EXTENDED REPORT

Retinal nerve fibre thickness measured with optical coherence tomography accurately detects confirmed glaucomatous damage

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Aim: To assess the accuracy of optical coherence tomography (OCT) in detecting damage to a hemifield, patients with hemifield defects confirmed on both static automated perimetry (SAP) and multifocal visual evoked potentials (mfVEP) were studied.
Methods: Eyes of 40 patients with concomitant SAP and mfVEP glaucomatous loss and 25 controls underwent OCT retinal nerve fibre layer (RNFL), mfVEP and 24-2 SAP tests. For the mfVEP and 24-2 SAP, a hemifield was defined as abnormal based upon cluster criteria. On OCT, a hemifield was considered abnormal if one of the five clock hour sectors (3 and 9 o'clock excluded) was at <1% (red) or two were at <5% (yellow).
Results: Seventy seven (43%) of the hemifields were abnormal on both mfVEP and SAP tests. The OCT was abnormal for 73 (95%) of these. Only 1 (1%) of the 100 hemifields of the controls was abnormal on OCT. Sensitivity/specificity (one eye per person) was 95/98%.
Conclusions: The OCT RNFL test accurately detects abnormal hemifields confirmed on both subjective and objective functional tests. Identifying abnormal hemifields with a criterion of 1 red (1%) or 2 yellow (5%) clock hours may prove useful in clinical practice.

Although standard automated perimetry (SAP) is an accepted clinical procedure for detecting glaucomatous damage, it is not without its problems. For example, it is said that significant retinal ganglion cell damage can take place before SAP reveals a deficit.[1] Optical coherence tomography (OCT) is an imaging technology developed to detect damage to the retina and retinal nerve fibre layer (RNFL). With the OCT, RNFL thickness is most often measured using peripapillary scanning around the optic disc.

A number of studies have reported that optical coherence tomography (OCT) can detect glaucomatous damage with moderate to reasonably high sensitivity and specificity.[2–15] In these studies, sensitivity/specificity ranged from 76%/81% to 91%/100%. To better understand the limits of a technique for detecting glaucomatous damage, it is useful to examine the conditions under which the technique misses glaucomatous damage. In the case of glaucoma, this is easier said than done as we lack a "gold standard" for defining glaucomatous damage. That is, there is no test for which a positive result necessarily means glaucomatous damage is present. To minimise this problem, Hood *et al*[16] defined a glaucomatous eye as one in which both SAP and multifocal visual evoked potential (mfVEP) tests were abnormal. The logic being that if these two very different functional tests were abnormal, then it is extremely likely that glaucomatous damage was present. Using this logic, they showed that the pattern electroretinogram was normal in over 25% of the eyes defined as abnormal on both SAP and mfVEP tests.

Here we use a similar approach to examine the OCT results for hemifields in which it was fairly certain that there was glaucomatous damage. In particular, for a hemifield to be classified as abnormal, it had to show an abnormal cluster of points on both the SAP and mfVEP tests. Thus, the accuracy of the OCT RNFL test was assessed for hemifields abnormal on two functional tests. The hemifields missed by the OCT were evaluated to see if the cause could be inferred. A preliminary report was presented at the 2006 meeting of the Association for Research in Vision and Ophthalmology.

METHODS

Subjects

Forty patients, with a mean age of 61.4 (SD 12.2) years, were selected from a larger set of patients enrolled in a prospective clinical study to include those tested with OCT, mfVEP and SAP. With the exception of two patients, all tests were performed within a 12-month period (median 86 days). All patients had at least one eye with a diagnosis of glaucoma (n = 38 patients) and/or optic nerve drusen (n = 2) and an abnormal 24-2 Humphrey visual field (HVF). To be considered abnormal, the HVF had to have a glaucoma hemifield test (GHT) outside normal limits and/or a pattern standard deviation (PSD) or mean deviation (MD) with $p<0.05$. Overall the average MD was −6.88 (5.71) dB. When the patient's eyes were categorised as less or more affected based upon the MD, the average MDs were −3.85 (3.79) dB (less affected eyes) and −9.91 (5.73) dB (more affected eyes).

The 25 individuals serving as controls had a mean age of 58.8 (SD 8.2) years and normal fundus examinations and normal 24-2 HVF tests. Informed consent was obtained from all subjects before their participation. Procedures adhered to the tenets of the Declaration of Helsinki and the protocol was approved by the committee of the Institutional Board of Research Associates of Columbia University.

Optical coherence tomography

The thickness of the peripapillary RNFL was measured with the Stratus OCT (Carl Zeiss Meditec, Inc, Dublin, California,

Abbreviations: GHT, glaucoma hemifield test; HVF, Humphrey visual field; mfVEP, multifocal visual evoked potentials; OCT, optical coherence tomography; PSD, pattern standard deviation; RNFL, retinal nerve fibre layer; SAP, static automated perimetry

Table 1 Number (%) of hemifields classified as abnormal

	HVF	VEP	OCT
Normal	53 (33%)	75 (47%)	51 (32%)
Abnormal	107 (67%)	85 (53%)	109 (68%)

USA) using version 4.0 software and the fast scan protocol. During a single recording, three scans are made around a ring 3.4 mm in diameter with a spatial resolution of 256 points and then averaged. The commercial software provides various summary statistics of the resulting RNFL scan and a comparison of these statistics to a normative database. The primary measure used here was the average thickness of 12 clock-hour segments. The software compares these values to an age-appropriate, normative database and indicates whether they fall within the top 5% (coded white), top 95% (green), bottom 5% (yellow) or bottom 1% (red). (Here 9 o'clock is the temporal clock hour of the right eye and the nasal clock hour of the left eye.)

Definition of abnormal hemifields

Each hemifield was classified as normal or abnormal based upon the following criteria. For the HVF and mfVEP tests, cluster criteria were used as previously defined.[17–20] In particular, for the HVF (total deviation plot), a hemifield was defined as abnormal if a cluster had two or more contiguous points at $p<0.01$, or three or more contiguous points at $p<0.05$ with at least one point at $p<0.01$. To avoid rim artifacts, the cluster could contain no more than one point from the outer ring of the 24-2 HVF points.[19 20] The mfVEP from a hemifield was considered abnormal if it contained a cluster on the monocular or interocular plot of two or more contiguous points at $p<0.01$, or three or more contiguous points at $p<0.05$ with at least one point at $p<0.01$. The central four points were excluded from this analysis.

For the OCT, the clock hour plot on the fast RNFL report was used. The OCT for a hemifield was considered abnormal if there was one red (1% level) or two yellow (5% level) clock hours anywhere within a hemisphere. For this analysis, the 3 and 9'clock hours were excluded. Only one of the 100 control hemifields was abnormal using these criteria. These criteria were selected before any of the data were analysed and were based upon the following logic. Clock hours 3 and 9 were excluded as they fall in both hemifields; typically these sectors are not affected by glaucoma in any case. Requiring only one yellow (5%) per hemifield seemed, a priori, too lenient, so a criterion of two yellow or one red was chosen. In fact, as we later learned, using a criterion of one yellow (5%) marginally increased test accuracy, but markedly increased the false positive rate (that is, OCT tests of controls classified as abnormal). Eight normal hemifields were classified as abnormal. Similarly, assigning the 3 and 9'clock hours to either or both hemispheres did not affect the results for the patients, but increased the false positive rate for the control subjects.

RESULTS

Table 1 shows the number of hemifields classified as normal or abnormal based upon the visual field and mfVEP criteria. With these criteria, the HVF and OCT tests yielded about the same number (107 vs 109) of abnormal hemifields or about two thirds of the hemifields. The mfVEP classified fewer, 85 (53%), of the hemifields as abnormal.

We were primarily interested in the OCT results for those hemifields classified as abnormal on both the HVF and mfVEP tests. Of the 160 hemifields, 77 (48%) were classified as abnormal on both tests. Of these 73 (95%) were classified as abnormal on the OCT.

Results for the four ''misses'', involving three patients, were scrutinised to see if we could generate plausible hypotheses to account for them. For two of the hemifields (different patients), the upper hemifields of the HVF and mfVEP showed relatively localised abnormalities, while the OCT of the inferior disc was normal. These are probably true OCT misses. All three tests replicated on a second test day and both eyes showed inferior thinning on direct ophthalmological exam and stereo photographs. Further, the abnormality was in the same region of the field on the both the HVF and mfVEP tests. Thus, it is likely that small local defects were missed by the OCT in these patients. The other two ''misses'' were in the upper hemifield of both eyes of the same patient. Both eyes had abnormal cup-to-disc ratios. The normal appearing OCT replicated on a second test performed on the same day. It is worth noting that the functional tests showed variation over time. In particular, the mfVEP recorded six weeks earlier did not show an abnormality in the upper hemifield of the right eye and the HVF obtained 4.5 months earlier did not show an abnormality in the upper hemifield of the left eye. On the other hand, all three tests were abnormal for the lower field of the left eye. Given the abnormal disc and abnormal lower hemifield, the most plausible explanation is that the glaucomatous damage was subtle in the upper hemifields and that all three tests had difficulty detecting this damage.

The main focus here was on the accuracy of the OCT when the mfVEP and HVF were both abnormal; we were not testing the relative accuracy of different tests. However, as the percentage of abnormal HVF and OCT were about the same, we asked about the sensitivity of the HVF for those hemifields classified as abnormal on the OCT and mfVEP. Of the 160 hemifields, 77 (48%) were abnormal on both the mfVEP and OCT. Of these 77, 73 (95%) were abnormal on the HVF—results identical to those for the OCT.

Sensitivity and specificity

To assess sensitivity/specificity, one eye per patient was selected from the glaucoma group using the following criteria. The HVF had to be outside the normal range for the GHT. If two eyes met this criterion, then the one with the smaller MD, or lesser deficit, was chosen. The mean (median) MD of this group was −5.84 (−4.80) dB. For the control group, the specificity was calculated separately for the right and left eyes and then averaged. The first five columns of table 2 show the results of this analysis for the most common criteria used in previous studies, the thickness of the superior (SQ), nasal (NQ), inferior

Table 2 Sensitivity and specificity (in percentage) for different OCT RNFL criteria

	SQ	NQ	IQ	TQ	Average	7 o'clock	1Y clock hour	1R	2Y/1R hemi	2Y or 1R anywhere
Sensitivity	68	28	78	40	78	68	95	90	**95**	95
Specificity	100	100	98	96	98	98	82	98	**98**	94

(IQ) and temporal (TQ) quadrants and the overall average thickness. Occasionally, results are shown for the individual clock hours. The fifth column shows the results for the clock hour with the highest sensitivity/specificity. One study,[5] reported sensitivity/specificity for 1 yellow (Y) or 1 red (R) at any clock hour and our results for these criteria are shown in columns 7 and 8. Finally, column 9 (bold) shows the results for the criteria used here (2Y or 1R within either hemifield omitting clock hours 3 and 9) and column 10 the results for 2Y or 1R anywhere including either hemifield and clock hours 3 and 9. Our criteria had the best overall sensitivity/specificity (95/98), although criteria of 2 yellow (Y) or 1 red (R) anywhere in the field did nearly as well (95/94).

DISCUSSION

The aim of this study was to see if the OCT fast RNFL scan detected an abnormality in hemifields in which both the 24-2 HVF and the mfVEP showed abnormalities. We can be fairly confident that there was glaucomatous damage present in these hemifields. Of the 160 hemifields for the 40 patients, 77 were abnormal on both tests. The OCT classified 73 (95%) of these as abnormal with our criteria of two yellow or one red. For the same criteria, only one of the 100 control hemifields was abnormal. Of course, by selecting hemifields with both abnormal HVF and mfVEP tests, we may have selected the more extreme field losses. However, if only the eyes with MD better than –6 dB are considered, then 25 hemifields from 23 eyes were abnormal on both mfVEP and HVF tests. Twenty four (96%) of these 25 hemifields were abnormal on the OCT. The OCT did an excellent job of distinguishing between the abnormal and control hemifields.

The success of the OCT test left us with only four ''misses'' to analyse. In two hemifields in the same patient, the most likely explanation was a relatively subtle degree of damage that all three tests had difficulty detecting. In the other two cases, the OCT probably missed a relatively focal lesion. In this regard, a study by Jeoung *et al*[7] is of interest. They found that while the OCT RNFL test detected 61 of 71 (85.9%) RNFL defects identified as abnormal on red-free photography, it only detected 3 out of 10 (30%) with an angular width of less than 10°.

The primary purpose here was not to examine the sensitivity and specificity of the OCT; many previous studies have done so.[2–15] However, the success of our 2Y/1R hemifield criteria suggested that a post hoc analysis of sensitivity and specificity might be of interest. Typically, studies of OCT sensitivity/specificity use the summary statistics available on the report, most commonly the average thickness.[6 8–11 13 14] While some have reported good sensitivity/specificity (for example, 91/100[13]) for average thickness, others have reported lower values (for example, 59/90[6] and 79/83[14]). Our results for average thickness (78/98) fall within the range of previous work. The sensitivity/specificity of some of the other criteria previously used are shown in table 2. Our hemifield criteria (2Y or 1R) did better than any of these criteria. In interpreting these values, it should be remembered that by requiring both mfVEP and HVF to be abnormal we are probably selecting eyes with relatively clear glaucomatous damage, although the MDs of this group were similar to those in previous studies. In any case, it will be interesting to see how well our criteria do in future studies of patients with subtle glaucomatous damage.

Finally, this study was not designed to determine whether the HVF or OCT test had the better sensitivity/specificity. In particular, we cannot conclude that the OCT is more sensitive than HVF. First, when we analysed the hemifields that were abnormal on both the OCT and mfVEP tests, the HVF test did as well (95% identified as abnormal) as the OCT. Second, we do not have a measure of the specificity of the HVF; a normal HVF was part of the inclusion criteria for the control group. Finally, a study of sensitivity/specificity is best done with patients with very early damage. However, the OCT identified 95% of the abnormal hemifields, while only classifying 1% of the control hemifields as abnormal. Considering that the OCT, when compared to the HVF test, takes less time, is less demanding on the patient, and has little or no learning curve, our results bode well for the future of this test.

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