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Thyroid-Associated Ophthalmopathy in Juvenile Graves' Disease: Clinical, Endocrine and Therapeutic Aspects

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Thyroid-associated ophthalmopathy or Graves' ophthalmopathy (GO), or thyroid eye disease (TED) refers to the eye changes observed in Graves' disease (GD). The orbital involvement is characterized by lymphocytic infiltration and edema of the retrobulbar tissues, resulting in marked swelling of extraocular muscles and orbital fat. Due to the increased volume or orbital contents the retrobulbar pressure rises, interfering with venous drainage (causing lid swelling) and pushing the globe forwards (causing proptosis or exophthalmos) [1, 2]. In severe cases, direct pressure on the optic nerve may result in loss of visual functions. The swelling of eye muscles hampers muscle motility, associated with double vision. The clinical manifestations of GO can thus be understood from a mechanistic point of view. However, the immunopathogenesis of GO remains largely unknown despite considerable progress made in this field in the last decade [3]. In this communication we review the pediatric aspects of GO and provide the latest information regarding the therapeutic approach of this disease.

Immunopathogenesis of Thyroid Eye Disease

The orbital fibroblasts are widely viewed as the target cells of the autoimmune attack in GO. During the early stages of the disease, macrophages, highly specialized T cells, mast cells, and occasional plasma cells infiltrate the orbital connective, adipose, and muscle tissues [4, 5]. Activation of T cells directed against a thyroid follicular cell antigen(s) that then recognizes and binds to a similar antigen(s) in orbital tissue is a probable but yet unproven theory [2].

Alternatively, macrophages and dendritic cells may nonspecifically initiate the orbital immune response, which is then propagated by recruitment of sensitized T cells. Several cytokines have been associated with the evolution of the orbital tissue changes in TED [6, 7]. These include interferon- γ [8], tumor necrosis factor- α , interleukin-1 (IL-1), and transforming growth factor- β [9] as well as other growth factors such as insulin-like growth factor-I (IGF-I) [10, 11] and platelet-derived growth factor [12, 13]. These compounds are now known to be produced both by infiltrating immunocompetent cells and by residential fibroblasts, adipocytes, myocytes, and microvascular endothelial cells. These cytokines and growth factors stimulate cell proliferation, glycosaminoglycan (GAG) synthesis, and expression of immunomodulatory molecules in orbital fibroblasts and microvascular endothelial cells [13–15]. An increase in connective tissue and extraocular muscle volume within the bony orbits caused by accumulating hydrophilic compounds (predominantly GAG, the hydrophilic nature of which can attract water by osmosis) leads to the clinical manifestations of TED and causes proptosis, extraocular muscle dysfunction, and peri-orbital edema [1, 2].

The orbital fibroblasts do express functional TSH receptors (TSH-R). This recent finding has led to the currently favored view that the TSH-R is the long sought after shared antigen between the thyroid and the orbit and that the TSH-R is the autoantigen involved in GO. Indeed, cytokine-induced differentiation of a particular subset of orbital fibroblasts into adipocytes is associated with increased TSH-R expression and adipogenesis [16].

Furthermore, TSH-R immunization of experimental animals results in histological changes in orbital tissues resembling GO [17].

A causative role of stimulating TSH-R antibodies (TSI) in the development of GO is very attractive as it allows a unifying hypothesis for the various clinical manifestations of GD: Graves' hyperthyroidism (GH), GO and thyroid dermopathy. Arguments against such a hypothesis cannot, however, be dismissed. TSI, in contrast to T cells, cross the placenta and may cause fetal and neonatal hyperthyroidism. GO, however, has never been observed in neonatal thyrotoxicosis TSI are almost always present in GH, but clinically apparent GO develops only in a subset of the patients. Lastly, serum TSI are only slightly related to the severity of GO, although more so to the activity of the eye disease [18]. Whereas TSI might contribute to further progression of GO, it remains doubtful if TSI act as the primary mediator in the immunopathogenesis of GO.

Consequently, the search for other antigens and antibodies involved in GO continues. Graves' IgG added to a culture of human skin fibroblasts increased the synthesis of collagen. The effect was not mimicked by TSH and rather specific for GO as IgG of Graves' hyperthyroid patients without GO were not

active in this respect [19]. Another study demonstrated that Graves' IgG was able to induce the release of T-cell chemoattractants from cultured orbital fibroblasts, notably IL-16 (a CD+ ligand that activates T cells) and RANTES (a C-C type chemokine) [20]. The authors postulated IgG binding to a surface receptor of the fibroblasts distinct from the TSH-R, because TSH had no effect and there was no relation with TSH-R antibodies. The induction of IL-16 and RANTES could be blocked by rapamycin and the authors speculated the surface receptor could be the IGF-I receptor as IGF-I post-receptor signaling is also blocked by rapamycin.

Several antibody markers of immune-mediated damage to eye muscle have also been identified and the great majority of patients with active ophthalmopathy have antibodies against one or more eye muscle antigens. However, none of the target antigens are localized exclusively in the eye muscle and all are intracellular, indicating that their exposure to the immune system would be a consequence of eye muscle fiber damage rather than its cause [21].

Activity and Severity of TED

The majority of Graves' patients have a mild and nonprogressive ocular involvement that does not require any specific or aggressive treatment, also because non-severe GO often tends to improve spontaneously. When evaluating a patient with TED, two basic questions have to be addressed. First, does the patient need treatment for TED and, in a positive answer, which kind of treatment is indicated.

The decision of whether ophthalmopathy must be treated should rely on the assessment of two different parameters, the activity and severity of the disease. The activity of the disease is neither synonymous nor coincident with the severity of the disease. In other words, an individual patient may have severe ocular manifestations but the disease may be inactive (fig. 1). To assess the activity of ophthalmopathy, Mourits et al. [22] proposed a clinical activity score (CAS), which in its original formulation included 10 different items (table 1) mainly, but not solely, reflecting inflammatory changes: giving one point to each manifestation, a score is obtained, with a range from 0 (no activity) to 10 (highest activity). A slightly modified CAS which does not include some of the items originally proposed by Mourits et al. [22] was proposed by an ad hoc committee of the four thyroid societies as a tool to record ocular changes over time after treatment of ophthalmopathy [23] (table 1). Definition of severity of GO is somehow arbitrary (table 2). Undoubtedly, optic neuropathy which can be subclinical and heralded only by changes in the visual evoked potentials, depicts per se a situation that can be sight threatening, especially if it is associated

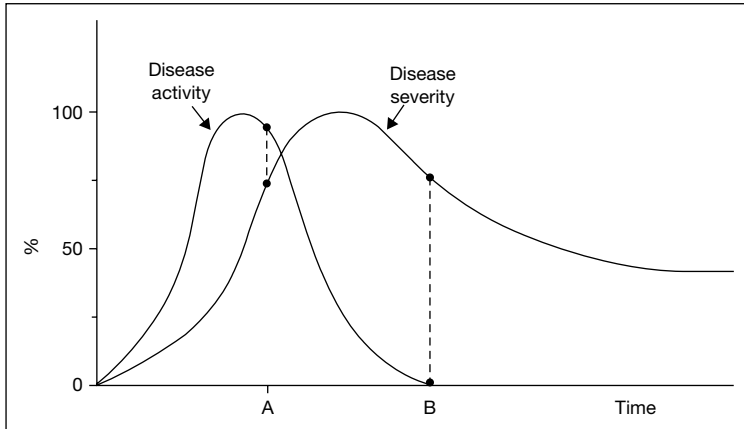


Fig. 1. Hypothetical relationship between disease activity and severity in the natural history of TED [60].

Table 1. Clinical activity score

Original formulation [22]	Revised formulation [23]
Painful, oppressive feeling on or behind the globe	spontaneous retrobulbar pain
Pain on attempted up, side, or down gaze	pain on eye movements
Redness of the eyelids	eyelid erythema
Diffuse redness of the conjunctiva	conjunctival injection
Chemosis	chemosis
Swollen caruncle	swelling of the caruncle
Edema of the eyelids	eyelid edema or fullness
Increase of 2 mm or more in proptosis in the last 1–3 months	
Decrease in visual acuity in the last 1–3 months	
Decrease in eye movements of 5 degrees or more in the last 1–3 months	

with an evident reduction of visual acuity. It has to be remembered that immunosuppression treatment is effective only in patients with active disease.

Juvenile Graves' Ophthalmopathy. Incidence and Symptomatology

The most accurate data on the incidence of GO is derived from a population-based cohort study in Olmsted County, Minn., USA [24]. The overall age-adjusted incidence rate was 16.0 cases for women and 2.9 cases for men per 100,000 population per year. Peak incidence rates were observed in the age groups

Table 2. Assessment of severity of Graves' ophthalmopathy

Degree of involvement	Parameter		
	proptosis ^a	diplopia ^b	optic neuropathy
Mild	19–20	intermittent	subclinical ^c
Moderate	21–23	inconstant	visual acuity 8/10–5/10
Marked	>23	constant	visual acuity <5/10
Severe ophthalmopathy: at least one marked, or two moderate, or one moderate and two mild manifestations ^d			

^aProptosis by exophthalmometer readings or CT/MRI measurements. Median normal value in our Italian population is 15 mm. Normal values show racial variation; accordingly, abnormal values should be considered those 4 mm or more above the respective median value.

^bDiplopia: intermittent, present only when fatigued; inconstant, present in secondary positions of gaze; constant, present in primary and reading positions.

^cAbnormal visual-evoked potentials or other tests, with normal or slightly reduced (9/10) visual acuity.

^dPatients with severe GO will need either medical or surgical treatment depending on the activity of eye disease.

Reproduced from Bartalena et al. [61].

40–49 and 60–69 years. The incidence rates start to increase as of the age of 20 years. Below the age of 20 years the occurrence of GO is a rare event. Incidence rates (cases per 100,000 population per year) are in the age groups 5–9, 10–14, and 15–19 years for females 3.5, 1.8 and 3.3, respectively, and for males 0, 1.7 and 0, respectively. Only 6 of the 120 incident cases of GO observed in this cohort study were below the age of 20 years. A more detailed study published recently from the same department found that of 1,662 cases ages <18 years, with thyroid-related abnormalities, evaluated at the Mayo Clinic in Rochester, Minn., USA, during the 15-year interval (1985 to 1999), 35 children with GO were identified. Of these, 6 had received radioactive iodine (RAI), 1 patient had RAI plus antithyroid drugs, 9 had partial or total thyroidectomy, and the rest antithyroid medications for their thyroid problem. Four patients did not require treatment. Of the 35 children with GO, 31 required no therapy with only supportive measures, 1 had eyelid surgery, and 3 had orbital decompression. None of the patients received steroids or external radiotherapy. They concluded that although the pediatric population has similar clinical manifestations of GO to adults, the disorder is less severe in children [25]. The low incidence of childhood GO might be related to the low incidence of Graves' disease during childhood. To analyze this further, we compared the prevalence

Table 3. Relative frequencies (%) of eye changes in patients with Graves' ophthalmopathy with onset in childhood or adulthood

	Childhood onset [26–29] (n = 42)	Adulthood onset [34] (n = 152)
Soft tissue involvement	48	75
Proptosis	36	63
Extraocular muscle involvement	2	49
Corneal involvement	26	16
Optic nerve involvement	0	21

of clinically apparent GO in young or adult consecutive patients with GH. Lid retraction by itself did not qualify for the diagnosis of GO, as this sign can be attributed to the hyperthyroid state, disappearing spontaneously once the euthyroid state has been reached. GO was present in 42 of 182 (23%) patients with childhood GH [26–29] and in 118 of 1,050 (18%) adult patients with GH [30–33]. It follows that children have about the same risk (or slightly increased) as adults to develop GO once they have contracted Graves' hyperthyroidism.

The severity of childhood GO appears to be less than that of adulthood GO. This is evident from a comparison of the relative frequency of the various eye changes between children and adults with GO. Taking together the 42 childhood GO cases from the four studies published so far [26–29] and contrasting then with 152 new consecutively referred adult GO patients [34], it is clear that soft tissue involvement and proptosis are the predominant changes in childhood GO whereas the more severe manifestations of restricted eye muscle motility and optic nerve dysfunction almost never occur in children (table 3). Remarkable is the high frequency of corneal involvement in children. This was, however, limited to punctate epithelial erosions and all cases originated from one study on Chinese children [29], whereas corneal involvement was absent in the three other studies on childhood GO [26–28].

Very recently, we embarked on a questionnaire study among members of the European Society for Paediatric Endocrinology (ESPE) and the European Thyroid Association (ETA) with the following specific aims. First, we wanted to know the proportion of GO cases among patients with Graves' hyperthyroidism in the age group of 18 years and younger. Second, we were curious whether childhood GO could be related to smoking prevalence. Third, we wanted to record the diagnostic and therapeutic approaches to a standard case (and some variants) of a 13-year-old girl with Graves' hyperthyroidism and