.[29] reported that the ERG for this same patient at 4 years of age was normal for the left eye (photopic a-wave, 40 μV; b-wave, 80 μV; scotopic a-wave, 40 μV; b-wave, 200 μV) but for the right eye was now subnormal (photopic a- and b-waves, 40 μV; scotopic a-wave, 40 μV; b-wave, 125 μV). However, again the ranges of normal responses for the technique employed were not given. Most reports, especially those of older patients, describe the ERG as undetectable, but usually averaging was not performed, and the lower limits of detectability were not given for the system used. Patients with pyridoxine-responsive gyrate atrophy have had some of the largest reported ERG amplitudes, with maximal bright white stimulus scotopic and photopic b-wave amplitudes in the 100- to 200-μV and 50- to 65-μV range, respectively (Figs 85–1 and 85–2). For those patients with sizable ERGs, although both rod- and cone-mediated responses are subnormal, the rod responses appear more subnormal than do those from the cone system.[4, 15, 45] The oscillatory potentials range from moderately to severely subnormal but are often still clearly discernible and, in rare instances, relatively preserved when compared with the loss of b-wave amplitude. The implicit times are usually normal, although mild prolongation of cone b-wave implicit times have been measured (Fig 85–1).[45]

The electro-oculogram (EOG) can range from low normal to severely subnormal.[15, 39, 48] Fast oscillations of the EOG were subnormal for three pyridox-

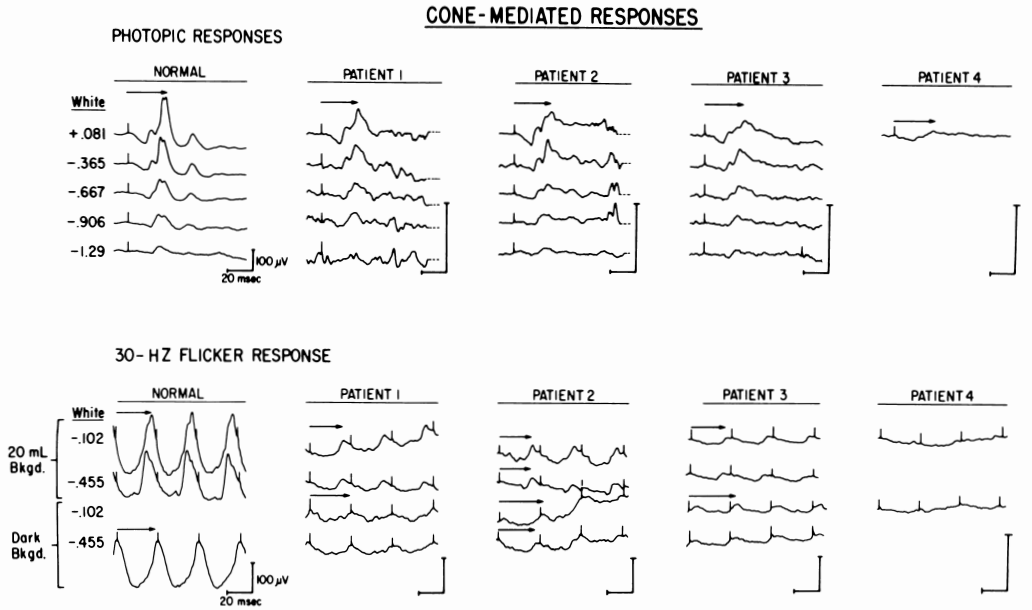

FIG 85–1.
Photopic cone and 30-Hz flicker ERGs from patients with pyridoxine-responsive (patients 1 to 3[16, 18, 46, 48, 50]) and pyridoxine-nonresponsive (patient 4[16, 18, 46, 48, 50]) gyrate atrophy. Note the prolonged implicit time for some of the 30-Hz flicker responses for patients 2 and 3. Note also that the calibration scale is different in height for the patients as *compared with* the normal ERG. The numbers to the left of the normal tracing indicate the intensity of the stimulus in log foot-lambert-seconds. (From Weleber RG, Kennaway NG: *Ophthalmology* 1981; 88:316–324. Used by permission.)

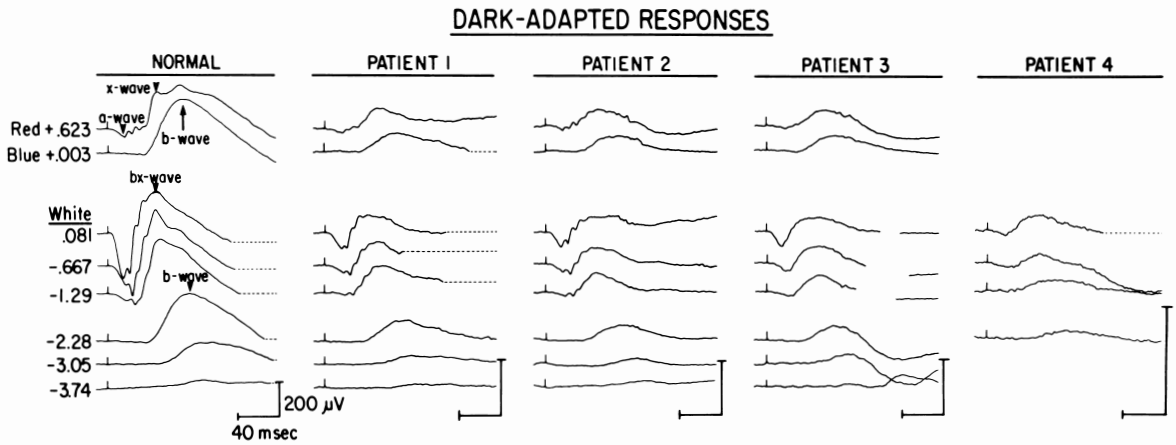

FIG 85–2.
Scotopic ERG responses from patients with pyridoxine-responsive (patients 1 to 3) and pyridoxine-nonresponsive (patient 4) gyrate atrophy. The calibration scale indicates 100 μV vertically and 20 ms horizontally for all tracings. Note that the calibration scale is different in height for the patients as compared with the normal ERG. The numbers to the left of the normal tracing indicate the intensity in log foot-lambert-seconds for the white light stimuli and in log microjoule/cm^2-steradian for the red and blue light stimuli. (From Weleber RG, Kennaway NG: *Ophthalmology* 1981; 88:316–324. Used by permission.)

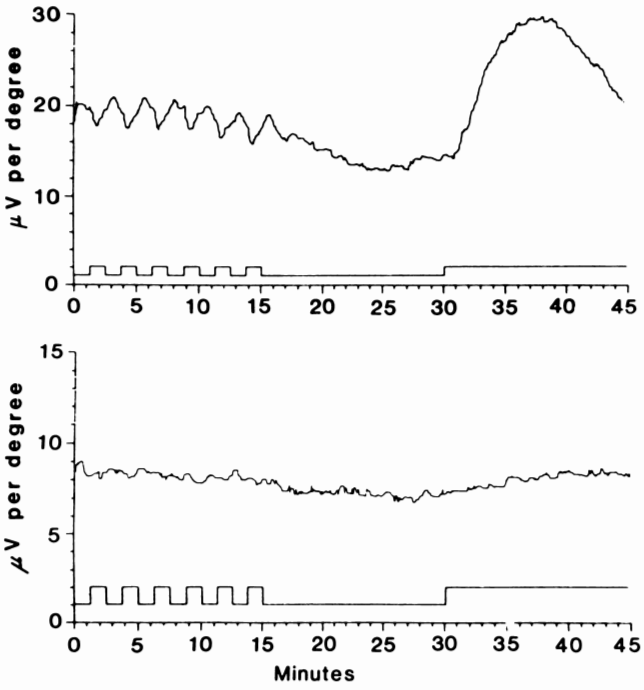

FIG 85–3.
EOG from a normal subject (light-to-dark ratio, 2.26; *above*) and a 38-year-old woman with pyridoxine-responsive gyrate atrophy (patient 3) (light-to-dark ratio, 1.25; normal, >1.85; *below*). (From Weleber RG, Kennaway NG: Gyrate atrophy of the choroid and retina, in Heckenlively JR (ed): *Retinitis Pigmentosa.* Philadelphia, JB Lippincott, 1988, pp 198–220. Used by permission.)

ine responders (Weleber and Kennaway[46] and R. Weleber, unpublished observations, 1983–1987) (Fig 85–3).

CLINICAL DESCRIPTION AND NATURAL HISTORY

Gyrate atrophy begins within the first decade of life as circular areas of total vascular atrophy of the choroid and retina in the mid and far periphery (Fig 85–4, Plate 15). As the individual ages, these lesions enlarge, coalesce, and eventually form the characteristic scalloped border between the atrophic peripheral choroid and retina and more intact posterior fundus. In some patients who are not responsive to pyridoxine, atrophy also develops around the optic nerve and in a ring around the macula. The earliest symptoms are loss of peripheral visual field (Fig 85–5) and night blindness (Fig 85–6). Eventually, progressive extension of the lesions toward the posterior pole produces constriction of visual fields and in most patients legal blindness from tunnel vision by the fourth to fifth decade. Loss of central vision can occur from cataracts, macular edema, or involvement of the atrophic process in the macula itself. All patients are myopic, with the degree of myopia ranging from mild to severe.

Dark adaptometry curves range from normal[39] to an elevation of both cone and rod segments (Fig 85–6).[39, 46, 48] Color vision is usually good until visual acuity falls below 20/40; *tritan* defects can occur.[39]

Careful funduscopy and fluorescein angiograph usually shows a zone of disturbed retinal pigment epithelium (RPE) between atrophic and more intact retina (Fig 85–7). These are areas into which the atrophic lesions will extend with time. Enoch et al.,[7] using detailed perimetry, have shown that the disruption of retinal function occurs abruptly in this zone, but that some function persists within islands of more peripheral, remaining retina.

Although intelligence is normal in the vast majority of cases, several patients have had abnormal electroencephalography results or frank seizures. Although of no discernible clinical significance, all but one[15] of the patients investigated have had abnormal inclusions within type 2 muscle fibers on muscle biopsy (Fig 85–8).[18, 19, 37] Abnormalities on electrocardiography have also been noted in several patients.[37]

Inheritance is clearly autosomal recessive. Carriers, who are clinically normal, can be distinguished from normal by an assay of enzyme activity in cultured fibroblasts.[18, 33]

KNOWN PATHOPHYSIOLOGY/ HISTOPATHOLOGY OF GYRATE ATROPHY

Histopathology

In only one case of gyrate atrophy have the eyes been studied histopathologically.[49] This 97-year-old lady (patient 6 in previous reports) had pyridoxine-responsive gyrate atrophy,[48, 50] and the kinetics of her mutant enzyme have recently been studied.[16] In the regions of atrophy there was total loss of all retinal and choroidal elements, but the retina posterior to the scalloped abrupt border was essentially intact.

The abnormalities on muscle biopsy appear as subsarcolemmal inclusions that on electron microscopy represent accumulations of tubular inclusions (see Fig 85–8). These defects within muscle are believed to be secondary to a localized deficiency of creatine phosphate created by end product inhibi-

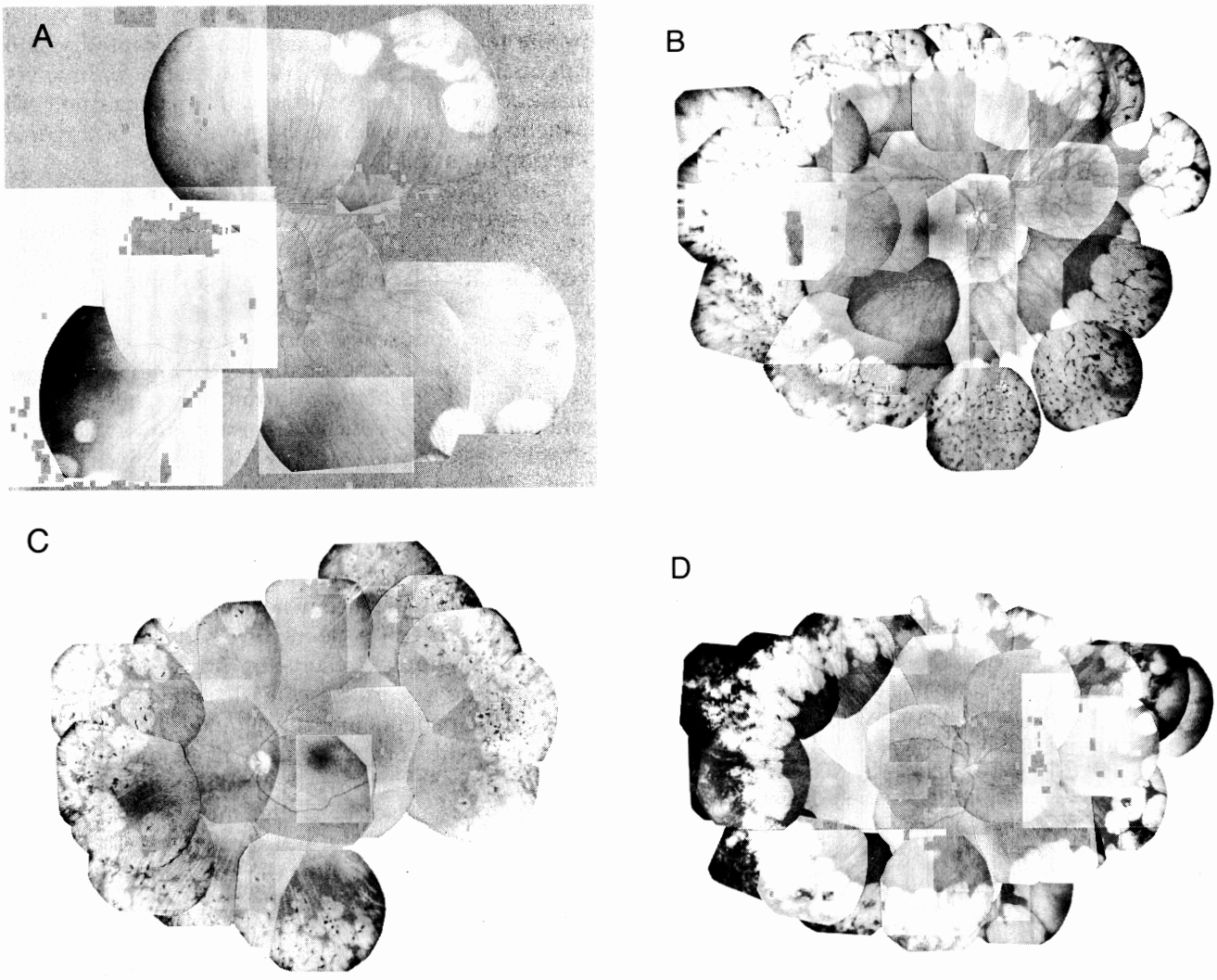

FIG 85–4.
Fundus appearance of the right eye of a 15-year-old girl with early pyridoxine-nonresponsive gyrate atrophy **(A)** (same patient as in Fig 12–1, Weleber and Kennaway[46]), a 28-year-old woman with pyridoxine-responsive gyrate atrophy **(B)** (patient 1), a 37-year-old woman with pyridoxine-responsive gyrate atrophy **(C)** (patient 3), and a 40-year-old man with pyridoxine-nonresponsive gyrate atrophy **(D)** (patient 4). (From Weleber RG, Kennaway NG: Gyrate atrophy of the choroid and retina, in Heckenlively JR (ed): *Retinitis Pigmentosa.* Philadelphia, JB Lippincott 1988, pp 198–220. Used by permission.) **(See also Color Plate 15.)**

tion of arginine glycine transamidinase by the high levels of ornithine in patients with gyrate atrophy.[35] However, since arginine glycine transamidinase activity has not been detected in the retina, such a mechanism cannot explain the pathophysiology in this tissue.[28]

Abnormal, swollen mitochondria have been observed in liver[1] and iridectomy specimens[44] and are believed to result from the toxicity of high ornithine levels within mitochondria.

Physiology

Although much is known about the enzyme defect and more recently about the molecular defects in gyrate atrophy, little is known as to how the enzyme deficiency actually produces the atrophy. Proposed theories have centered on the possibility of direct toxic effects of elevated ornithine levels within mitochondria and a localized deficiency of either creatine or proline within the retina. Evidence does ex-

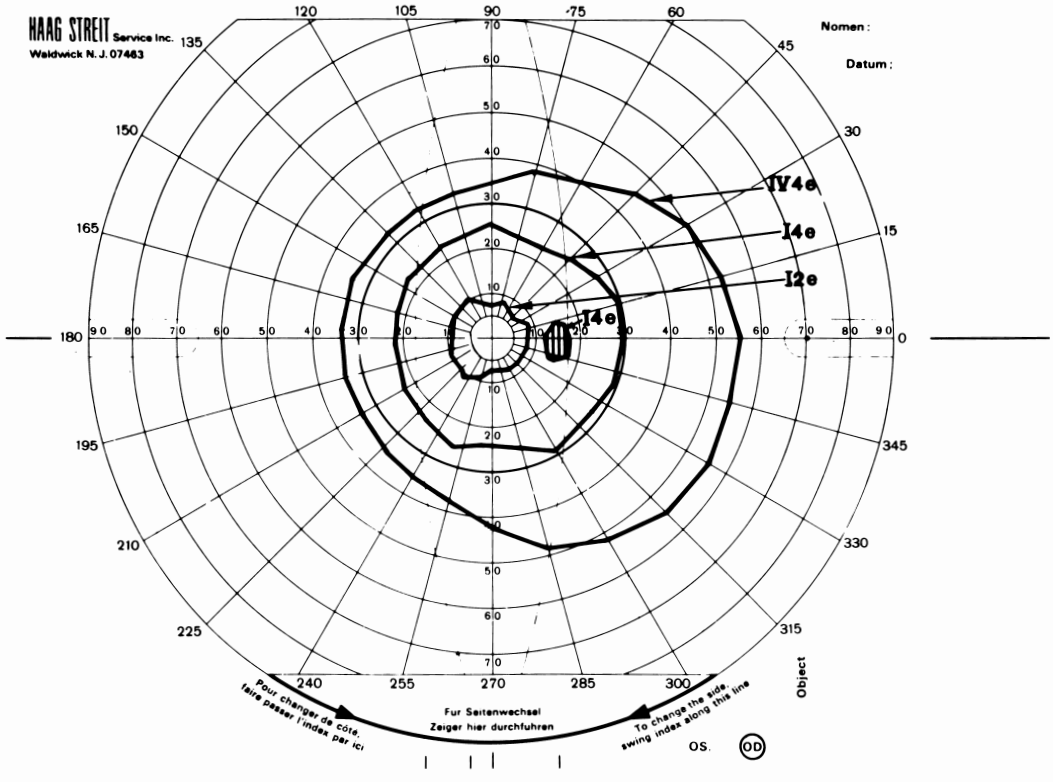

FIG 85–5.
Visual field by Goldmann perimetry for a 15-year-old girl with pyridoxine-nonresponsive gyrate atrophy (same patient as Fig 85–4,A). Note that the visual field is more contracted than would be anticipated from the appearance of the retina. (same patient as in Fig 12–1, Weleber and Kennaway[46]).

ist that ornithine concentrations similar to those seen in patients are toxic to RPE cells in vitro.[6] Whereas creatine phosphate is a known major source of energy for muscle, its role as an energy store for the eye is unknown. The most tenable theory for the ocular pathology is localized deficient proline synthesis within the retina.[30]

Biochemistry

Although in her original report Takki alluded to the finding of deficient OAT, Sengers et al. were the first to demonstrate conclusively that OAT was the defective enzyme in gyrate atrophy.[31] This deficiency was confirmed by others in lymphocytes[40] and cultured fibroblasts.[17, 23, 32] OAT is a pyridoxal phosphate–dependent enzyme (Fig 85–9) that catalyzes the interconversion of ornithine and glutamic-γ-semialdehyde, the latter being metabolized to either glutamate or proline. The vast majority of patients with gyrate atrophy are not responsive to pyridoxine. However, six patients,[4, 10, 18, 32, 47, 48, 50] none of Finnish extraction, have been found to respond to pyridoxine either in vivo, with approximately a 50% reduction of serum ornithine levels, or in vitro, with elevation of residual OAT activity and increased concentrations of pyridoxal phosphate. The residual OAT activity is greater in patients who respond to pyridoxine. Characterization of the mutant enzyme in pyridoxine-responsive and -nonresponsive patients has provided interesting correlations with the clinical and biochemical features in these patients.[16] In pyridoxine-responsive gyrate atrophy, the K_m for pyridoxal phosphate is elevated, and the enzyme shows increased heat lability in some cases. Surprisingly, although her enzyme showed the greatest heat stability of the mutant enzymes studied, the pyridoxine-responsive patient with the mildest disease had the highest K_m for pyridoxal phosphate. Western blot analysis of mitochondrial proteins by using antiserum to human OAT demonstrated reduced but easily detectable protein in four pyridoxine-responsive patients and normal protein in two of five patients who did not

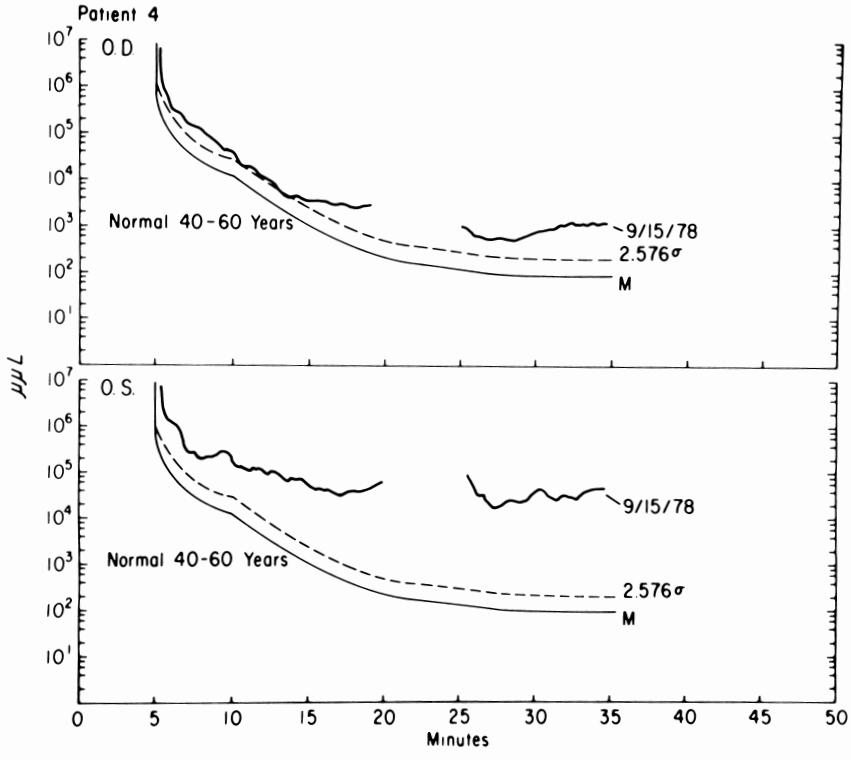

FIG 85–6.
Full dark adaptation curves for a 40-year-old man with pyridoxine-nonresponsive gyrate atrophy (patient 4). Note that the cone and rod segments of the curve are only mildly elevated for the right eye but markedly elevated for the left eye. (From Weleber RG, Kennaway NG: Gyrate atrophy of the choroid and retina, in Heckenlively JR (ed): *Retinitis Pigmentosa.* Philadelphia, JB Lippincott, 1988, pp 198–220. Used by permission.)

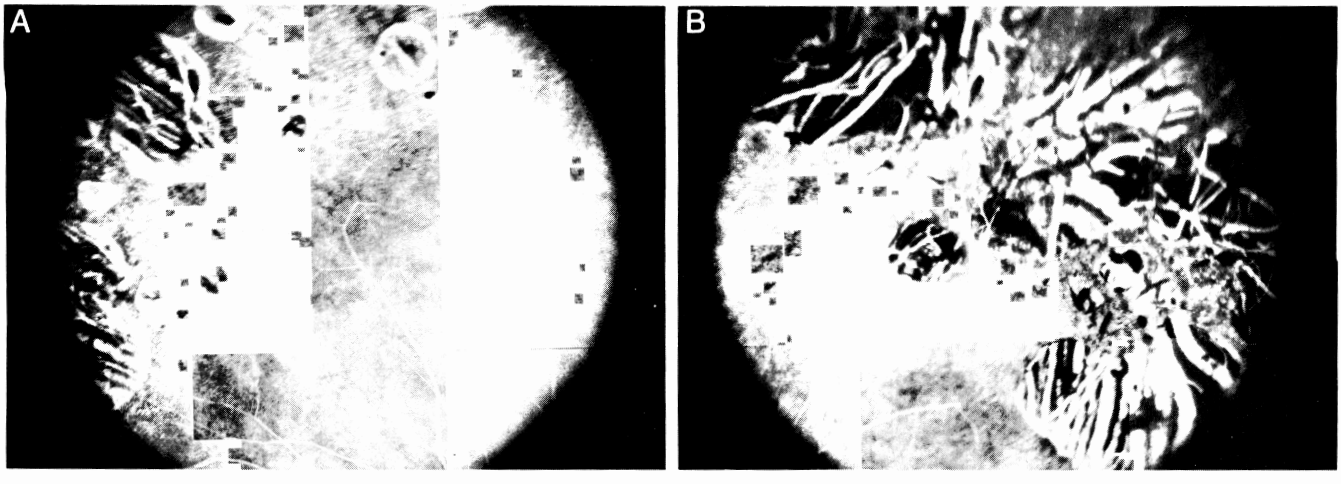

FIG 85–7.
Fluorescein angiograms of the zone between the areas of atrophy and more intact retina in the left eye of a 37-year-old woman with pyridoxine-responsive gyrate atrophy (patient 3, same patient as in Fig 85–4,C). Note the diffuse RPE transmission defects in the zone just posterior to areas of atrophy. (From Weleber RG, Kennaway NG: Gyrate atrophy of the choroid and retina, in Heckenlively JR (ed): *Retinitis Pigmentosa.* Philadelphia, JB Lippincott, 1988, pp 198–220. Used by permission.)

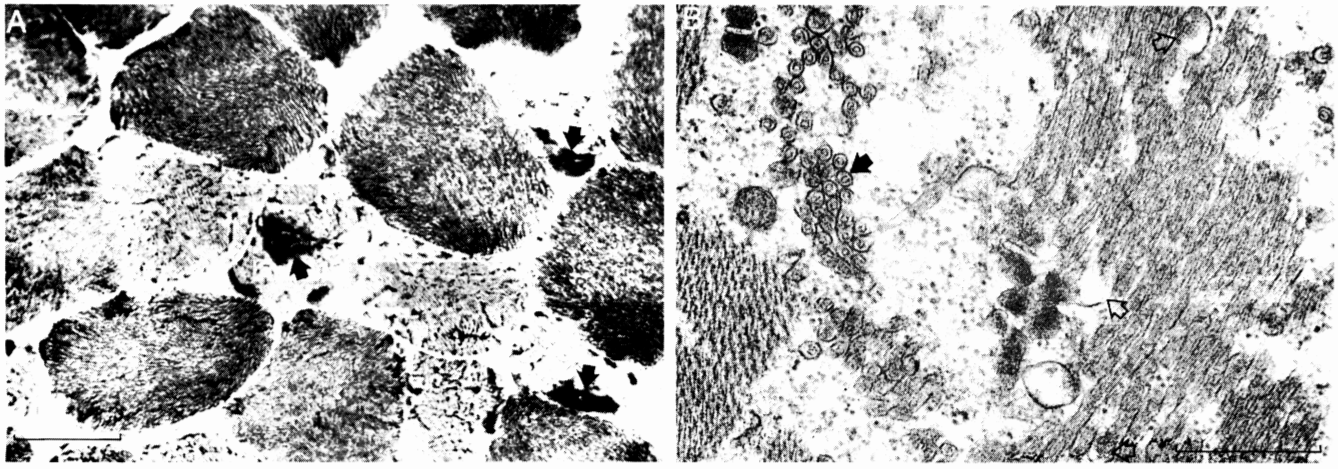

FIG 85–8.
Muscle biopsy material from a patient with pyridoxine-responsive gyrate atrophy (patient 2) demonstrates subsarcolemmal inclusions *(solid arrows)* in type 2 muscle fibers on light microscopy (NADH–tetrazolium reductase stain) **(A)** and tubular aggregates *(solid arrows)* and dilated saccules *(open arrows)* on electron microscopy **(B).** Calibration bars indicate 20 μm for light micrography and 0.5 μm for electron micrography. (From Kennaway NG, Weleber RG, Buist NRM: *Am J Hum Genet* 1980; 32:529–541. Used by permission.)

respond to pyridoxine. Three other nonresponsive patients showed very low to undetectable OAT protein. Low residual enzyme activity in mitochondrial preparations from patients not responsive to pyridoxine has made enzyme kinetic studies difficult, but the K_m for ornithine and pyridoxal phosphate appear normal. These studies indicate heterogeneity within as well as between pyridoxine-responsive and -nonresponsive patients with gyrate atrophy.[16]

Therapeutic trials for patients with gyrate atrophy have involved a reduction of plasma ornithine levels by supplementation with vitamin B_6 for the uncommon pyridoxine-responsive patients or by reduction of protein and hence arginine in the diet. Arginine restriction has lowered ornithine levels to within the normal range, and this has been associated with apparent mild short-term improvement of visual function.[14, 20] Mild short-term improvement was also noted in pyridoxine-responsive patients given supplemental vitamin B_6.[45] Others have reported either no improvement or worsening of fundus lesions while receiving diet or pyridoxine supplementation.[3] Vannas-Sulonen et al. have reported continued progression despite normal or near-normal plasma ornithine concentrations achieved with dietary arginine restriction.[42] Proline supplementation has been tried as a means of therapy,[9] but no conclusive evidence of its benefit on a long-term basis has been shown. Creatine supplementation reversed some of the abnormalities as seen on muscle biopsy samples but had no effect on the eye.[36, 43]

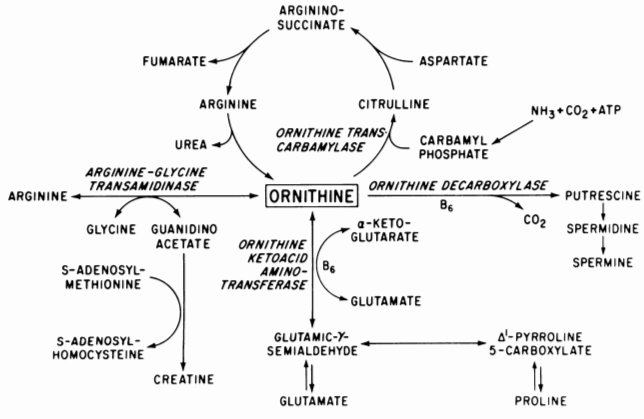

FIG 85–9.
Biochemical pathways involved in the metabolism of ornithine. (From Weleber RG, Kennaway NG, Buist NRM: *Int Ophthalmol* 1981; 4:122–132. Used by permission.)

Molecular Genetics

O'Donnell et al. in 1985 demonstrated that the gene for OAT resides on chromosome 10.[22] The mRNA for human OAT was cloned and the sequence for human cDNA determined in 1986 by Inana et al.[13] Barrett et al.[2] and Ramesh et al.[25] in 1987 localized OAT gene sequences to the long arm of chromosome 10 and the short arm of the X chromosome, the latter probably representing nonfunctional pseudogenes. O'Donnell et al. showed that only the gene sequence on chromosome 10 tran-

scribes OAT activity.[24] Most patients with gyrate atrophy have apparently normal OAT mRNA[12, 27] and a variable amount of immunoreactive OAT protein.[12, 16] These findings suggest that the underlying molecular defect may be subtle, such as a point mutation that has resulted in poor translation of mRNA, a labile gene product, defective transport to the mitochondria, or a gene product that is inactive. A variety of defects have recently been characterized at the molecular level, including several instances of single base changes,[12, 26] possibly affecting the pyridoxal phosphate binding site,[26] the recognition signal for mitochondrial uptake,[26] or in one case, the initiator codon,[21] which results in a loss of the entire mitochondrial leader frame and 113 amino acids of the mature protein. For one patient OAT gene expression was completely lacking due to a a deletion of part of the gene.[11, 12] These studies attest to the heterogeneity of gyrate atrophy at the molecular level.

RELEVANT TESTING AND DIFFERENTIAL DIAGNOSIS

The differential diagnosis of gyrate atrophy includes choroideremia, especially in later stages, paving-stone peripheral retinal degeneration, which can be seen in high myopia, and a uncommon form of peripheral atrophy of the choroid and retina that begins in middle age or older patients with fundus features that closely mimic gyrate atrophy but are milder.[46] These latter patients and indeed all patients with other disorders that might be confused with gyrate atrophy have failed to show hyperornithinemia and have shown normal OAT activity in cultured fibroblasts or lymphocytes. Choroideremia can usually be easily distinguished from gyrate atrophy, especially in the early stages, by the characteristic fundus appearance and fluorescein angiogram. The fundus in choroideremia shows a somewhat patchy but more generalized loss of RPE and choriocapillaris. The best means of establishing the diagnosis of gyrate atrophy is by measurement of serum or plasma ornithine levels. Additional testing is indicated for determining pyridoxine responsiveness. This can be achieved by measuring ornithine levels before and after supplementation with vitamin B_6. Pyridoxine responsiveness can also be demonstrated by an assay of OAT activity in cultured fibroblasts with and without increased levels of pyridoxal phosphate. Chronic supplementation of the diet with vitamin B_6 is not recommended unless pyridoxine responsiveness is shown by in vitro or in vivo methods. Because of the risks involved in the severe protein restriction that is required to reduce plasma ornithine levels, dietary restriction of arginine is not recommended except as part of an investigative protocol at a center where adequate metabolic monitoring can be done.

Perimetric visual field testing is indicated for periodic assessment of the level of visual impairment and is the most practical means of functionally monitoring the disease for progression. ERG and EOG are valuable for establishing the severity of retinal dysfunction and are useful for following those rare patients who have sizable responses.

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