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## Atypical Manifestations

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### **What Are the Atypical Manifestations of Graves' Orbitopathy?**

The clinical features of Graves' orbitopathy (GO) with eyelid retraction (Dalrymple's sign), lid-lag (von Graefe's sign), lagophthalmos, exophthalmos, motility disorders and dysthyroid optic neuropathy (DON) are all well known. The underlying disease is autoimmune thyroid disease and it is often associated with pretibial myxedema and acropachy. The combination of bilateral exophthalmos, lid retraction, stare and enlarged thyroid are virtually pathognomonic for GO. Some ocular signs are relatively specific and these include proptosis and lid-lag or stare, proptosis plus restrictive extraocular myopathy, or the presence of isolated enlarged vessels over the insertions of the medial or lateral rectus muscles. Conjunctival or periorbital edema is also quite common in GO. These typical manifestations of GO have already been described in previous chapters. This chapter reviews the most common atypical manifestations of GO: unilateral or asymmetric exophthalmos, euthyroid GO and globe subluxation as an extreme variant of exophthalmos.

### **How Do You Explain Unilateral Graves' Orbitopathy (We Don't have Graves' Hyperthyroidism in Just One Thyroid Lobe, Have We?)**

Hyperthyroidism of Graves' disease is known to involve the entire thyroid gland, unlike GO which clinically may either be unilateral or bilateral. To our knowledge only one case of 'single-lobe' autoimmune hyperthyroidism is known in the literature. Dimai et al. reported a 31-year-old Caucasian female patient who presented with clinical and laboratory evidence of hyperthyroidism and unilateral goitre [1]. High-resolution ultrasonography of the thyroid gland revealed a morphology indicative of an autoimmune thyroid disease strictly

limited only to the right lobe.  $^{123}\text{I}$ -scintigraphy showed a homogenous, several-fold increased uptake of the radionuclide in the right lobe of the thyroid gland, whereas the uptake in the left lobe did not differ from the uptake in normal controls. Cytology of the fine-needle aspirate of the right lobe revealed a remarkable inflammatory background mainly by presence of lymphocytes, a finding which was not seen in the cytology of the left lobe. Furthermore, both serum antibodies to TSH receptors and thyroid peroxidase were significantly increased. Consequently, hyperthyroidism of Graves' disease with involvement of only one lobe of the thyroid gland was diagnosed.

GO is the most common cause of both unilateral and bilateral proptosis in adults [2–8, 22, 23]. The literature about real unilateral GO is relatively scarce and heterogeneous. However, to date there are no conclusive data and explanations for unilateral GO. Sattler [9] and others have noted more prominent orbital findings on the ipsilateral side of prominent thyroid enlargement in cases of asymmetric thyroid gland swelling, but this thyroid abnormality has rarely been observed and described in patients with unilateral GO ever since. Drescher and Benedict [2] have made the most accurate statement in evaluating unilateral or asymmetric GO when they stated: 'The data presented... are not intended to be comparable..., since dissimilar criteria were used... in the selection of cases'. The mean prominence in their series of 200 normal eyes was 17.3 mm Hertel readings. The mean of measurements for the 'base eye' in all cases in their series, excluding cases of exophthalmic goitre and those of exophthalmos of unknown origin was 17.2 mm. This compares closely with the normal figure. The mean of measurements for the 'base eye' for the group with exophthalmic goitre, however, was 19.1 mm, thus a difference of 1.9 mm. This variation was statistically significant and exceeded 5-fold the standard deviation of the mean. Thus, they found that in cases of unilateral exophthalmic goiter the supposedly uninvolved eye that lies within the 'normal' range of prominence is more prominent by an average of almost 2 mm than the eye in cases of exophthalmos of any other cause. Accordingly, since exophthalmos obviously involves both orbits, it is believed preferable to use the term 'asymmetric exophthalmos' when discussing cases of exophthalmic goitre in which clinically ocular involvement appears to be unilateral (figs. 1–3). Hence, almost all patients with GO, even asymptomatic cases, show some degree of clinical signs with extraocular muscle involvement demonstrable by an abnormal ultrasound pattern or raised intraocular pressure in upgaze [10–17]. In our own series of 105 patients with Graves' disease, 76 (72.3%) patients had only minor clinical signs of thyroid eye disease (NOSPECS class 2), but 100 (95.2%) had a sound evidence of GO ultrasonographically with enlarged extraocular muscles and altered ultrasound pattern of the enlarged extraocular muscles correlating with GO. Six patients (5.7%) had unilateral disease of whom 1 patient (0.9%) with monomuscular active GO (enlarged inferior rectus muscle



**Fig. 1.** Unilateral GO in an elderly male diabetic patient who was a heavy smoker and presented dysthyroid optic neuropathy restricted to the right eye.



**Fig. 2.** Asymmetric active GO.



**Fig. 3.** Asymmetric inactive GO.

with low reflectivity) and another patient with inactive fibrotic changes of his right inferior and medial rectus muscle (enlarged muscles with high reflectivity) were shown. All others had involvement of at least two or more extraocular muscles. Two patients were borderline in relation to thickness and reflectivity of their extraocular muscles but developed clinical signs of bilateral GO 3 and 7 months

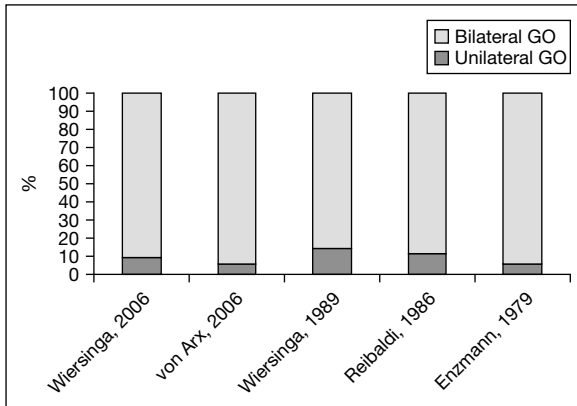
**Table 1.** Characteristics of unilateral versus bilateral eye disease in 90 patients with untreated GO

|   | Unilateral eye disease<br>(group A, n = 13) | Bilateral eye disease<br>(group B, n = 77) | p value<br>(A vs. B) |
|---|---|--|----------------------|
| Sex   | 9 F, 4 M                                    | 57 F, 20 M                                 | n.s.                 |
| Age at study entrance, years                                | 49.7 ± 16.2                                 | 43.6 ± 13.1                                | n.s.                 |
| Age at onset of eye disease, years                          | 48.6 ± 15.6                                 | 41.3 ± 13.1                                | n.s.                 |
| Proptosis, mm   | 20.7 ± 3.4 <sup>1</sup>                     | 20.3 ± 3.8 <sup>2</sup>                    | n.s.                 |
| Thyroid disease (past or present)                           | 8 (62%)                                     | 62 (81%)                                   | n.s.                 |
| Age at onset of thyroid disease, years                      | 47.6 ± 15.1                                 | 37.4 ± 12.1                                | <0.05                |
| Age at onset of eye disease, years                          | 47.7 ± 15.2                                 | 40.6 ± 12.7                                | n.s.                 |
| Interval between onset of thyroid<br>and eye disease, years | 0.1 ± 0.4                                   | 3.2 ± 8.2                                  | <0.05                |

<sup>1</sup>Affected eye only; <sup>2</sup>mean of both eyes.

Values are mean ± SD. n.s. = Non-significant. From Wiersinga et al. [28].

later respectively. Only 5 patients (4.7%) showed neither signs nor any symptoms of GO [unpubl. data]. Similar data have been generated by other investigators [18–20]. A number of patients with presumed thyroid aetiology of unilateral GO have been shown to have CT and ultrasound evidence of unilateral disease with muscle enlargement without evident abnormal thyroid studies [21]. As already mentioned in previous chapters, there is CT, MRI and/or ultrasound evidence for orbital involvement in almost all patients with autoimmune hyperthyroidism. Clinical evidence of bilateral GO occurs in 80–90% of cases. In unilateral GO clinical signs and symptoms can be found in one orbit only and true unilateral cases are present in 10–20% of patients [22–26]. Variants of different clinical presentations are often called atypical. Among patients referred to a specialized diagnostic ophthalmology unit, the percentage of unilateral cases is even higher. In one study, 11.6% of the patients had apparent unilateral disease [27] and in a study of 90 untreated patients with autoimmune thyroid eye disease referred to a single centre 14% had unilateral findings (table 1) [28]. Many patients with presumed unilateral disease have subtle signs of the other orbit such as increased IOP in upgaze or enlarged extraocular muscles on CT and/or MRI [29]. A study by Enzmann et al. [30] revealed 50% of presumed unilateral GO as having bilateral orbital disease, when evaluated by CT scan. Only 6% were confirmed to be unilateral, all other cases were found to be asymmetric. In patients with unilateral exophthalmos evaluated by ophthalmologists, the aetiology is GO in 10–30% of cases. In a recent (unpublished) retrospective observational case control series of the Orbital Center at the Academic Medical Center, Wiersinga and co-workers



**Fig. 4.** Frequency of unilateral GO.

identified 28 cases with unilateral GO [31]. The prevalence of unilateral GO was 9%. In their series patients with unilateral GO tend to be older than patients with bilateral disease (54 vs. 44 years;  $p = 0.099$ ) and are euthyroid in a significantly higher number of patients (28.6 vs. 1.8%;  $p = 0.001$ ). In the majority of their patients with unilateral GO, unilateral extraocular muscle enlargement was found on CT scans. A large number of unilateral GO patients developed bilateral disease after an unpredictable interval of time. Factors that influence progression to bilateral disease remain unknown. They conclude that unilateral GO probably represents an early stage of Graves' disease, initially limited to only one eye and often associated with subclinical thyroid involvement. These data are in support of the view that the less-prominent and clinically less-affected eye is also involved in GO. Thus, although the clinical presentation of GO may often be asymmetric, it is believed to be truly unilateral in a minority of cases, as we may expect in a systemic disease (fig. 4).

### **Will Unilateral Graves' Orbitopathy Proceed to Bilateral Graves' Orbitopathy?**

In our own series of 105 patients with Graves' disease, 5 of 6 patients with unilateral GO developed bilateral disease. The same phenomenon occurred in the patients of the Amsterdam group, where a large number of unilateral GO patients developed bilateral disease after an unpredictable interval of time. Kalman and Mourits reported a case of late recurrence of unilateral GO on the contralateral side after 7 years. A 44-year-old woman with left unilateral GO underwent

two-wall orbital decompression on the left side. After strabismus surgery and left upper eyelid surgery, she was discharged. Seven years later, the patient developed GO on the right side, and she underwent a two-wall orbital decompression on the right side. They concluded that at least in patients with unilateral GO, late recurrence of the disease in the contralateral orbit may occur [32]. Kamminga et al. [33] reported 2 cases with unilateral GO and ipsilateral recurrence after 35 years in the first case and unilateral onset of GO with progression to bilateral disease within weeks in the second case. According to the literature only a small number of patients with presumed unilateral disease (5–11%) do not progress to bilateral disease and have pure unilateral GO [28, 34].

### **Is the Clinical Presentation of Unilateral Graves' Orbitopathy Different from Bilateral Graves' Orbitopathy?**

According to the literature, the clinical presentation of unilateral or asymmetric GO is not different from bilateral disease relating to symptoms and ocular signs. The hypothesis of a syndrome with an underlying systemic disease as the cause of GO is supported by Werner et al. [14] reporting on 47 patients with consistent bilateral orbital involvement in Graves' disease. Ultrasonic changes, primarily in extraocular muscles, were minimal to moderate in 44 patients, equivocal in 2 and absent in only 1 patient. Saltzman and Mellicker [7] reviewed 8 cases from the literature with exophthalmos preceding thyrotoxicosis and an additional case of unilateral exophthalmos also preceding thyrotoxic symptoms and signs by 20 months. They conclude that unilateral GO might be a forerunner of thyrotoxicosis. In an earlier report on 90 consecutive untreated patients Wiersinga et al. [28] found no differences in 13 patients with unilateral disease. The distribution of age, sex and NOSPECS classes in these patients was similar to those patients with bilateral eye disease, but the interval between the onset of thyroid and eye disease was much shorter in cases of unilateral, than in cases of bilateral eye disease. Patients without clinically evident thyroid disease ( $n = 20$ ; 22%) were not different from patients with thyroid disease in age, sex or ophthalmological presentation. They concluded that unilateral GO may represent an early stage of the disease, that as a rule already is or develops shortly afterwards into bilateral disease (table 1) [28].

### **How Does Unilaterality Affect Treatment?**

Unilaterality does not affect treatment, neither of the underlying systemic autoimmune or thyroid disease, nor the orbitopathy itself. On the other hand, it