Clinical Features in Affected Individuals From 21 Pedigrees With Dominant Optic Atrophy

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Objective: To assess phenotypic variation of affected individuals from British families with autosomal dominant optic atrophy.

Design: Eighty-seven patients from 21 families showing evidence of linkage to chromosome 3q were identified via the Genetic Clinic of Moorfields Eye Hospital, London, England. Genetic linkage analysis was carried out with markers from chromosome 3q28-qter. Patients underwent clinical examination and psychophysical and electrophysiological testing.

Results: Best-corrected visual acuity ranged from 20/20 (6/6 m) to light perception. Although visual acuity was not significantly worse in older patients in the group ($\chi^2=3.20, df=4, P>.50$), it did deteriorate with age in one third of the families. Subtle or temporal pallor of the optic disc occurred in 96 (55%) of 174 eyes and total atrophy in 76 (44%). Tritanopia was found in 6 (7.5%) of 80 patients; 65 (81.2%) had a mixed color deficit. A cecocentral scotoma was found in the vast majority. Peripheral motion detection threshold was elevated in areas of visual field with raised mean surround sensitivity but not elsewhere. Pattern visual evoked potentials were of reduced amplitude and delayed. Pattern electroretinograms showed a reduced N95 component in keeping with primary ganglion cell dysfunction.

Conclusions: There is wide intrafamilial and interfamilial phenotypic variation in autosomal dominant optic atrophy, with visual function in some, but not all, families deteriorating with age. There is evidence of degeneration of the ganglion cell layer predominantly from central retina, but this is not the exclusive result of either parvocellular or magnocellular cell loss.


Autosomal dominant optic atrophy (DOA), Kjer type,1 is a disorder that leads to optic nerve pallor and reduced visual acuity.2 First described by Batten in 1896,3 the disease appears with an insidious onset of variable visual loss, optic nerve pallor, cecocentral visual field scotoma, and color vision deficit.4-8 Histopathological9,10 and electrophysiological11-13 studies suggest that the underlying defect is retinal ganglion cell degeneration accompanied by optic atrophy.

Genetic linkage studies have localized a DOA gene (OPA1; MIM 16550014) to the q28-qter region of chromosome 3.15 There is no evidence so far of genetic heterogeneity.16-18 The gene is highly penetrant19 but shows variable expression. The critical genetic interval has recently been further refined,20,21 facilitating positional cloning of the gene.

Autosomal DOA linked to chromosome 3q has been described in pedigrees from Denmark,15,22 France,16 the United Kingdom,18,23 Cuba,23 and the United States.27 To assess the phenotypic variability and prognosis in patients from British pedigrees, and to investigate the pathophysiological basis of the disease, individuals in 21 families showing close linkage to polymorphic microsatellite markers from the chromosome 3q28-qter region were examined by a single observer (M.V.). We describe the clinical features in 87 affected individuals (174 eyes) from these families and the results of electrophysiological and psychophysical tests of optic nerve function.

Results of linkage analysis in 18 of the families have been reported.21,33,34 Additional data, including haplotypes in the 21 families, will be published elsewhere. The families showed linkage to a disease locus on chromosome 3q28-qter.

The median age at examination was 37 years (range, 2-84 years), and median age at onset of symptoms was 5 years. The age at onset of symptoms showed a bimodal distribution with peaks at 5 and between 21 and 30 years of age. The median period since onset of symptoms, i.e,
PATIENTS AND METHODS

PATIENTS

Families with DOA were identified from the database of Moorfields Genetic Clinic, London, England. The clinical criteria for inclusion of families in the study were optic nerve pallor, reduced visual acuity, abnormal color vision, and a cecocentral visual field defect in at least 1 member of the family older than 6 years, with evidence of autosomal dominant inheritance. Twenty-one pedigrees had DNA marker haplotype data compatible with genetic linkage to the OPA1 gene locus on chromosome 3q28-pter.

One hundred thirty-five individuals from the 21 families (87 affected and 48 unaffected) were examined by a single ophthalmologist (M.V.). Of the affected individuals, 39 (49%) were male and 48 (51%) were female.

A full ocular history was elicited. Ophthalmic examination included best-corrected visual acuity, color vision, and ocular motility. The eye was examined by slitlamp biomicroscopy, with special attention to the optic nerve head and the nerve fiber layer. Fundus photographs were obtained, when possible, for subsequent evaluation.

The optic nerve was classified as either normal or showing subtle diffuse pallor, temporal pallor, or total atrophy. The nerve fiber layer abnormalities visible with the direct ophthalmoscope and the 90-diopter (Volk aspheric) lens were noted.

The study was approved by the Ethical and Scientific Committee of Moorfields Eye Hospital, and written informed consent was obtained from participants.

PERIMETRY

Humphrey 30-2 photopic perimetry was performed on 64 individuals from 16 families, 50 of whom (15 families) were affected. An overall assessment of patients’ observer reliability was made during the test, which was administered to the better-seeing eye. The appearance of the scotoma and its variables were recorded. These included scotoma mean deviation (defined as the mean elevation or depression of the patient’s overall field compared with the normal reference field), pattern deviation (representing the difference in decibels between the patient’s test result and the age-corrected normal values at each tested point in the visual field adjusted for any changes in the height of the measured hill of vision), and total deviation (the difference in the patient’s results as described above and their statistical significance). In 31 affected individuals, high-spatial-resolution perimetry (fine matrix mapping) of the central visual field was performed by means of the automated Humphrey field analyzer. Fine matrix mapping measures the luminance sensitivity across a fine grid matrix of 100 locations with a spacing of 1° between adjacent points. This enabled us to assess the central field immediately adjacent to the scotoma and to visualize the transition from the normal field to scotoma.

Twenty-eight affected individuals had peripheral motion detection threshold (MDT) measurement at 15° from fixation in a quadrant least affected by the scotoma. The 2 major subclasses of retinal ganglion cell, the parvocellular and the magnocellular, are classified on the basis of their projections to the layers of the lateral geniculate nucleus. Sensitivity to movement displacement is considered to be predominantly a magnocellular (M-cell) function. These measurements allowed us to assess the degree to which magnocellular ganglion cell function was affected in patients with DOA, in a part of the visual field where there was relative preservation of luminance sensitivity.

COLOR VISION

Color vision testing was performed with Hardy-Rand-Rittler plates and the Mollon-Reffin test (a minimalist 100-hue test).29

ELECTROPHYSIOLOGY

Pattern and flash visual evoked cortical potentials and pattern electroretinograms (PERGs) were recorded by means of techniques based on internationally recommended standards. Gold foil electrodes were used for the PERGs. Recordings were obtained in 13 affected individuals from 8 families. Special attention was paid to the PERG as this is presumed, at least in part, directly to reflect ganglion cell function.28

VISUAL ACUITY

Best-corrected visual acuity was measured in 87 patients. It ranged from light perception to 20/20 (6/6 m), with a median of 20/120 (6/36 m) (Table 1). No sex difference was found. Few patients showed asymmetry in visual acuity; 11 patients (13%) had a difference of 2 lines or more in Snellen visual acuity between eyes.

There was no significant relationship between visual acuity and age in the group of 87 affected individuals ($\chi^2=3.20, df=4, P>.50$). An analysis of the scatterplot of best-corrected visual acuity vs age was performed for the 7 largest families (Figure 1). These cross-sectional data (Figure 2) suggest that in some families (pedigrees A, C, F, and L) visual acuity is worse in older affected individuals, suggesting that visual acuity declines with age. In other families (pedigrees I, M, and N) this does not appear to be the case.
There was considerable intrafamilial variability in visual acuity in some families. Five families (pedigrees A, C, L, M, and N) had a spread of visual acuities of more than 0.6 logMAR units. In 3 of these families (A, C, and L), older individuals had worse visual acuity.

Visual acuity also varied considerably between families. For example, a single-factor analysis of variance of visual acuity shows that visual acuity in pedigree I is significantly less affected than that in pedigree L (analysis of variance = 29.8, df = 1, P = 8.4 × 10^-5).

Four patients (5%) had horizontal nystagmus. These patients had visual acuities of light perception, hand motions, counting fingers, and 3/60.

**OCULAR MOTILITY**

Nine (10%) of the affected individuals had a history of strabismus (6 had undergone surgery: 5 for esotropia and 1 for exotropia). At the time of examination, 1 had esotropia and 2 had exotropia. Four individuals (5%) from 2 families had horizontal nystagmus.
MORPHOLOGICAL CHARACTERISTICS OF THE NERVE FIBER LAYER AND OPTIC DISC

Optic nerve head abnormalities were seen in 86 (99%) of the patients (172 eyes) (Table 2). One patient (1%) was thought to have normal optic discs but had abnormal color vision and the full disease haplotype shown by all the affected members of that family. Typical wedge-shaped temporal pallor of the disc (Figure 3, A) was seen in 76 eyes (44%). Total atrophy (Figure 4, A) was seen in the same number. Subtle diffuse pallor was seen in 20 eyes (12%) (10 patients), and 7 of these patients were younger than 40 years. Intrafamilial variation in the appearance of the optic disc was observed among patients of similar ages. Minor degrees of interocular asymmetry were seen, but no patient had asymmetry sufficient to place the optic nerve appearance in different categories. Best visual acuity was generally associated with least degree of pallor, as assessed by direct ophthalmoscopy. However, it was possible to identify some patients with equally gross visual field deficits, some of whom had total atrophy of the disc, and some of whom had temporal pallor. Overall, there was no significant relationship between patient age and disc category, but in pedigrees A, C, F, and L (where visual acuity declined with age), there was a correlation (r=0.74).

PSYCHOPHYSICAL TESTS

Seventy-eight affected individuals had color vision tested by means of Hardy-Rand-Rittler plates. Nine (11%) showed normal results and 6 (8%) were unable to see any of the plates. The remaining 63 (81%) showed a mixture of deficits. Of these, 6 patients (8%) had a tritan defect and 57 (73%) had a mixed red-green/blue-yellow defect. A modified 100-hue test, the Mollon-Reffin test,29 was used in 80 patients. The mean scores in each of the 3 color axes (deutan, proton, and tritan) tended to rise with age, but the tritan axis was always the worst (Figure 5). Six (7.5%) of 80 patients had isolated tritanopia, but most patients (65 patients [81.2%]) had a mixed color defect. However, 2 patients (2.5%) had an isolated proton defect. Overall, the best color vision was associated with young age and better visual acuity, but when the data were analyzed by pedigree, some families (eg, pedigree I) showed little relationship between color vision and age, and some (eg, pedigree L) showed a significant association. This is in line with the decreased visual acuity seen with age in these pedigrees.

Sixty-four individuals (including 50 affected patients) from 16 families had Humphrey 30-2 visual fields under photopic conditions. Age and duration of disease were correlated with mean field deviation in the 50 affected individuals. In the older patients, and those affected for longer, mean deviation diverged from the agematched norm (correlation coefficient r=−0.4 for duration of disease vs mean deviation). The patients showed a spectrum of cecocentral scotomata, ranging from a small discrete enlargement of the normal blind spot (Figure 3, B) to a subtotal visual field loss (Figure 4, B). The fine matrix maps of the central visual field varied from mildly to grossly elevated threshold sensitivity, with 22 (73%) of 30 patients showing a superior visual field defect with a greater than 1-log unit increase in intramap sensitivity (Figure 3, C). The abnormal fine matrix maps showed elevation of threshold sensitivity particularly in the superotemporal field in 15 patients (50%). There was a sharp transition between more normal and elevated thresholds in 26 (87%) of 30 patients, which was particularly pronounced in the horizontal meridian. In addition, 33 (66%) of the visual field defects were predominantly in the superotemporal visual field in 50 affected patients (eg, Figure 6).

Twenty-eight patients, with documented visual field defects on photopic Humphrey 30-2, had peripheral MDT testing (Figure 7). The patient group mean (±SD) MDT was 7.52±2.79 compared with a published control group mean MDT of 3.82±1.99.26 This was statistically significant (P<.001). As the mean age of the patient group was lower than that of the control group, we analyzed the comparison after excluding 4 patients

**Table 2.** Optic Disc Morphological Characteristics in 87 Affected Individuals (174 Eyes) With Autosomal Dominant Optic Atrophy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age, y*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-20</td>
</tr>
<tr>
<td>Normal</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Subtle pallor</td>
<td>8 (4.6)</td>
</tr>
<tr>
<td>Temporal pallor</td>
<td>26 (14.9)</td>
</tr>
<tr>
<td>Total atrophy</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Total</td>
<td>36 (20.6)</td>
</tr>
</tbody>
</table>

*Values are numbers (percentages) of eyes. Percentages may not total sums because of rounding.*
ELECTROPHYSIOLOGICAL CHARACTERISTICS

Electrophysiological data (to be published in detail elsewhere) were obtained in 13 affected patients (26 eyes) from 8 families. In 9 of the 13 patients, the pattern visual evoked potential was absent in 1 or both eyes. Most recordable pattern visual evoked potentials were of abnormal latency, but the magnitude of the delays was not profound (peak times, 116-135 milliseconds); amplitudes were low or subnormal. Pattern electroretinograms fell within the normal range in 9 eyes of 7 patients. Fourteen eyes showed younger than 22 years. This resulted in a mean (±SD) age of 46.25±13.1 years for the patient group vs 54.10±3.6 years for the controls—not statistically different (P=.05). The age-adjusted patient group mean MDT was 7.51±2.98, still a statistically significant difference (P=.001) between mean MDT of the patient group and normal controls.
a clearly abnormal N95:P50 ratio in keeping with ganglion cell dysfunction. All eyes that showed additional involvement of the P50 component were severely affected, but in no eye was the PERG extinguished, even though visual acuity was as poor as hand motions or light perception. Flash visual evoked potentials were mostly within the normal range, but in 2 very severely affected patients there was an amplitude of less than 2.5 µV. In 1 mildly affected patient there was no absolute pattern visual evoked potential abnormality, but the visual evoked potential in 1 eye showed significant relative latency increase and amplitude reduction compared with the fellow eye, and the PERG showed N95 reduction. Significant interocular asymmetries in at least one electrophysiological measure were present in 6 of 13 patients.

This study highlights the phenotypic variation in patients with DOA from British families. Although the defective gene in DOA is unknown, the families described show linkage to DNA markers in the chromosome 3q28-ter region.21,33,34 The clinical heterogeneity seen in this study indicates a highly variable expression of the OPA1 gene. The observed phenotypic variation may have a number of explanations, including allelic heterogeneity, change in disease severity with age, and the effects of other modifying genetic or environmental factors. Both intrafamilial and interfamilial phenotypic variation is seen. Some of the interfamilial variation could result from the effect of different mutations, which can be investigated once the gene is isolated, or from different age structures within families. Intrafamilial variation may result from many factors, among them, but not exclusively, age. Even patients of similar age from the same family can show considerable clinical variation. Such phenotypic heterogeneity is not unusual in autosomal dominant disease. The reasons for it are unknown but may include the modifying effects of other genes involved in retinal and ganglion cell development, the genetic background of the individual, or physiological and environmental factors.

Optic disc abnormalities are seen in the vast majority of patients. Best color vision and least field loss was present in patients with the least degree of clinical optic atrophy.

In the families we studied, most affected individuals had substantial visual impairment; only 5 patients in this study (6%) had visual acuity of 20/30 (6/9 m) or better (although we have no longitudinal data). However, visual acuity in affected individuals varied within families from hand motions to 20/20 (6/6 m). Longitudinal studies of visual acuity33 have shown that visual acuity of some individuals declines over a period of 20 years while in others it does not. Our data support this. The observation that some families have a marked decline in visual acuity with age while others do not has important implications for counseling.

Distribution of age at diagnosis was bimodal. One group was initially diagnosed in infancy, often by a watchful mother, herself affected, and another was diagnosed...
at 11 to 30 years of age, with poor vision usually detected at school, or rarely subsequently as an incidental finding. Although nystagmus is rare, it was seen in 4 (5%) of our patients from 2 families, and those individuals had particularly poor visual acuities from an early age.

Histopathological reports\(^5,10\) suggest that the primary abnormality in DOA is loss of retinal ganglion cells, particularly those originating in the papillomacular bundle of the retinal projection. The clinical appearance of optic nerve pallor also suggests a ganglion cell disease. It is not possible to say whether the ganglion cell deficit is caused by a reduced population at birth followed by a normal rate of ganglion cell loss, or by ganglion cell loss caused by an unknown pathological process, starting at an early age and possibly continuing into adult life.

The PERG findings of a reduction in N95 and/or the N95:P50 ratio are in keeping with ganglion cell abnormality.\(^13,35\) Similar findings have been reported in other heredofamilial optic atrophies, including DOA, but not by all authors.\(^36\) Some eyes with highly abnormal pattern visual evoked potentials have involvement of the P50 component of the PERG, but the majority show a marked reduction in N95:P50 ratio (G.E.H., unpublished data, 1997). Others have described mean reduction of P50 amplitude in a group of patients including 4 with juvenile optic atrophy.\(^37\) No longitudinal data have been published to enable PERG changes with disease progression or duration to be assessed.

In this study, we found that color vision deficiencies were not restricted to tritanopia, even in early disease or mildly affected patients. Indeed, a number of children who had relatively good visual acuities had marked protan or protan-deutan deficits. This suggests that the ganglion cell population affected is not exclusively that mediating the blue-yellow color channel.\(^38\)

The MDTs show that the increase in the peripheral MDT seen in this condition accompanies the loss in photopic field sensitivity but does not precede it. In contrast to glaucoma,\(^39,40\) both parvocellular and magnocellular pathways are affected and the magnocellular pathway is not preferentially affected early in the disease. Our field tests suggest that the central, papillomacular fibers are mainly susceptible. Fine matrix mapping of the central visual field shows that the majority of sensitivity loss is in the superotemporal visual field and has abrupt borders.

The superotemporal visual field loss (as illustrated in Figure 6) has been noted previously.\(^3,41\) Why there should be preferential involvement of the ganglion cells represented in the superior field, and hence inferior papillomacular bundle, is not known. It is unlikely to be an artifact of the testing procedure, as it has been noted with the use of a variety of techniques of field testing.\(^41\) It is also not explained in this example by eccentric fixation, which some patients with DOA use. Fixation was monitored clinically and during field testing. The scanning laser ophthalmoscope was used to determine that there was no eccentric fixation. The pattern of ganglion cell loss may be attributable to anatomical factors or the disease gene may not be uniformly expressed in all macular ganglion cells.

Our data support the view that the neuropa-thological basis of DOA is a selective degeneration of the ganglion cells with an ascending optic neuropathy. The outer retinal components remain intact. Both parvocellular and magnocellular ganglion cells are affected early on. This suggests that the gene responsible for DOA might be expressed in both the major ganglion cell subtypes. Such widespread expression in the major ganglion cell classes would not explain the apparent preferential loss of ganglion cells in the papillomacular projection from the macula. There may be local anatomical or physiological factors responsible for this.

Several transcription regulators, known to be involved in ocular development and ganglion cell differentiation,\(^42\) have been proposed as candidate genes for DOA, including HRY,\(^43\) which maps to 3q28-q29. HRY is the human homolog of 1 of the Hes family of helix-loop-helix transcription regulators. It is expressed at high levels in neuroretinal progenitors in mice\(^44\) and humans.\(^33\) In gene-targeted mice lacking Hes1 function, there is premature retinal progenitor differentiation leading to disrupted retinal organization.\(^45\) HRY has been positioned on a YAC contig spanning the DOA region.\(^20\) However, we have screened all 4 exons of this gene and a fifth upstream putative untranslated exon in 36 patients from 18 families with DOA and in 10 normal controls and found no mutations (M.V., unpublished data, 1997). Pou4f2 genes, members of the Pou-homeodomain transcription regulator family, have also been shown to be expressed in ganglion cells\(^46\) and in particular subsets of retinal ganglion cells.\(^47\) Mutation of the Pou4f2 gene by gene targeting in mice causes loss of a subset of retinal ganglion cells,\(^48\) resulting in a 70% reduction in total number. However, the human homolog of Pou4f2 (BRN3B) FISH maps to chromosome 4q31.2,\(^49\) and no human phenotype has been associated with it. To date, no other relevant genes have been shown to lie in the region of interest on chromosome 3q or have been shown to be expressed only in ganglion cells. Although a mouse model of optic atrophy\(^50,51\) maps to human chromosome 3q, comparison of gene order between mice and humans shows that the mouse locus is centromeric to the DOA locus. The mouse gene itself has not been identified.
The current refinement of the DOA locus has facilitated a positional cloning approach. Even without the identification of additional candidate genes in the critical region, the gene may soon be identified. The isolation of the human gene not only will improve our understanding of the disease mechanism of DOA, but may also shed light on the mechanisms of ganglion cell differentiation and development in the human retina.

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