Sight-threatening Graves' orbitopathy: Twenty years' experience of a multidisciplinary thyroid-eye outpatient clinic

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Summary

Context: Sight-threatening Graves' orbitopathy affects 3% to 5% of patients with Graves' orbitopathy.

Objectives: To describe the management of patients with sight-threatening Graves' orbitopathy seen in a multidisciplinary thyroid-eye outpatient clinic dedicated to Graves' orbitopathy (GO).

Patients and methods: We enrolled all patients with sight-threatening GO (dysthyroid optic neuropathy and corneal ulcer as defined in the EUGOGO statement) seen and treated in our GO multidisciplinary thyroid-eye outpatient clinic over the last two decades.

Results: A total of 31 patients (median age 51 years old) including 24 women (77%) and 58% active smokers. This population represented 47 cases (case = eye) of sight-threatening GO. Dysthyroid optic neuropathy (DON) occurred in 40 eyes, corneal ulcer in 15 eyes and both in 8. At presentation, the clinical features of DON were reduced visual acuity (85%), visual field defects (80%), optic disc swelling (42%) and reduced colour vision (100%). At one year, surgical orbital decompression (OD) was performed in 82.5% of DON cases. Only seven eyes with DON were treated with pulses of intra-venous glucocorticoids. For 10 patients, several therapeutic strategies (OD n = 4, punctal plug n = 1, amniotic membrane graft n = 2, tarsorrhaphy n = 2, botulinum toxin injection = 3 and eyelid surgery n = 2) were used to treat corneal ulcer. For each ophthalmological parameter, more than 85% of DON cases had recovery or improvement after treatment. For visual acuity in corneal ulcer, it was 71.4%.

Conclusion: We report 47 cases of sight-threatening GO. Orbital decompression was performed in the majority of DON cases and several therapeutic strategies were necessary to treat corneal ulcer. The results are satisfactory in sight-threatening Graves' orbitopathy due to multidisciplinary management.

KEYWORDS
cornea, dysthyroid optic neuropathy, orbital decompression, sight-threatening Graves' orbitopathy

1 | INTRODUCTION

Graves' orbitopathy (GO) is a frequent cause for consultation with 16 cases reported per 100 000 women per year and 2.9 cases per 100 000 men per year.[1] Mild or moderate GO is the most common presentation in these cohorts whereas forms for which visual prognosis can be compromised—sight-threatening orbitopathy—are rare, occurring in 3%-5% of patients.[2] Sight-threatening GO includes two different clinical entities as follows: dysthyroid optic neuropathy (DON) and corneal ulcer. DON, which is more frequent than corneal ulcer, represents a diagnostic and therapeutic challenge. Although the mechanisms are known (compression or stretching of the optic nerve), diagnosis requires thorough ophthalmological evaluation including visual acuity, visual field, funduscopy and colour vision evaluation. Management of DON, a medical emergency, is based on general measures (multidisciplinary approach, smoking cessation, restoration of normal thyroid function, etc), medical treatment with intra-venous glucocorticoids and/or a surgical approach with orbital decompression. Because of the low frequency and severity of DON, few studies describe the different therapeutic strategies available and only one study compares medical versus surgical strategies.[3] Corneal ulcer occurs in less than 2% of patients and requires a specialized management approach using different methods (tarsorrhaphy, botulinum toxin injection, orbital decompression, amniotic membrane graft, punctal plug, eyelid surgery or radiotherapy). As for DON, published data are very rare for each therapeutic strategy.[4-6] The aim of our clinical and retrospective study is to describe the management of patients with sight-threatening GO seen in a multidisciplinary outpatient clinic dedicated to patients with GO between 1995 and 2015.

2 | PATIENTS AND METHODS

In a single-centre, descriptive and retrospective study, we report data recorded during multidisciplinary thyroid-eye outpatient consultation at Toulouse University Hospital between 1995 and 2015. We have included all of the patients seen for sight-threatening GO in our GO multidisciplinary outpatient clinic over the last 20 years. According to the EUGOGO statement, sight-threatening GO was defined as DON and/or corneal ulcer. DON was diagnosed if optic disc swelling was present. In the absence of optic disc swelling, DON was diagnosed in the presence of two or more anomalies such as decreased visual acuity, defective visual field, change in colour vision and/or radiological compression or stretching of the optic nerve. Thirty-four patients were seen with sight-threatening GO and 31 of them were enrolled in the study. Three patients were excluded because of lack of data due to initial treatment in another University Hospital.

The aim of our study is to describe the management of patients with sight-threatening GO seen in GO-specific multidisciplinary thyroid-eye outpatient clinic between 1995 and 2015. For each patient, the following data were recorded:

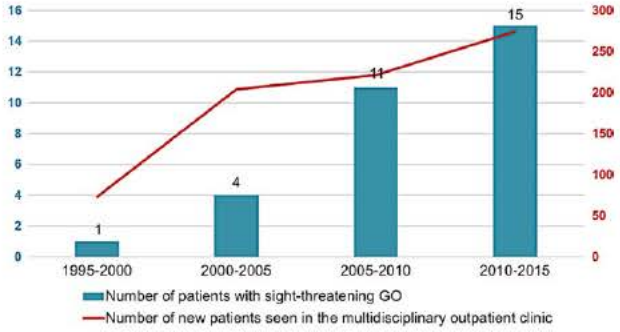

FIGURE 1 Number of patients seen from 1995 to 2015 [Colour figure can be viewed at wileyonlinelibrary.com]

- Patient characteristics: sex, age at diagnosis of thyroid and eye diseases, ophthalmological history, smoking habits;
- Thyroid disease and management;
- Grave's orbitopathy history: clinical features, management and long-term results.

In the case of DON, the following data were assessed during ophthalmological examination: eye protrusion, visual acuity, presence of optic disc swelling, visual field and colour vision. Imaging results were also recorded (orbital CT scan or MRI).

Data analysis was performed with Excel functionalities (median and quartile). Statistical analysis is expressed with median and quartile values (IQR 25 and IQR75). Qualitative variables were compared between groups using Fisher's exact test. Student's *t* test was used to compare the distribution of quantitative data (or Mann-Whitney's test when the distribution departed from normality). The significance threshold was $P < 0.05$.

3 | RESULTS

3.1 | Population characteristics

Between 1995 and 2015, thirty-four patients were seen for sight-threatening orbitopathy. Thirty-one patients were included in our analysis, representing 4.0% of all patients seen over the two decades (772 patients since 1995).

3.2 | Changes in the number of patients seen between 1995 and 2015

We observed an increasing number of patients with sight-threatening orbitopathy. Between 1995 and 2000, sight-threatening orbitopathy represented 1.4% of the population of our multidisciplinary consultation compared to 2.0% between 2000 and 2005, 5.0% between 2005 and 2010 and 5.5% between 2010 and 2015 (Figure 1).

The clinical characteristics of the 31 patients are summarized in Table 1.

Women represent 77% of our population (24 patients), active smokers 58% (18 patients), and Graves' disease was the predominant thyroid disease. Only two patients (6.5%) had Hashimoto thyroiditis.

TABLE 1 Population characteristics (31 patients)

	Median (IQR 25 and IQR 75)
Age on diagnosis of thyroid disease	49 years (42.5-54.5)
Age on diagnosis of Graves' orbitopathy	50 years (43.5-56.5)
Age on diagnosis of sight-threatening orbitopathy	51 years (46.5-58)
	No. patients
Sex (F/M)	24/7
Thyroid diseases	
Graves' disease	29
Hashimoto thyroiditis	2
Smokers	
Yes	18
No	13
Treatment for thyroid diseases at time of sight-threatening orbitopathy	
Antithyroid drug	17
Total thyroidectomy	11
Radioiodine treatment (alone)	2

A median delay of 6 months was observed between the initial signs of dysthyroid orbitopathy and sight-threatening GO. Only FOUR patients (12.9%) presented a sight-threatening form at the beginning of their Graves' orbitopathy.

On diagnosis of sight-threatening GO, seventeen patients (54.8%) were treated with antithyroid drugs, eleven patients (35.5%) had previously undergone total thyroidectomy and two patients (6.5%) had only received radioiodine treatment. Three other patients (9.7%) had received radioiodine treatment, two before surgery and one due to residual post-operative thyroid tissue. Therefore, five patients (16.2%) received radioiodine treatment before the onset of sight-threatening GO.

All patients with surgical or radioiodine treatment had replacement levothyroxine therapy. On diagnosis of sight-threatening GO, eleven patients (35.5%) had a normal TSH concentration with a median TSH of 0.49 µIU/mL (0.36-2.4) and eleven patients (35.5%) presented hypothyroidism (median TSH at 10.5 µU/mL; 7-15.5).

3.3 | Clinical features of the 31 patients

All 31 patients had bilateral orbitopathy, but only sixteen patients had a bilateral sight-threatening GO and fifteen had a unilateral sight-threatening GO (respectively, 51.6% and 48.4%) representing forty-seven eyes with sight-threatening GO.

3.3.1 | DON: Clinical features and management

Twenty-four patients (77.4% of the study population) had DON, representing 40 eyes with DON. Seventy-one percent of these patients are women (17 patients). Twelve patients received oral or intravenous glucocorticoid therapy before DON was diagnosed (50%).

The initial clinical features of DON are summarized in Table 2. The data are expressed in terms of the number of affected eyes. For all parameters, the number of assessed eyes is specified. Initial median eye protrusion based on Hertel values was 25 mm (23-26) on thirty-four eyes. At presentation, clinical features of DON were reduced visual acuity (85%, 34 eyes), visual field defects (80%, 28 eyes), optic disc swelling (42%, 15 eyes) and reduced colour vision (100%, 7 eyes). For two patients (8.3%), ocular protrusion was less than 21 mm.

Two patients (four eyes) had an orbital decompression (OD) without any medical treatment (8.3% of DON patients). Four patients (six eyes) developed DON whilst receiving a glucocorticoid therapy for mild to severe orbitopathy, and they had orbital decompression (16.7% of DON patients). Eighteen patients (30 eyes) were treated with pulses of intra-venous glucocorticoids (75% of DON patients). After a few pulses, the ophthalmological examination was repeated to assess the efficacy of the medical strategy. Among the 18 patients, 13 (23 eyes) had orbital decompression because of deterioration in the optic neuropathy for two patients (four eyes), no improvement for four patients (seven eyes) and relapse when glucocorticoid treatment was decreased or withdrawn for six patients (11 eyes). For one patient (one eye), orbital decompression was performed because of globe subluxation. Hence, in our population, only five patients (seven eyes) had medical treatment with glucocorticoids without surgery. Various protocols of intra-venous glucocorticoids were used from one pulse of 500 mg intra-venous methylprednisolone to 14 pulses of 500 mg intra-venous methylprednisolone (3 a week) but no protocol exceeded a cumulative dose of 7 g of methylprednisolone.

3.3.2 | Corneal ulcer: Clinical features and management

Corneal ulcer occurred in thirteen patients (41.9% of the study population; twelve women and one man), unilateral in eleven patients

TABLE 2 Clinical features of dysthyroid optic neuropathy

Parameters	No. eyes
Visual acuity (in 40 eyes)	
Reduced	34 (85%)
Normal	6 (15%)
Visual Field (in 35 eyes)	
Altered	28 (80%)
Normal	7 (20%)
Optic disc swelling (in 36 eyes)	
Yes	15 (42%)
No	20 (56%)
Cannot be assessed	1 (2%)
Colour vision (in 7 eyes)	
Reduced	7 (100%)
Normal	0
Apical crowding and/or optic nerve stretch (in 20 eyes)	
Yes	12 (60%)
No	8 (40%)

TABLE 3 Follow-up period of DON patients: Outcomes of ophthalmological parameters

Parameters	No. eyes
Visual acuity (in 34 eyes)	
Recovery "ad integrum"	9 (26.5%)
Improvement	17 (50%)
Unchanged	3 (8.8%)
Unavailable data	5 (14.7%)
Visual Field (in 28 eyes)	
Recovery "ad integrum"	4 (14.3%)
Improvement	5 (17.9%)
Unavailable data	19 (67.8%)
Optic disc swelling (in 15 eyes)	
Complete disappearance	5 (33.3%)
Improvement	4 (26.7%)
Unchanged	1 (6.7%)
Unavailable data	5 (33.3%)

and bilateral in two (respectively, 84.6% and 15.4%), so fifteen eyes presented corneal ulcer. Six patients developed corneal ulcer on the same eye affected by DON and corneal ulcer occurred twice on the same eye in three patients.

Visual acuity was decreased in ten patients (76.9%). Corneal ulcer was further complicated by abscess formation in three patients, leading to eye necrosis in one case.

Two patients developed corneal ulcer during glucocorticoid therapy and one patient after orbital decompression because of an entropion. In one case, corneal ulcer was caused by night-occlusion with compress.

Local treatment was used in all patients (eye drops and night-occlusion) and proved effective as the sole treatment in three patients (23%). In the other patients, different medical or surgical strategies were necessary to manage corneal ulcer (OD n = 4, punctal plug n = 1, amniotic membrane graft n = 2, tarsorrhaphy n = 2, botulinum toxin injection n = 3 and eyelid surgery n = 2).

3.4 | Long-term results and complications

After treatment of DON, the median eye protrusion was 20 mm (18-22.5) ($P < 0.0001$). The follow-up data were collected between 2 and 46 months after the last treatment for each patient (median follow-up at 8 months; 4-14). The follow-up data of visual acuity, visual field and funduscopy are summarized in Table 3. In 76.5% of cases (26 eyes in 34 altered), visual acuity was improved or recovered. For visual field or funduscopy, it was 32.2% and 60%, respectively (9 eyes in 28 altered and 9 eyes in 15 altered, respectively). But available data represented 14.7% for visual acuity, 67.8% for visual field and 33.3% for funduscopy. Colour vision was evaluated in only 2 eyes (2 in 7 eyes, 28.6%) with normalization of this parameter. So, if we only consider available data, all ophthalmological parameters improved in more than 85% of DON cases. Finally, in term of patients, twelve patients had partial recovery of ophthalmological parameters and nine had complete recovery (respectively, 50% and 37.5% of DON patients). Data were unknown for all ophthalmological parameters in three patients (12.5%). Two patients required new treatment (glucocorticoid therapy in one case, a second orbital decompression in another) in relation to a new episode of DON on the same eye.

No severe side effects were reported in our population in relation to glucocorticoid therapy. After orbital decompression (22 patients), four patients presented hypoesthesia in the cutaneous territory of intra-orbital nerve (18.1% of patients with DO). Three weeks after decompression, one patient developed a sinus infection leading to bilateral optic neuropathy treated with antibiotics and glucocorticoid therapy. This patient had a total recovery. Another patient developed an entropion after orbital decompression leading to corneal ulcer.

Among 10 patients with corneal ulcer and altered visual acuity, five patients had a partial or total recovery (50%). Three patients experienced no change after treatment (30%). The following data were not known for two patients (20%). Corneal opacity occurred in two patients (15.3% of patients with corneal ulcer). With regard to the different strategies used, amniotic membrane graft was effective in one patient (2 grafts performed). For another patient, the approach failed, culminating in abscess and eye necrosis. Botulinum toxin injections were effective in one patient, ineffective in a second patient and led to recurrent corneal ulcer in a third. Repeated botulinum injections (2 injections) were required in the first two patients.

Long-term outcomes were not statistically different between active smokers and non-smokers or according to thyroid function status (Supporting Information Tables S1 and S2).

4 | DISCUSSION

In this study, we describe the management of sight-threatening orbitopathy in patients seen in a multidisciplinary thyroid-eye outpatient clinic between 1995 and 2015.

Since 1995, 772 patients were seen for Graves' orbitopathy (GO) in our outpatient clinic. Sight-threatening GO occurred in 34 patients, representing 4.4% of our population. Previously published data described sight-threatening GO as a rare complication of GO occurring in 3%-5% of patients.[2] Our results are consistent with these data. Moreover, among the thirty-one patients enrolled in this study, DON was the principal form of sight-threatening GO before corneal ulcer (58% of patients with DON, 23% with corneal ulcer and 19% with both clinical entities), and comparable to previous studies. The population characteristics were quite similar to previous studies but with some differences. The median age of sight-threatening GO was 51 years old, which is younger than in other studies (median age 56-57 years old) except in the studies conducted by Wakelkamp et al or Jeon et al (median age 52 and 50 years old, respectively).[3,7,8] Women represent 77% of our population, which is comparable to other studies, but this figure is higher than in the study conducted by Currò et al where women represented 58% of the population.[3,9] Graves' disease is the principal aetiology of thyroid pathology and radioiodine treatment was performed in 16% of our population. This is consistent with the EUGOGO study on DON carried out in 2007.[10] Interestingly, the number of patients seen for GO and for sight-threatening forms increased substantially between 1995 and 2015. But, this increase was not parallel. Indeed, between 1995 and 2000, sight-threatening GO represented 1.4% of the population of our outpatient clinic compared to 2.0% between 2000 and 2005 5.0% between 2005 and 2010% and 5.5% between 2010 and 2015. To explain these data, two hypotheses could be done. First, our data could suggest that GO has become increasingly severe in recent decades. Nevertheless, this hypothesis is not consistent with the PREGO study, which describes an increase in mild and inactive GO in Europe between 2000 and 2012.[11] The second hypothesis is the fact that the appeal of our outpatient clinic has probably grown over the years, increasing the number of patients seen for sight-threatening GO.

More common than corneal ulcer, DON poses a diagnostic challenge. As described by Wiersinga and Kahaly,[12] DON was diagnosed if optic disc swelling was present. In the absence of optic disc swelling, DON was diagnosed if two or more anomalies were present including decreased visual acuity, visual field defect, change in colour vision and/or radiological compression or stretching of the optic nerve. This definition requires thorough ophthalmological evaluation including visual acuity, visual field, funduscopy and colour vision evaluation. Patients with decreased visual acuity only cannot be considered for DON diagnosis. It is important for physicians to note this last point in order to avoid over-diagnosis of DON. In our DON population, clinical features at presentation were as follows: reduced visual acuity in 85% of cases, visual field defects in 80%, optic disc swelling in 42% and reduced colour vision in 100% (n = 7) of cases. Radiological signs were present in 60% of cases with DON. Concerning visual acuity and visual fields, our results are quite similar to previous studies,[9,10,13] but optic disc swelling is more frequent in our population than in the study conducted by Currò (17.5%). Radiological signs are present in 60% of cases in our population compared to 88%-100% of cases in the other studies. We cannot draw colour vision comparisons with other studies because of the lack of data (7 eyes out of 40).

DON represents both diagnostic and therapeutic challenges. Intra-venous glucocorticoids and orbital decompression are the two principal strategies used to treat DON. Orbital radiotherapy is indicated as adjuvant treatment. Some case reports describe the use of new immunological treatment (as tocilizumab)[14] but given the lack of larger scale studies, we cannot consider these treatments as conventional DON therapy. So far, just one randomized study compares medical versus surgical treatment for DON[3] leading to EUGOGO recommendations for intra-venous corticoids as first-line treatment before surgery.[15] In terms of intra-venous glucocorticoid protocols, Guy JR et al treated DON with four pulses of 250 mg intra-venous methylprednisolone on three consecutive days,[16] Mourits et al administered four pulses of 500 mg on 2 days,[9] Wakelkamp et al propose daily pulses of 1 g on three consecutive days, repeating the same strategy the following week.[3] No difference was observed between pulses of 500 mg or 1 g in the study carried out by Currò et al.[13] In our study conducted between 1995 and 2015, various intra-venous glucocorticoid protocols were used, ranging from one pulse of 500 mg intra-venous methylprednisolone to 14 pulses of 500 mg intra-venous methylprednisolone (3 a week). However, no protocol exceeded a cumulative dose of 7 g of methylprednisolone. Moreover, management of DON required orbital decompression in 82.5% of cases. Medical treatment (pulses of intra-venous glucocorticoids with or without orbital radiotherapy) was performed alone in only 17.5% of cases. These data are very different from the literature. Currò et al[13] treated 42.5% of their cases of DON with medical treatment alone. In two previous studies, this rate of orbital decompression varied between 60% and 66%.[3,9] Therefore, we cannot be sure that this difference is not related to a different classification of sight-threatening GO in other studies that could lead to over-diagnosis of DON and thus explain the improved response to medical treatment. On the other hand, this difference could also be attributed to the various intra-venous glucocorticoid protocols used in our study.

Corneal ulcer, the other entity of sight-threatening GO, is less frequent than DON and sparse data are available about its management.[4-6] In our study, corneal ulcer was very difficult to treat. Local treatment (eye drops and night-occlusion) alone is mostly ineffective (3 patients out of 13 treated with local treatment alone). Ten patients required the use of different medical or surgical strategies (orbital decompression, punctal plug, amniotic membrane graft, tarsorrhaphy, botulinum toxin injection and eyelid surgery). The efficacy of one or other of these strategies is inconclusive because of the small number of studied patients. However, we are convinced that corneal ulcer requires close attention and treatment from the earliest symptoms.

Patient follow-up is also critical in the management of sight-threatening orbitopathy. To establish whether treatment is effective,

patients must be assessed 1 or 2 weeks after initial treatment. Currò et al[13] show that initial medical treatment does not lead to poor prognosis on visual parameters even if is ineffective. In a cohort of moderate to severe GO, Bartalena shows that patients whose condition deteriorated at 6 weeks have no chance to improve thereafter.

Indeed, the criteria for improvement are not very clear in the various studies. It is also important to monitor corticosteroid therapy for side effects. Nevertheless, the intra-venous route appears safer than the oral route and cumulative doses under 8 g reduce serious side effects.[17-19] No severe adverse drug reactions were observed with glucocorticoids in our population. Long-term follow-up produced good outcomes mostly in patients with DON or corneal ulcer. In a recent study, complete recovery of visual acuity was obtained using a combination of therapies (medical treatment, OD and radiotherapy) in 66.7% of DON patients.[20] In addition to the use of different strategies, a multidisciplinary approach is required to ensure the more effective management of sight-threatening GO.

Our study has some limitations. Firstly, it is a retrospective study. Some initial assessment or long-term follow-up data are unavailable. Various intra-venous glucocorticoid protocols were used between 1995 and 2015. Nevertheless, our study describes one of the most important cohorts of sight-threatening GO (47 cases), including 15 cases of corneal ulcer. Orbital decompression was performed in the majority of DON cases and several therapeutic strategies were necessary to treat corneal ulcer. However, with multidisciplinary thyroid-eye management, results are satisfactory for the majority of patients.

CONFLICT OF INTEREST

The authors report no conflict of interest regarding the data shown in this article.

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