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Introductory Chapter: The Dysthyroid Optic Neuropathy

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1. Introduction

Graves' orbitopathy — often known as Basedowian ophthalmopathy — is an autoimmune disorder that occurs in 5% of patients affected by the thyroid disease [1].

Graves' orbitopathy (GO) mainly affects retrobulbar soft tissue [2] and it is the extra thyroidal manifestation of Graves' disease and the most common cause of exophthalmos. The GO can have a major impact on the patient life, from both functional and aesthetic point of view; to some extent, it can be considered as an event deeply affecting the quality of life of the patients. The most serious consequence of GO is perhaps the *dysthyroid optic neuropathy (DON)*, which is due to compression caused by the swelling of extraocular muscles and orbital fat [3].

Many studies in the latest two centuries concentrated on GO and its treatments [4]. Ocular changes associated with thyroid disease, in fact, have been described by Graves in 1835 and by Von Basedow in 1840, but they are likely to be observed and studied by Parry in 1786, who published posthumously a paper on GO in 1825.

Despite ongoing advances in basic science and clinical research, the pathogenesis of GO is still unclear and highly effective therapeutic strategies remain elusive. The diagnosis of GO is mainly based on laboratory tests devoted to investigate thyroid dysfunction and/or autoimmunity. Recently, however, imaging approaches (among which we cite computed tomography, magnetic resonance imaging, ultrasound, and colour Doppler imaging) are increasingly adopted both in the diagnosis stage and in the follow-up, after proper clinical or surgical treatments have been applied [5, 6]. Imaging techniques, in particular, are relevant to spot morphological abnormalities affecting the orbital structures as well as to classify early stages of the diseases. In addition, imaging techniques are useful to identify

those patients who are likely to get affected from DON in advance; such knowledge is crucial for an early treatment, and on the long run, it is effective in avoiding visual loss.

This chapter mainly focuses on DON, and it aims at illustrating the most recent advances in its diagnosis and treatment. The chapter is structured as follows: we introduce the Graves' orbitopathy, and then, we detail the main features of DON as well as the diagnostic procedures usually followed in clinical practice.

2. The Graves' orbitopathy

Graves' orbitopathy (GO) is the most common extra-thyroidal manifestation of Graves' disease (GD). It roughly occurs in 25–50% of patients who are affected from the GD [4].

GO may occur during or after the onset of hyperthyroidism and less frequently in euthyroid or hypothyroid patients [4].

Some studies highlighted a strong association between immunogenic hyperthyroidism and orbitopathy, which forces us to conjecture that the antigen responsible for these diverse conditions may be shared by the thyroid gland and orbital tissues [7].

GO displays an *active phase* (also called *inflammatory stage*) and an *inactive phase* (also called *fibrotic stage*). In the active phase, we notice, on one hand, an expansion of tissue, which is generally due to inflammation, the accumulation of glycosaminoglycans and an increased fat content; such an expansion is balanced by the space constraint imposed by the bony orbit. The signs and symptoms of the GO during the active stage include lid retraction, proptosis, conjunctival injection, chemosis, diplopia, corneal ulceration, and rarely, disthiroid optic neuropathy (DON), which will be later described.

The active stage length generally varies from 18 to 24 months; such a stage is then followed by an inactive stage, which is mainly characterised by clinical signs such as lid retraction, proptosis, and restrictive strabismus.

The management of patients with GO is challenging, and in the absence of objective evidence of thyroid dysfunction, GO is hard to diagnose [8].

The main clinical features to diagnose GO are discussed in Bartley and Gorman [9]: an effective indicator of GO is when eyelid retraction occurs in association with thyroid dysfunction or abnormal regulation, exophthalmos, optic nerve dysfunction, DON, or extraocular muscle involvement. If eyelid retraction is absent, further laboratory tests are needed.

More recently, magnetic resonance imaging (MRI) has been employed to distinguish the acute inflammatory active disease from fibrotic stage disease [10]. MRI is a mandatory choice in the management of doubtful cases (e.g., asymmetrical orbital involvement), and it is required to exclude any other orbital pathology.

Several classification systems are today available to assess the clinical manifestations of GO. The first one is due to Werner [11], who introduced the so-called NO SPECS classification;

this is an acronym which stands for *No physical signs or symptoms, Only signs, Soft tissue involvement, Proptosis, Extraocular muscle signs, Corneal involvement, and Sight loss*.

NO SPECS classification was subsequently updated, and it is now largely adopted in clinical practice, along with its variants [12]. The modified version of NOSPECS is reported in **Table 1**.

Class	Grade	Suggestion for grading
O		No physical signs or symptoms
I		Only signs
II		Soft tissue involvement
	0	Absent
	a	Minimal
	b	Moderate
	c	Marked
III		Proptosis (3 mm or more of normal upper limits with or without symptoms)
	0	Absent
	a	3 or 4 mm over upper normal
	b	5 to 7 mm increase
	c	8 mm increase
IV		Extraocular muscle involvement (usually with diplopia)
	a	Absent
	b	Limitation of motion at extremes of gaze
	c	Evident restriction of motion
	d	Fixation of a globe or globes
V		Corneal involvement (primarily due to lagophthalmos)
	0	Absent
	a	Stippling of cornea
	b	Ulceration
	c	Clouding, necrosis and perforation
VI		Sight Loss (due to optic nerve involvement)
	0	Absent
	a	Disc pallor or choking, or visual field defect, vision 20/20 or 20/60
	b	The same but vision 20/70–20/200
	c	Blindness, vision less than 20/200

Table 1. NO SPECS modified classification.

NO SPECS classification is conceived to measure the degree of severity of GO, and therefore, it is not suitable to distinguish the active GO stage from the inactive one. This implies that NO SPECS classification allows for identifying a treatment on the basis of the symptom severity rather than on the actual progression of the disease. To this end, Mourits et al. [13] introduced the *Clinical Activity Score (CAS)*, with the goal of discriminating the active from the inactive stage of the disease. CAS table was subsequently updated [14].

3. The dysthyroid optic neuropathy

Dysthyroid optic neuropathy (DON) is the most feared complication of thyroid eye disease, and it constitutes an important factor of permanent or temporary disability.

Fortunately, DON occurs with a low incidence; in fact, some studies estimate that it affects 4–8% of patients affected by thyroid eye disease [15].

Some researchers propose inflammatory [16, 17] and ischemic models [18] to explain DON; however, the most widely accepted explanation is that DON depends on the mechanical compression of the optic nerve at the orbital apex by the enlarged extraocular muscles [19].

The main features to diagnose dysthyroid optic neuropathy (DON) are listed below:

1. Impaired colour vision
2. Optic disc swelling/atrophy
3. Abnormal visual acuity
4. Relative afferent pupillary defect
5. Abnormal VEPs
6. Crowded apex on scanning
7. Abnormal visual fields
8. Atrophy of the optic nerve head
9. Edema

Patients with GO are assumed to be affected by DON if at least one of the aforementioned features is present and no other cause for the defect is observed; unfortunately, visual impairment in GO is sometimes linked with other factors, as observed by Dayan and Dayan [20]. This implies that direct optic nerve function testing in GO patients is the source of misleading results which makes a DON diagnosis hard.

The availability of effective clinical tests is of great relevance in DON management: when diagnosed, DON needs urgent treatment with medical (e.g., high dose intravenous methylprednisolone) or surgical decompression (e.g., bone removal decompression) to avoid permanent or progressive visual loss [16]. Kazim et al. [17] analysed a set of five patients in

whom the extraocular muscle enlargement was one of the causes of DON, and they proved that orbital fat decompression was an effective alternative to bony decompression.

Treatments above carry a considerable risk of morbidity, and hence, a correct diagnosis is a key ingredient to ensure that those patients affected by DON are treated promptly, while those unaffected are spared the risks associated with treatment.

The diagnosis of GO and DON is based primarily on clinical signs from laboratory test results which aim at detecting thyroid dysfunction and autoimmunity. The visual field along with optical coherence tomography (OCT) provides rich information about DON and its severity. In **Figure 1**, we report the visual field of an individual with a severe DON complication.

More recently, *imaging studies*, such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), and colour Doppler imaging (CDI), can also be extremely important in both the diagnosis and clinical or surgical follow-up [3].

Imaging studies are able to analyse extraocular muscle involvement and may help distinguish the early acute inflammatory stage from the fibrotic and inactive stage of the disease [10]. In case of patients prone to develop DON, the extensive usage of imaging approaches makes a timely diagnosis possible, avoiding permanent visual loss.

Giaconi et al. [5] analysed the utility of CT imaging in identifying patients with DON. They found that patients with Graves' orbitopathy who have severe optic nerve crowding, intracranial fat prolapse and/or muscle index greater than 50% present on orbital CT scans are more likely to have coexisting optic neuropathy.

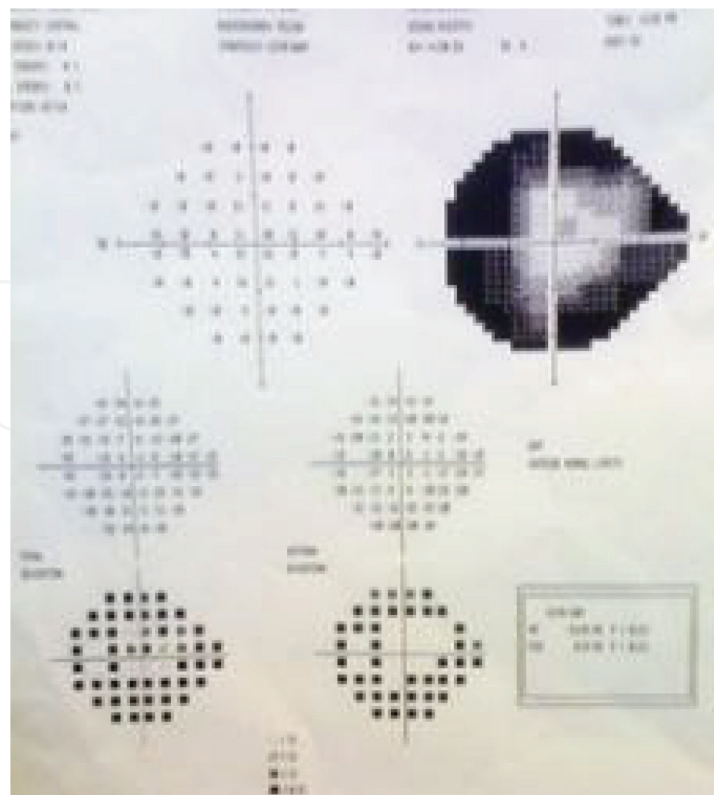


Figure 1. Visual field of a patient with severe DON complication.

An important result to cite is due to Goncalves et al. [3], who targeted at assessing the ability of multi-detector CT to detect DON. The proposed study involved 93 patients who underwent a complete neuro-ophthalmic examination, as well as a CT scan. For each individual, orbital fat and muscle volume were estimated on the basis of their attenuation factors. The authors computed a pair of metrics, namely: (a) *the volumetric crowding index*, defined as the ratio of the soft tissue to the orbital fat volume, and (b) *the volumetric orbital apex crowding index*, which is the ratio of the extraocular muscles to the orbital fat volume. Two groups of orbits (with and without dysthyroid optic neuropathy) were compared.

The main result of such a study was that the orbital volumetric crowding index was the most effective predictor of dysthyroid optic neuropathy in comparison with the previously described computed tomography indexes.

4. Conclusions

This chapter targets at describing the main features of the dysthyroid optic neuropathy (DON), one of the most severe complications of Graves' syndrome.

We first described the clinical signs and test laboratory, which are commonly used to diagnose DON. We also focused on modern imaging techniques such as ultrasonography and magnetic resonance which represent one of the most promising tools that ophthalmologist can use to promptly diagnose DON. There are in fact only few studies on small groups of patients revealing the high potential of imaging techniques and their ability to overcome the common drawbacks that the laboratory test incurs.

We believe that, in the near future, we need to test imaging techniques on large samples to get a more accurate assessment of their potentialities and limitations.

A lot of work is still needed in the field of DON treatments: in fact, only steroid drugs (methylprednisolone) are commonly used, and from a surgical standpoint, the only available therapeutic options are bone and fat compression. A novel and important research avenue is the study of effective surgical procedures which can actually improve the quality of life of patients.

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