Subclinical Visual Field Alterations are Commonly Present in Patients with Graves' Orbitopathy and are Mainly Related to the Clinical Activity of the Disease

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Key words
- Graves' disease
- Graves' Orbitopathy
- visual field
- computerized perimetry
- optic nerve

Abstract

The present study was aimed to investigate optic nerve involvement by computerized perimetry in 40 (29 women, 11 men) consecutive GO patients not showing definite dysthyroid optic neuropathy (DON). All patients presenting visual acuity defects, pallor or swelling of the optic nerve, concomitant eye disease, evidence of apical crowding or optic nerve stretching at either MRI or CT imaging were excluded. Normal perimetry occurred in 7 patients (17.5%), 5 patients (12.5%) had "indeterminate" results and 28 patients (70%) presented abnormal perimetry. Particularly, 7 isolated paracentral, 5 pericentral and 16 combined peri and paracentral scotomas were found. On the contrary, 15/20 patients in the group without GO had normal perimetry, isolated scotomas were found in 5 cases (1 pericentral and 4 paracentral) and no case of combined scotoma occurred. The difference between the 2 groups was statistically significant ($\chi^2 = 9.17$; $p = 0.025$). Overall, the sensitivity resulted 70%, the specificity 75% and the positive predictive value 84.84%. In patients with GO, the proportion of visual field alterations was significantly increased for Clinical Activity Score ≥ 3 ($p = 0.0005$), while no relationship occurred with proptosis degree ($p = 0.115$). In conclusion, a great proportion of GO patients without clinically evident DON presents visual field defects, mainly related to GO activity.

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Introduction

The definition of Graves' Orbitopathy (GO) encompasses a series of pathological changes taking place inside and around the orbit, in association with autoimmune thyroid disease (Burch & Wartofsky, 1993, Bartalena et al., 2000, Bartalena et al., 2004). The natural history of GO commonly recognizes two distinct phases: an initial dynamic phase of "active disease", characterized by conspicuous lymphocyte and mononuclear cells infiltration and by fibroblast proliferation (Wiersinga & Prummel, 2001, Prabhakar et al., 2003). In its late phase, the disease progresses into a static "inactive" state, characterized by fibrosis (Burch & Wartofsky, 1993, Bartalena et al., 2004, Wiersinga & Prummel, 2001). The clinical manifestations of GO are mainly due to volume increase of the intra-orbital connective/adipose tissue and of the extraocular muscles, with consequent incongruity of the orbital cavity (Burch & Wartofsky, 1993, Bartalena et al., 2000, Bartalena et al., 2004). Occasionally, optic nerve involvement may occur, with consequent sight loss (Burch & Wartofsky, 1993). The progression of active GO to clinically evident Disthyroid Optic Neuropathy (DON) is observed in 3–5% patients (Burch & Wartofsky, 1993). In the absence of visual loss, other signs have been suggested as possible indicators of DON development, such as changes in colour vision and in the optic nerve head on ophthalmoscopy (Neigel et al., 1988). Most patients with other evidence of DON present visual field defects (Dickinson & Perros, 2001, MacKeag et al., 2006). Abnormal visual field examination has also been reported in individual Graves' disease patients with normal visual acuity (Gasser & Flammer, 1986, Trobe et al., 1978). Indeed, the specificity of perimetric alterations in GO patients has been challenged (Dickinson & Perros, 2001).

The present study was aimed to investigate the frequency of visual field defects by computerized perimetry in 40 consecutive GO patients not presenting definite DON.

Patients

The study was approved by the Ethics Committee of our institution and informed consent was obtained by each patient.

Forty consecutive GO patients (11 males and 29 females), aged 30–72 yr (mean age: 45 ± 12) were enrolled. Smokers were 27 (9 males, 18 females). The median duration of GO, estimated according to the patient's history as presence of ocular symptoms or signs, was 3 months (range 1–8 months). At the first ophthalmologic evaluation, 32 patients (80%) were hyperthyroid and 8 (20%) were euthyroid. In the hypertyroid group, the median duration of hyperthyroidism was 2 months (range 2–13 months). Among the 8 euthyroid patients, 5 had previous antithyroid therapy (methimazole for 6–18 months), withdrawn 6–24 months before (median 9 months). The remaining patients (n = 3) were diagnosed as euthyroid GO. The control group included 20 Graves' disease patients without GO (6 males and 14 females), matched for age, thyroid functional status and smoking habits. This group included 18 hyperthyroid patients and 2 euthyroid patients in remission.

Table 1 Clinical characteristics of patients with Graves' Orbitopathy

	Number of Patients
proptosis	
< 20 mm	20 (50%)
≥ 20 < 25 mm	17 (42.5%)
≥ 25 mm	3 (7.5%)
diplopia	
absent	20 (50%)
constant	4 (10%)
inconstant	4 (10%)
intermittent	12 (30%)
visual acuity (Snellen fraction)	
1	29 (72.5%)
> 0.8 < 1	11 (27.5%)
tonometry	
< 20 mmHg	34 (85%)
≥ 20 mmHg	6 (15%)
Clinical Activity Score (CAS)	
< 3	14 (35%)
≥ 3 < 5	17 (42.5%)
≥ 5	9 (22.5%)

Methods

Ophtalmological and orthoptic assessment

Eyelid position was established by measuring the lid fissure at the midline in primary gaze. Proptosis measurement was performed always by the same observer, using Hertel exophthalmometer. Corneal and conjunctival status was evaluated by slit lamp evaluation. Best corrected visual acuity was expressed as a Snellen fraction and colour vision was tested using Ishihara colour tables. Ocular motility was evaluated with respect to the presence of manifest strabismus; monocular ductions were measured in degrees of excursion from the primary position and both cover test and Hess's screen were also performed. The evaluation of optic disc alterations was performed by fundus examination. Tonometry was measured in primary position and in upper and lateral gaze, using Goldman applanation tonometry. Patients were also investigated for the presence of excessive watering, photophobia, grittiness, double vision and blurred vision.

Assessment of disease activity

GO activity was estimated as Clinical Activity Score (CAS) using the EUGOGO atlas (Dickinson & Perros, 2001). Briefly, one point was added when each of the following items was present: spontaneous pain behind the globe, pain on attempted upgaze, redness of the conjunctiva, redness of the eyelid, chemosis, swelling of the caruncle, and eyelid swelling. CAS score < 3 was considered inactive, ≥ 3 < 5 borderline and > 5 active disease.

Computerized visual field examination

Visual field analysis was performed by the Humphrey field analyzer HFA II model 750, using the 30-2 threshold test and evaluated using the software provided by the manufacturer (STATPAC for windows). All patients were previously instructed and experienced automated threshold perimetry examination prior to enter in the study protocol. To be considered reproducible individual field defects had to be confirmed in at least two separate testing sessions performed within 2 weeks. The results obtained starting from the second visual field examination were taken into consideration for data analysis. In each patient, sensitivity loss at a given location was confirmed within ± 2 dB. The locations of defects were confirmed within ± 6°. Scotoma was defined as at least 2 adjacent points of ≥ 5 decibels sensitivity loss for each point or as 1 or more points of at least 10 decibels sensitivity loss.

Exclusion criteria

All patients presenting any of the following conditions were excluded from the study: 1) previous treatment for GO; visual acuity < 0.67. Snellen fraction; 2) altered colour vision; 3) evidence of keratopathy at slid lamp evaluation; 4) swelling or pallor of the optic disc at fundoscopy; 5) concomitant eye disease that might affect the results of the test (such as severe myopia, astigmatism, cataract, glaucoma, maculopathy); 6) evidence of apical crowding or optic nerve stretching at either MRI or CT imaging.

Statistics

The comparisons of the frequency distributions were performed using the χ test or the Fisher exact test, when appropriate.

Results

Clinical characteristics of the GO patients

Table 1 summarizes the main clinical findings of the patients included in GO group. Proptosis > 20 mm was present in 20/40 (50%) patients. Diplopia was present in 20/40 patients (50%). Twenty-nine out of 40 patients (72.5%) had no visual acuity reduction (i.e 20/20; Snellen fraction = 1). Eleven others (27.5%) presented a mild decrease in visual acuity (Snellen fraction < 1 ≥ 0.8). Eye pressure above 20 mm Hg was present in 6 patients (15%), while 34/40 (85%) had normal tonometry. Nine patients (22.5%) presented active GO (CAS ≥ 5), borderline GO activity (CAS ≥ 3 < 5) occurred in 17/40 patients (42.5%) and fourteen (35%) had non-active disease (CAS < 3).

Table 2 Results of Thyroid Function Parameters, Thyroid Autoantibodies and Perimetry in Graves' disease patients with and without GO

	GO (n = 40)	No GO (n = 20)
thyroid function parameters		
TSH (μU/ml) (range:0.35–4.5)	0.81 ± 1.07	0.45 ± 1.11
FT_3 (pg/ml) (range: 2.3–4.2)	6.48 ± 5.92	6.12 ± 6.02
FT_4 (pg/ml) (range 7–17.6)	23.25 ± 27.82	24.22 ± 29.12
autoantibodies		
Anti-Tg (U/ml) (negative < 60)	194.7 ± 114.3	92.7 ± 84.9
Anti-TPO (U/ml) (negative < 60)	421.5 ± 319.6	342.7 ± 274.8
TRAB(U/l) (negative < 1.0)	10.1 ± 14.3	8.7 ± 12.2
positive anti-Tg[a]	28 (70%)	15 (75%)
positive anti-TPO[b]	34 (85%)	16 (80%)
positive TRAB[c]	31 (77.5%)	15 (75%)
visual field[d]		
normal	7 (17.5%)	15 (75%)
indeterminate	5 (12.5%)	0
scotoma	28 (70%)	5 (25%)
pericentral	5	1
paracentral	7	4
pericentral + paracentral	16	0

Orbitopathy vs No Orbitopathy
[a]Anti-Tg: $\chi^2 = 0.16$; NS
[b]anti-TPO: $\chi^2 = 0.042$; NS
[c]TRAB: $\chi^2 = 0.046$; NS
[d]Visual field: $\chi^2 = 9.17$; p = 0.025

Prevalence of visual field alterations in GO patients and in Graves' patients without GO

The results of visual field examination in the population under study were compared to a group of Graves' disease patients without GO, matched for sex and age, with comparable thyroid functional status (**Table 2**). Anti-Tg, anti-TPO and anti-TSH receptor (TRAB) antibody profiles are also summarized in **Table 2** and were not significantly different between the 2 groups.

In the GO group, normal perimetry was present in 7 patients (17.5%) only. Five patients (12.5%) presented visual field defects at the first ophthalmologic evaluation not confirmed at further control, were classified as indeterminate and were included in the normal perimetry group for further data analysis. In 28/40 cases (70%) various types of visual field defects were present. In particular, isolated scotomas occurred in 12 patients (5 pericentral, 7 paracentral) and 16 patients presented combined (pericentral + paracentral) scotomas. On the contrary, 15/20 patients in the group without GO had normal perimetry, isolated scotomas were found in 5 cases (1 pericentral and 4 paracentral) occurring in 4 hyperthyroid and in one euthyroid patients. No case of combined scotoma was observed. The difference between the 2 groups was statistically significant ($\chi^2 = 9.17$; p = 0.025). By considering the overall data, the sensitivity was 70%, the specificity resulted 75% and the positive predicting value (PPV) 84.84%.

Frequency of visual field alterations in relation to proptosis

Perimetric abnormalities were observed in 10/22 (45.5%). patients with proptosis < 20 mm, in 10/15 (66.6%) subjects with proptosis ≥ 20 < 25 mm and in all 3 cases with proptosis > 25 mm (**Fig. 1**). The frequency of visual field defects occurring in patients with proptosis > 20 mm did not significantly differ from that observed in patients with proptosis < 20 mm (Fisher exact test p = 0.115).

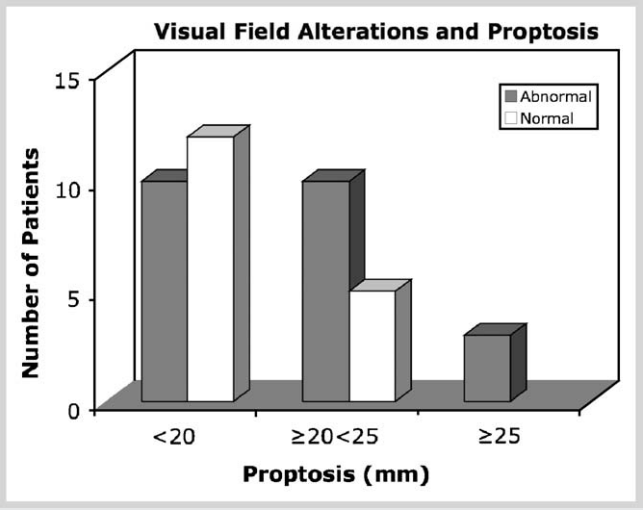

Fig. 1 Frequency of visual field alterations in GO patients according to proptosis degree.

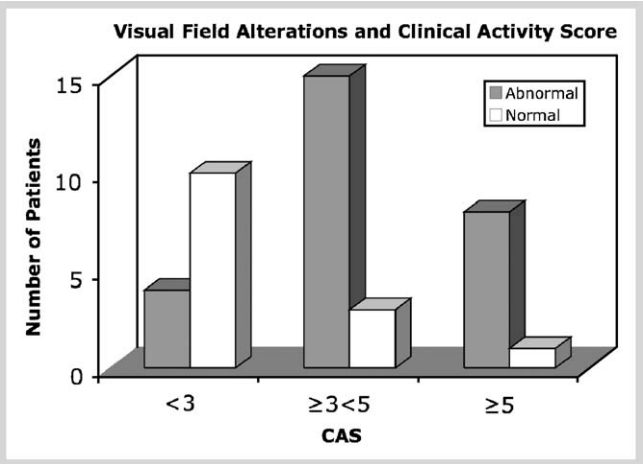

Fig. 2 Frequency of visual field alterations in GO patients according to the Clinical Activity score (CAS).

Frequency of visual field alterations in relation to CAS

Fig. 2 illustrates the analysis of visual field results in relation to CAS. Visual field abnormalities occurred in 4/14 (28.6%) patients with inactive disease (CAS < 3). A sharp rise in the frequency of abnormal perimetric tests was observed in patients with active GO. In fact, 15/18 (83.3%) patients with borderline activity GO (CAS ≥ 3 < 5) and 8/9 patients with frankly active GO (CAS ≥ 5) had visual field alterations. The frequency of patients with altered visual field in the group of patients with CAS ≥ 3 was significantly increased as compared to the group with CAS < 3 (Fisher exact test p = 0.0005).

Discussion

In classical forms, the clinical manifestations of GO are proptosis, alterations of extra-ocular muscle motility, peri-orbital edema, congestion of the conjunctiva, eyelid retraction to various extents (Burch & Wartofsky, 1993, Bartalena et al., 2000, Bartalena et al., 2004). DON occurs in fewer than 5% of unse-

lected patients with Graves' disease, as a result of apical compression due to the increased volume of either or both the orbital connective tissue and the extraocular muscles (Burch & Wartofsky, 1993, Day & Carroll, 1962, De Santo, 1980). In terms of clinical manifestations, the patients with DON complain decreased visual acuity, which may occur insidiously (Trobe et al., 1978) or rapidly (Burch & Wartofsky, 1993, Bartalena et al., 2000, Hedges & Scheie, 1955, Henderson, 1958).

Most patients with other evidence of DON present visual field defects (Dickinson & Perros, 2001, MacKeag et al., 2006). Abnormal visual field examination as the unique sign of optic nerve damage has also been reported in individual Graves' disease patients with normal visual acuity (Gasser & Flammer, 1986, Trobe et al., 1978). Indeed, the specificity of visual field defects as the unique finding for DON diagnosis is controversial (Dickinson & Perros, 2001). In the present report, we observed a remarkably high prevalence of visual field alterations in GO patients. What could be the clinical relevance of these findings? It could be argued that such a high prevalence of perimetric alterations would depend on a high rate of false positive results, since normal fluctuations can with automated perimetry be erroneously interpreted as evidence of visual field defect (Henson et al., 2000). In this respect, a high rate of misinterpretation in our series seems unlikely, since we classified as abnormal only the results of the patients whose visual field alterations were confirmed in 2 different occasions. In addition, if this were the case, one should expect a comparably high frequency of misinterpretation in the control group (i.e. hyperthyroid Graves' patients without GO). On the contrary, the frequency of visual field defects was markedly low in such patients and significantly reduced as compared to the GO series. Thus, the presence of perimetric alterations was rather specific (75% specificity) for GO patients, as also indicated by a PPV of 84.84%. One alternative hypothesis could be that the observed perimetric defects would reflect subclinical involvement of the optic nerve, particularly in those patients (11/40) who showed a mild reduction of the visual acuity. However, in the absence of acquired altered color vision or reduced acuity, this alternative seems highly unlikely. On the other hand, the possible mechanisms leading to a subclinical optic nerve involvement in our series of GO patients cannot be easily explained. In fact, a direct mechanical effect in terms of optic nerve compression should be ruled out, since all patients with TC or MNR evidence of apical crowding or optic nerve stretching were excluded from the study. In addition, no significant relationship was observed with proptosis, nor with GO severity or intraocular pressure (data not shown). On the contrary, visual field defects were significantly associated to GO activity. In fact, the major finding emerging from our study relates to the observation that patients with CAS ≥ 3 were more likely to present perimetric alterations as compared to patients with CAS < 3. In other words, the inflammation would have a more detrimental effect on the visual field in patients with more active GO. In this perspective, it cannot be excluded that an involvement of the optic nerve in the inflammatory process taking place inside the orbit would be responsible for the perimetric alterations in GO patients. Possibly, TRAB could be involved in this process, since it has been shown that these auto-antibodies may play an important role in triggering and maintaining the autoimmune process in the orbit (Eckstein et al., 2006). Based on our data, showing no significant difference in TRAB levels between the groups of Graves' patients with and without GO, a role of TRAB in determining subclinical optic nerve involvement seems unlikely. In addition, when TRAB results were analyzed according to perimetric alterations among the various subgroups, no correlation between TRAB values and the presence of visual field defects was observed (data not shown). In this respect, however, it should be emphasized that our protocol was not originally designed to address this question. Therefore, we cannot exclude that other factors (i.e. the reference range for TRAB positivity used in our laboratory, the great proportion of patients with positive TRAB in both groups, the dispersion over a wide range of individual TRAB-positive values) could have influenced to some extent this kind of data analysis.

Since visual field defects were present in approximately half the series of patients with no other evidence of optic nerve damage, other mechanisms such as the alteration of the tear film profile known to occur in GO patients (Khurana, 1992) as well as irregular refractive errors due to lid position and/or excessive tearing induced by increased corneal exposure could eventually play a role in determining the visual field defects in GO patients.

In conclusion, patients with active GO present a remarkably higher prevalence of visual field defects as compared to Graves' disease patients without GO. Further studies will clarify the mechanisms leading to such abnormalities and their exact clinical relevance.

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