The Pupil in Dominant Optic Atrophy

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Purpose. To compare visual and pupil afferent function in dominant optic atrophy (DOA).

Methods. Patients with DOA who belonged to families showing evidence of linkage to the locus on chromosome 3q28-qter were recruited from the Moorfields Genetic Register. Patients and healthy control subjects underwent visual and pupil perimetry using a modified automated perimeter (Octopus 1-2-3; Interzeag, Schlieren, Switzerland). Five stimulus locations were tested: fixation, and at 17° eccentricity along the 45° and 135° meridians in all four quadrants. The visual deficit (difference in decibels between the patient's luminance threshold and that in age-matched healthy control subjects) was compared directly with the pupil deficit (difference in decibels between the stimulus intensity giving the patient's pupil response and that giving an equivalent pupil response in healthy control subjects) at each test location.

Results. Visual deficits and pupil afferent deficits were found at all five locations. The visual deficits were significantly greater than the pupil deficits at the four peripheral locations (median difference = 6.3 dB, $P < 0.001$). At fixation, the difference was not significant (median difference = 2.3 dB, $P = 0.407$).

Conclusions. Pupil function appears less affected than visual function at four of five locations tested. This result provides evidence that the retinotectal fibers serving the pupil light reflex are less susceptible to damage from the *OPA1* genetic defect than the retinogeniculate fibers serving vision. (*Invest Ophthalmol Vis Sci.* 2001;42:675–678)

The response of the pupil to light is invariably diminished in optic neuropathies. When tested with a full-field light stimulus, the size of the afferent pupil defect correlates well with the proportion of field lost in kinetic perimetry[1] or the mean defect in static automated perimetry.[2,3] When tested using smaller light stimuli presented at discreet locations in visual space (pupil perimetry), the pattern of afferent pupil deficit matches well the pattern of visual loss.[4] These findings may be interpreted either as evidence that the afferent pupil drive is conveyed by collateral branches of the retinogeniculate fibers mediating visual perception or that pupil afferent and visual afferent fibers in the optic nerve have similar susceptibility to damage.

The universality of this correlation between afferent pupil and visual function was recently brought into question by reports that patients with Leber's hereditary optic neuropathy (LHON) show better pupil responses than would be expected from their poor visual function.[5–7] The existence of pupillovisual dissociation led us to hypothesize that the afferent pupil drive in humans may be conveyed by a subpopulation of ganglion cells, which are largely separate from the retinogeniculate system. In LHON, these pupil afferent fibers appear to be less susceptible to the damaging effects of the Leber's mutation than the visual afferent fibers.[7]

Compared with LHON, autosomal dominant optic atrophy (DOA) is a more common inherited disease of the optic nerve with a prevalence of approximately 1:10,000.[8] The majority of pedigrees show linkage to a locus on chromosome 3q28-qter (*OPA1*)[9] although genetic heterogeneity has now been demonstrated both in the United States[10] and in the United Kingdom.[11] DOA shares some clinical features in common with LHON, both conditions being characterized by bilateral, symmetrical, central scotomata with relative preservation of the peripheral field.[12] We are not aware of any published studies of pupil function in DOA, although there is a single reported case of paradoxical pupillary constriction to darkness.[13] In the present study we have investigated afferent pupil and visual function in a genetically homogeneous cohort of patients with DOA to determine whether pupillovisual dissociation is unique to LHON or can be demonstrated in other inherited ganglion cell disorders. A preliminary account of this study has been published elsewhere.[14]

Methods

Subjects

Patients with clinically definite DOA were identified from the Moorfields Genetic Clinic register. They were recruited into this study if linkage analysis confirmed that they came from a family or pedigree showing evidence of linkage to chromosome 3q28-qter,[9] if their visual function was poor (eligible for partial sight or blind registration), and if they had no other medical condition and were not taking any drugs likely to affect the visual system or the pupil light reflex pathway (for example, patients with diabetes mellitus were excluded). Eighteen patients from eight different pedigrees meeting these criteria were examined (median age, 38 years; range, 16–66; male-to-female ratio, 10:8). In all cases the onset of visual loss had been in the first decade, with an interval of between 12 and 56 years before evaluation in this study. For comparison, the tests were also performed on 24 healthy control subjects (median age, 28 years; range, 21–51; male-to-female ratio, 12:11). The study followed the tenets of the Declaration of Helsinki and was approved by the Ethical and Scientific Committee of Moorfields Eye Hospital. All patients with DOA and healthy control subjects gave informed written consent before participating in this study.

Tests

Corrected distance acuity was determined using an illuminated Snellen chart under standard room lighting conditions. Visual and pupil perimetry were performed under mesopic conditions on the preferred eye according to the methods described in Bremner et al.[7] In brief, an automated static perimeter was used to estimate the perceptual thresholds at five locations in the visual field (fixation, and at 17° eccentricity in the 45° and 135° meridians in each of the four quadrants). To test pupil afferent function, a standard intensity (4000 apostilb [asb]) su-

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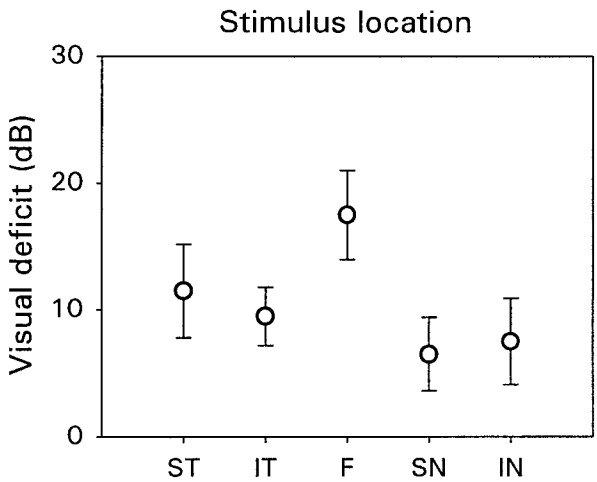

FIGURE 1. Results of threshold visual perimetry in patients with DOA. Median visual deficit ±95% confidence intervals (defined as the difference between the patient's perceptual threshold and that measured in healthy age-matched control subjects) at each of five stimulus locations: fixation (F) and at 17° eccentricity along the 45° and 135° meridians in the quadrants of the visual field.

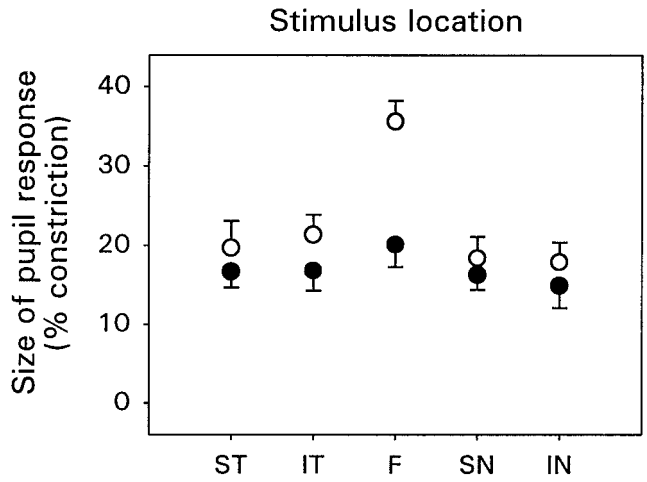

FIGURE 2. Results of pupil perimetry. A standard intensity (4000 asb) suprathreshold light stimulus was presented at each of the five stimulus locations shown along the abscissa. The median size of the pupil response (expressed as percentage of constriction of the pupil area) ±95% confidence intervals is shown for patients with DOA (*filled symbols*) and healthy control subjects (*open symbols*).

prathreshold light stimulus (duration 500 msec) was then presented repeatedly at the same five locations and the pupil responses recorded using infrared video pupillographic techniques. The order of stimulus presentation and the interstimulus interval (median, 5 sec; range, 4–6 sec, allowing full recovery to baseline diameter between stimuli) were varied pseudorandomly using customized software. In each patient and at each test location the visual deficit (in decibels) was defined as the difference between the patient's perceptual threshold and that found in normal age-matched control subjects. The pupil deficit (in decibels) was defined as the difference between the stimulus intensity giving the patient's pupil response and that giving an equivalent pupil response in normal age-matched control subjects.[7]

Analysis

Standard descriptive statistics have been used to summarize the visual and pupil deficits at each of the five stimulus locations. Medians are quoted rather than means, because with the patient selection criteria, we could not assume the data were normally distributed. At each location, the estimates of visual deficit were compared with the estimates of pupil deficit by Wilcoxon's signed-ranks test. These results from patients with DOA were compared with previously published results from patients with LHON.[7]

RESULTS

The visual acuities in this cohort of patients with DOA were all poor, ranging from 6/18 to 1/120 (median 3/60). Only 2 of 18 patients could read more than the test plate of the Ishihara pseudoisochromatic color plates. Static perimetry within the central 30° field showed three patterns of loss: a central scotoma (seven patients), diffuse loss (six patients), or patchy loss (five patients). Threshold estimations confirmed deficits at all five test locations, with the deficits being on average greater at fixation (median = 17.5 dB) than at the eccentric locations (median deficit range, 6.5–11.5 dB; see Fig. 1).

When examined by slit lamp, the patients with DOA all had pupils of normal size and appearance and that constricted normally during an accommodative effort. The pupillary responses to standard-intensity (suprathreshold) light stimuli presented at each of the five test locations were recorded. The latency and morphology of the reflex responses in the patients with DOA appeared grossly normal (after allowing for differences in response size), but the responses were generally smaller than those recorded from healthy control subjects. The results are summarized in Figure 2. At fixation, the pupil responses were more than 40% smaller in the patients with DOA than in the control subjects ($P < 0.001$, Student's unpaired *t*-test). At the four eccentric locations there was less difference in the size of the pupil responses (superotemporal [ST]: 15% smaller, $P = 0.03$; inferotemporal [IT]: 21% smaller, $P = 0.006$; superonasal [SN]: 11% smaller, $P = 0.11$; inferonasal [IN]: 17% smaller, $P = 0.05$).

The measurements of pupil response size in patients with DOA were converted into estimates of afferent pupil deficit by interpolation from previously published data relating stimulus intensity and pupil response size in normal subjects.[7] Figure 3 shows these pupil deficits plotted against the corresponding estimates of visual deficit for light stimuli presented at fixation. In some patients, the estimate of pupil deficit was greater than the estimate of visual deficit. In other patients, the pupil deficit was smaller, but overall, there was no significant difference between estimates of pupil and visual deficit at fixation ($P =$

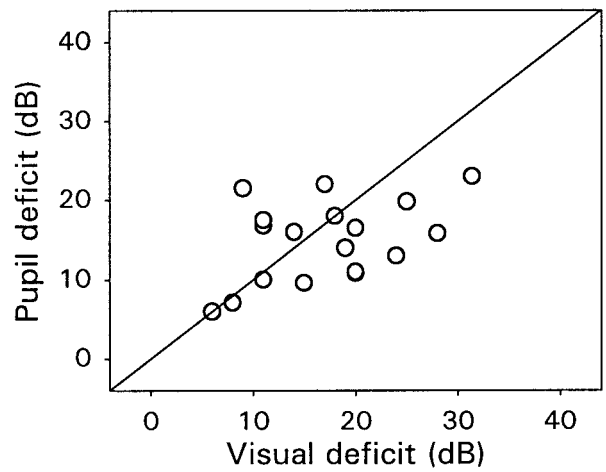

FIGURE 3. Comparison of estimates of visual deficit and pupil deficit at fixation in patients with DOA. *Diagonal line*: Equity where pupil deficit is equal to visual deficit.

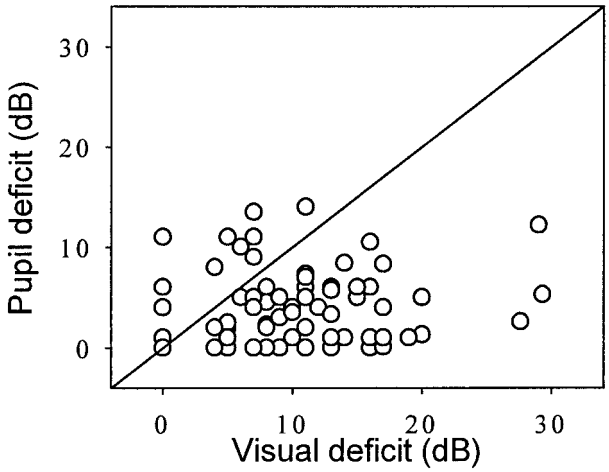

FIGURE 4. Scatterplot comparing estimates of visual deficit and pupil deficit at the four peripheral test locations (ST, IT, SN, IN) in patients with DOA. *Diagonal line*: equity where pupil deficit is equal to visual deficit.

0.407, Wilcoxon signed-ranks test). In contrast, a significant difference was found at the four peripheral test locations (see pooled data in Fig. 4). When the stimulus was presented peripherally, the pupil deficits were generally smaller than the visual deficits, with the median difference being 6.3 dB ($P <$ 0.001, Wilcoxon signed-ranks test).

We summarize the averaged results for each of the five test locations in Figure 5. At fixation, the average pupil and visual deficits were not significantly different. Peripherally, the average pupil deficit was smaller than the average visual deficit at all four test locations. The difference between estimates of pupil and visual deficit peripherally showed some variation according to the tested quadrant (ST = 9.5 dB; IT = 5.3 dB; SN = 5.4 dB; IN = 6.3 dB), but these differences did not achieve statistical significance ($P >$ 0.05, analysis of variance [ANOVA]). The size of this pupillovisual dissociation appeared similar in all the pedigrees examined and did not appear to correlate with age, gender, pattern of visual field loss, extent of visual deficit or duration of visual symptoms.

There was some variation in the degree of pupillovisual dissociation found in different patients with DOA. This is

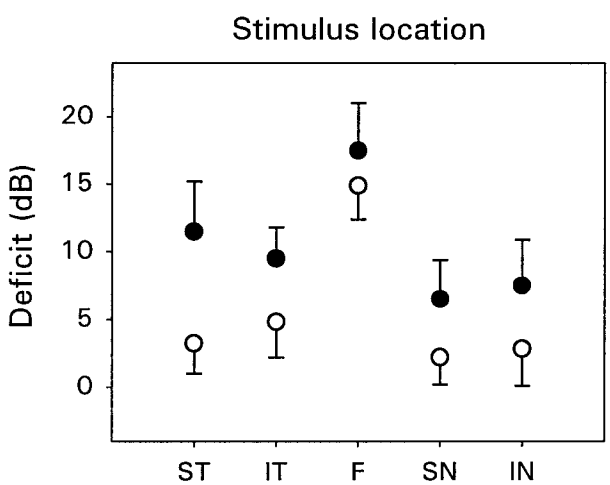

FIGURE 5. Comparison of visual and pupil deficits in DOA. Data are median estimates of pupil deficit (*open symbols*) and visual deficit (*filled symbols*) ±95% confidence intervals at each of the five stimulus locations tested.

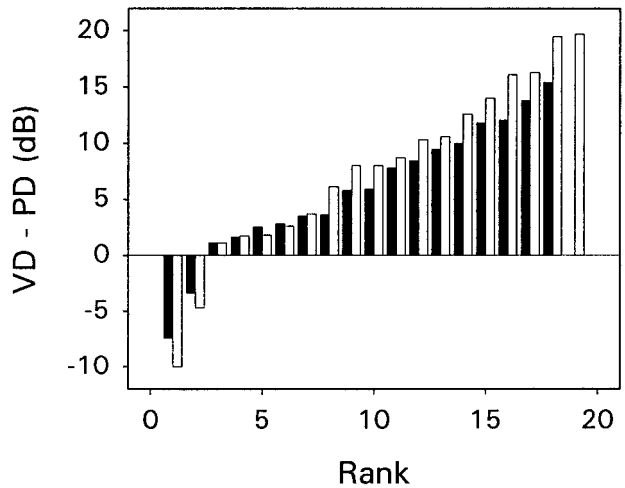

FIGURE 6. The distribution of results among patients with DOA (*filled bars*) and LHON (*open bars*). *Ordinate*: Average pupillovisual dissociation shown by each patient, calculated by determining the mean of the difference between corresponding estimates of visual deficit (VD) and pupil deficit (PD) for all locations tested in the visual field. A positive value indicates that, on average, visual deficits exceeded pupil deficits in that particular patient (and vice versa). *Abscissa*: Rank order of patients according to degree of pupillovisual dissociation.

illustrated in Figure 6: The ordinate shows the average difference between corresponding estimates of visual and pupil deficit in each patient (from all test locations), and the abscissa shows the rank order of these observed differences. Measurements from patients with DOA are shown in filled bars on the histogram. There were two patients who showed more pupil deficit than visual deficit, but in the remaining 16 patients, the visual deficits exceeded the pupil deficits. These estimates of pupillovisual dissociation appear evenly distributed, and there is no evidence of subgroups within this cohort showing different results. For comparison, we show data from patients with LHON[7] (open bars; n = 19): The distributions of results from both cohorts of patients are similar.

DISCUSSION

In this study, we investigated visual and pupil function in patients with DOA recruited from the Moorfields Genetic Register. In all the pedigrees tested, the inheritance pattern was unequivocally autosomal dominant with linkage to the same locus on 3q28-qter. On this basis our cohort appears to be genetically homogeneous, although once the *OPA1* gene is identified it may turn out that different pedigrees have different mutations. The penetrance of *OPA1* is almost 100%,[15] but its expression is highly variable, with visual loss ranging from subclinical deficit to blindness.[12] For the purposes of this investigation we have selected patients with severe visual loss (median VA = 3/60), and it may not be possible to generalize our results to patients with DOA at the milder or subclinical end of the spectrum.

The pupils in this cohort of patients with DOA were normal in size and appearance with no signs of efferent deficit. We did not specifically look for paradoxical constriction in response to darkness, but this abnormal light-off response is of dubious localizing or clinical value and has been reported in only one case of DOA in the literature.[13] The only pupil abnormality found in our cohort of patients with DOA was an afferent defect in the pupil light reflex, supporting the clinical impression of DOA as an isolated optic neuropathy with no associated dysfunction in the central or autonomic nervous systems.

When visual and pupil perimetry results were compared at peripheral test locations, the visual deficits significantly exceeded the pupil deficits. Is this pupillovisual dissociation real or an artifact due perhaps to eccentric fixation, patient strategy, or our method of estimating the visual and pupil deficits? Fixation is always an issue when attempting perimetry in patients with central scotomata. Without directly visualizing the retinal locations stimulated during perimetry, we cannot exclude the possibility that some or all our patients with DOA adopted nonfoveal fixation. However, our experience in healthy control subjects has been that unlike testing function at fixation, measurements of pupil and visual sensitivity at 17° eccentricity remain similar, even with quite marked degrees of eccentric fixation. Moreover, when monitoring eye position using the video camera images during testing, it was our impression that patients adopted similar fixation strategies in both types of test. If this was the case then visual and pupil function were compared at approximately the same locations.

We have considered the possibility that our method of evaluating pupil function systematically underestimates the size of the pupil deficit, giving rise to spurious pupillovisual dissociation. The pupil response amplitudes are routinely normalized with respect to the baseline pupil area. We have reanalyzed our data using absolute measurements of pupil response amplitude and found no difference in the overall results. Furthermore, when testing a different cohort of patients recovering from demyelinating optic neuritis (Bremner FD, unpublished data, 2000) we found that the pupil deficits exceeded the visual deficits, demonstrating that pupil-sparing is not an inevitable consequence of our methodology.

The data at fixation showed a smaller nonsignificant difference between pupil and visual deficits in contrast to the striking pupillovisual dissociation seen peripherally. At present, we are not certain how to interpret this different result. It may be that after many years of central visual loss the patients with DOA adopted eccentric fixation. The effect of this would be a substantial overestimation of the pupil deficit, but it might make less difference to measurements of luminance threshold. The general point is that in patients with central visual loss, pupillovisual dissociation may be more difficult to assess at fixation, when the preferred retinal locus (PRL) has a substantial influence but easier to detect in the periphery, where the PRL has less effect on the measurements.

The results of this study are in broad agreement with those obtained in patients with LHON, namely that estimates of visual deficit exceed those of pupil deficit. Moreover, the degree of this pupillovisual dissociation in DOA (6.6 dB) is similar to that found in LHON (7.5 dB).[7] These findings suggest that pupil afferent fibers are not as susceptible to damage as retinogeniculate fibers from either the *OPA1* defect or any of the primary LHON mutations.

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