Review

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An update on thyroid-associated ophthalmopathy in children and adolescents

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Abstract

Background: Risk of developing thyroid-associated ophthalmopathy (TAO) in children and adolescents is similar or may be even slightly higher than in adults. The aim of this article is to review and summarize current knowledge regarding diagnostic and therapeutic measures in pediatric TAO.

Content: MEDLINE and EMBASE papers were searched using the terms 'pediatric Graves' ophthalmopathy' 'pediatric Graves' orbitopathy', 'thyroid-associated ophthalmopathy in childhood and adolescence' from the year 1970 to December 2015.

Summary: TAO usually accompanies hyperthyreosis in Graves' disease, but may also occur in patients with hypothyreosis due to chronic lymphocytic thyroiditis (Hashimoto's disease) or in euthyroid patients. Current information regarding epidemiology, pathogenesis, symptoms and treatment of TAO in children and adolescents is presented. The course of the disease is usually mild, eye disturbances often regress after restoring euthyroidism and a 'wait and see' policy is appropriate in the majority of patients. In rare cases, sight-threatening complications [dysthyroid optic neuropathy (DON) or corneal breakdown] may develop and immediate surgical intervention might become necessary.

Outlook: Close cooperation between pediatric endocrinologists and opthalmologists is extremely important to ensure best care and quality of life in patients with thyroid gland dysfunction. Further investigations on pathogenesis and course of TAO in children and adolescents should be performed for better management of this disease in this group of patients.

Keywords: adolescents; children; Graves' ophthalmopathy; thyroid-associated ophthalmopathy (TAO).

Introduction

Thyroid-associated ophthalmopathy (TAO or thyroid eye disease, Graves' orbitopathy, Graves' ophthalmopathy) is an inflammatory disease of the eye and orbital tissues. Involvement of the orbit is characterized by infiltration of the lymphocytic cells, swelling of the peribulbar tissues and extraocular muscles and orbital fat expansion. Increased volume of the orbital tissues leads to venous outflow impairment and protrusion of the eye (proptosis). In advanced cases, congestion of the optic nerve may lead to its severe dysfunction. Edema of the extraocular muscles may cause eye motility limitations with consequent diplopia. Although many mechanisms leading to thyroid eye disease development are already known, the understanding of the immunopathogenesis of this disease remains a big challenge [1]. TAO in most cases accompanies hyperthyreosis in Graves' disease, but it may occur in patients with hypothyreosis due to chronic lymphocytic thyroiditis (Hashimoto's disease) or in euthyroid patients [2]. Graves' disease is the main cause of thyreotoxicosis in children and adolescents – the incidence rate is 0.79/100,000 children in Denmark [3], up to 6.5/100,000 in Hong Kong [4] with a predominance in girls. Apart from many clinical symptoms of Graves' disease such as goitre, tachycardia and acceleration of metabolism, TAO may develop in children as well. According to previous studies, the thyroid eye disease is usually mild with proptosis and soft tissue involvement as predominant manifestations [5–8]. Nevertheless the quality of life of children and adolescents with TAO may be impaired. As pathogenesis and course of TAO are not fully understood further studies are warranted to optimize the treatment of the disease.

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Epidemiology of thyroid-associated ophthalmopathy in children and adolescents

TAO in the course of thyroid gland disease is less common in children and adolescents than in adults, this may be the reason why there is less research on pediatric ophthalmopathy. Since the beginning of the 20th century scientists have started investigations concerning ocular symptoms in children with thyroid gland diseases. In 1937, Bram analyzed a population of children under the age of 12 years and stated that Graves' disease with goitre and proptosis occurred in 2.5% of patients [9]. Until to date, few large-scale analyses concerning TAO in children and adolescents have been performed. They were carried out mainly among children with Graves' disease, but in chronic lymphocytic thyroiditis symptoms of thyroid ophthalmopathy have also been observed [10]. The incidence rate of TAO in children is 1.7–3.5 cases per 100,000 population per year, and 0.79–6.5 cases per 100,000 children [6]. TAO is more common in girls than in boys and more often occurs in adolescents (11–18 years old, 68.2%) than in children under 11 years old (31.8%) [6]. Smoking is a well-known risk factor for development and exacerbation of TAO, passive smoking also seems to have an influence on developing ophthalmopathy in children. Higher incidence of ophthalmopathy in children over 11 years old may be caused by increasing active smoking prevalence in adolescents. Krassas et al. have also observed a higher incidence of ophthalmopathy in children under 11 years old in countries where tobacco consumption is higher [6].

Pathogenesis of thyroid-associated ophthalmopathy

There are few studies concerning TAO pathogenesis in children and adolescents [11–14], but we may suspect that mechanisms leading to development of this disease are similar to those in the adult population. In adults, investigations revealed that pathologic changes in extraocular muscles and orbital fat cause ophthalmopathy. Glycosaminoglycan accumulation in endomysium, predominantly hyaluronan and chondroitic sulfate, leads to extraocular muscles enlargement. High hyaluronan hydrophilicity leads to excessive water binding in orbital tissue and muscles and their secondary edema [15]. Involvement of the orbit in thyroid eye disease is also characterized by infiltration of inflammatory cells. In early stages of the disease, connective tissue, orbital fat and muscles are infiltrated by T lymphocytes, mast cells and plasmatic cells. It was found that orbital fibroblasts are the main target of the autoagression process [16]. Activation of fibroblasts leads to their proliferation and differentiation into myofibroblasts and adipocytes and secondary production of glycosaminoglycans, chemokines and cytokines, which enhance inflammatory reaction in the orbital tissues [17, 18]. Activated orbital fibroblasts in patients with TAO show increased response to proinflammatory cytokines in comparison with healthy adults. This leads to excessive production of the cytokines: IL-1α, IL-1β, IL-6, IL-8, macrophage chemoattractant protein (MCP-1) and transforming growth factor-β (TGF-β) [19, 20]. IL-6 increases immunoglobulin production, β-cells differentiation and enhances thyrotropin receptor (TSHR) expression on the fibroblast surface [21]. Previous studies revealed that thyrotropin receptor is the main autoantigen in TAO in patients with Graves' disease [22]. High level of autoantibodies stimulating TSH receptor (TSAb) correlates with thyroid ophthalmopathy activity and severity in adults and in children [23]. Nevertheless, antibodies against TSH receptor may be absent in patients with TAO in course of other thyroid gland diseases, e.g. in chronic lymphocytic thyroiditis. In these patients factors leading to pathologic changes may include antibodies against ocular muscle antigens: calsequestrin, collagen XIII, flavoprotein (Fp) and protein G2s [24]. Oxidative stress may also have a negative influence on the course of TAO. Studies revealed higher levels of oxidative stress indicators (8-hydroxy 2′deoxyguanosine, malondialdehyde, hydrogen peroxide) in fibroblasts of patients with Graves' ophthalmopathy as compared with healthy controls [25]. Pathological changes in the orbit may be provoked by tobacco smoke due to increase of oxidative stress, adipogenesis and hyaluronan production [26].

Symptoms and signs of thyroid-associated ophthalmopathy

Results of previous studies show that symptoms of TAO in children and adolescents are similar to those of adult population, a third to two thirds of pediatric patients have ocular disturbances, but they are usually mild. Results of studies regarding TAO in pediatric population are summarized in Table 1.

Most common signs in children include: pain, foreign body sensation, hypersensitivity to light, excessive tearing and less often diplopia. Graefe sign (lid lag), eyelid

Table 1: Studies on thyroid-associated ophthalmopathy (TAO) in children and adolescents.

Study	Age, years	Thyroid function	Number of examined patients (number of patients with ophthalmopathy)	Symptoms (number of patients with symptoms)
Uretsky et al. [8]	< 21	Graves' disease	34 (23)	– Eyelid retraction, lid lag (13) – Soft tissue inovolvement (6) – Proptosis (1) – Extraocular muscles involvement (2) – Corneal involvement (1)
Young [27]	5–20	Hyperthyroidism; thyroiditis; thyromegaly	33 (16)	– Eyelid retraction, lid lag (12) – Soft tissue involvement (3) – Proptosis (1)
Grüters [28]		Thyrotoxicosis	43 (16)	– Upper eyelid retraction – Lid lag – Proptosis
Durairaj et al. [29]	< 18	Hyperthyroidism (31); primary hypothyroidism (1); euthyroidism (3)	35	– Eyelid retraction (29) – Lid lag (26) – Conjunctival injection (17) – Chemosis (8) – Corneal staining (12) – Lagophthalmos (13) – Proptosis (26) – Superior limbic keratitis (6) – Extraocular muscle motility defect (4)
Lee et al. [11]	2–18	Graves' disease	80 (31)	– Eyelid retraction – Chemosis – Proptosis
Chan et al. [5]	< 16	Graves' disease	83 (52)	– Upper eyelid retraction (4) – Lower eyelid retraction (32) – Lid edema (5) – Lid lag (5) – Lagophthalmos (8) – Diffuse conjunctival injection (4) – Proptosis (10) – Extraocular muscle motility defect (1)
Holt et al. [30]	< 21	Graves' disease	163 (85)	– Lid lag/retraction (23) – Chemosis (1) – Exposure keratopathy (2) – Proptosis (20) – Restrictive strabismus (5)
Eha et al. [31]	3–16	Graves' disease	11	– Eyelid retraction (10) – Proptosis (10) – Extraocular muscle motility defect (4)
Goldstein et al. [32]	0–17	Graves' disease	152 (26)	– Eyelid retraction (6) – Corneal punctuate staining (3) – Proptosis (10)
Acuna et al. [12]	3–17	Graves' disease	49 (26)	– Proptosis (22) – Eyelid retraction – Lid lag – Conjunctival injection – Lagophthalmos – Keratitis – Extraocular muscle motility defect

retraction (very often upper eyelid), proptosis and soft tissue involvement are dominant symptoms in pediatric patients [1, 5, 6, 32]. However, in rare cases myopathy and dysthyroid optic neuropathy (DON) in children and adolescents in course of Graves' disease may also occur [33]. With puberty, higher incidence of serious complications such as restrictive strabismus and exposure keratopathy were noted [30].

It was observed that after restoring euthyroidism in pediatric patients with TAO, position and motility disturbances mostly improve, in contrast to proptosis which persists or just decreases [8, 31, 34]. In children and adolescents, persisting proptosis may be explained by changes in exophthalmometry, because measurements tend to increase with age. Nucci et al. revealed a change in mean values of exophthalmometry from 9.1 to 11.6 mm in children aged between 3 and 10 years [35].

There are limited studies on influence of TAO on changes in eye refraction, but some studies showed increased risk of developing myopia in this group of patients. Jankauskiene et al. revealed that in children with thyroid eye disease and protrusion ≥ 17 mm myopia was noted more often than in control group [36]. Other studies found worsening of previously diagnosed myopia [37] and higher incidence of astigmatism in patients with TAO [38]. Refraction changes in course of thyroid gland diseases may be associated with proliferation of orbital matrix and enlargement of extraocular muscles, which cause remodeling of the eye bulb and elongation of optical axis. Some authors suspect influence of thyroid hormones on ciliary muscle tonicity, and therefore changes in refraction.

Diagnosis of thyroid-associated ophthalmopathy in children and adolescents

There are no specific biochemical determinants of the thyroid eye disease, but scientists try to find prognostic factors for development and activity of this disease. TSH receptors which are present in thyroid and orbital tissues, and are expressed by lymphocytes, fibroblasts and adipocytes play a crucial role in pathogenesis of TAO. TSH-receptor antibodies (which are common in Graves' disease) can be responsible for pathological changes in the orbit. Therefore for assessing activity of TSH-receptor antibodies measurements of thyroid-stimulating immunoglobulin (TSI) and thyroid-binding inhibitory immunoglobulins (TBIIs) are performed [39]. In adults, Graves' disease TSI level can be a useful marker of ophthalmopathy activity and can facilitate the decision regarding treatment [40]. Preliminary studies in children and adolescents found a positive correlation between TSI levels and thyroid ophthalmopathy development. It may become prognostic factor of orbital tissues inflammation in Graves' disease [12]. Other biochemical markers were also investigated – Lee et al. showed the relationship between high levels of free triiodothyronine (FT3), thyroid peroxydase (TPO) and TAO [11]. Diagnostics of TAO based on laboratory findings need further studies. Currently the diagnosis is based on the presence of ocular signs and symptoms, presence of thyroid autoimmunity and exclusion of an alternative diagnosis [41]. For examination of children and adolescents, the methods and classifications compiled for adults are used. Evaluation of disease activity and severity is crucial in assessment of patients with ophthalmopathy:

– Activity refers to the presence of inflammation of eye and orbit tissues. Patients may report: grittiness, watering, photophobia or orbital pain. To assess activity of ophthalmopathy. Mourits et al. proposed Clinical activity score (CAS) [42] scale, which is widely used and recommended by European Group on Graves' Orbitopathy (EUGOGO) as a standard for activity evaluation.

  For initial CAS, items 1–7 are scored:

  1. Spontaneous orbital pain.
  2. Gaze-evoked orbital pain.
  3. Eyelid swelling that is considered to be due to active (inflammatory phase) Graves' orbitopathy.
  4. Eyelid erythema.
  5. Conjunctival redness that is considered to be due to active (inflammatory phase) Graves' orbitopathy.
  6. Chemosis.
  7. Inflammation of caruncle or plica.

  Patients assessed after follow-up can be scored out of 10 by including items 8–10.

  8. Increase of ≥ 2 mm in proptosis.
  9. Decrease in uniocular ocular excursion in any direction > 8°.
  10. Decrease of acuity equivalent to 1 Snellen line.

  A score of more than four points suggests an active phase of ophthalmopathy.

  In activity assessment magnetic resonance imaging (MRI) may be helpful in revealing inflammatory changes in extraocular muscles [43]. Assessment of ophthalmopathy activity by ultrasound evaluation of extraocular muscles' thickness and reflectivity should be made with caution [44].

– Severity specifies degree of functional and cosmetic changes in active or inactive phase of TAO [45]. For severity assessment NOSPECS classification is used [46] – depending on occurrence and intensity of signs/symptoms, six severity classes are distinguished. Detailed description of each symptom is recommended by European Group on Graves' Orbitopathy (EUGOGO).

EUGOGO elaborated classification of patients with TAO depending on symptoms' intensification [47]:

– Sight-threatening Graves' ophthalmopathy – patients with DON and/or corneal breakdown
– Moderate-to-severe Graves' ophthalmopathy: ≥ 1 symptom
  a. Eyelid retraction ≥ 2 mm
  b. Moderate soft tissue involvement
  c. Proptosis ≥ 3 mm (over normal value for race and gender)
  d. Diplopia (constant/inconstant)
– Mild Graves' ophthalmopathy: ≥ 1 symptom
  a. Eyelid retraction < 2 mm
  b. Mild soft tissue involvement
  c. Proptosis < 3 mm (over normal value for race and gender)
  d. Inconstant/no diplopia
  e. Corneal exposure responsive to lubricants

In assessing TAO activity and severity the Vision Inflammation Strabismus Appearance (VISA) classification, elaborated in 2006, may also be used [48].

Management of thyroid-associated ophthalmopathy in children and adolescents

Treatment of thyroid disease is crucial in the management of TAO in children and adolescents. Therefore, close cooperation between ophthalmologists and endocrinologists is extremely important. In treatment of hyperthyreosis, in course of Graves' disease, antithyroid drugs are frequently administered and their use often causes improvement in ocular condition [49]. Radioiodine is another treatment option for hyperthyreosis, but it is contraindicated in children aged < 5 years because of the potentially higher risk of developing thyroid cancer [50]. In some cases radioiodine therapy causes exacerbation of TAO. This complication is mainly observed in adults and concomitant oral steroid treatment may be effective in reducing this side effect [51].

Thyroidectomy (mostly subtotal) is the oldest treatment modality of Graves' hyperthyroidism and in most cases it is effective in ocular condition improvement [52]. In rare situations temporary exacerbation of ophthalmopathy may occur. This may be explained by the release of antibodies, which adhere to the orbital tissue receptors and cause progression of proptosis [53].

In children and adolescents, TAO symptoms are mostly mild and often regress after restoring euthyroidism. "Wait and see" policy in most of the cases is adequate. Improvement of quality of life in these patients is very important, therefore recommendation of local protective agents: lubricant eye drops, gels and selen supplementation is necessary.

Sometimes, after thyroid function normalization there is no improvement in ocular condition or even deterioration, in these cases pharmacological treatment may be needed [6]:

– Steroids – oral administration: prednisone 5–20 mg daily; in moderate-to-severe ophthalmopathy Krassas and Gogakos recommend starting a dose of 20 mg daily for 4–6 weeks and then tapering the dose accordingly [1]. Intravenous steroids may be taken into consideration. In adults this route of administration has been proved to have fewer side effects [54]. It has to be kept in mind that prolonged steroids' administration may cause many side effects: weight gain, immunosuppression and growth failure in children.
– Somatostatin analogs (SM-as)-octreotide (Sandostatin). Preliminary research showed improvements in ocular conditions in adults and children with thyroid ophthalmopathy [55]. This treatment is still very expensive and there is too little evidence on the efficacy and safety of SM-as administration in children and adolescents to recommend its routine use.
– Immunomodulatory therapies – rituximab (anti-CD 20 monoclonal antibody), tocilizumab (monoclonal antibody to IL-6 receptor), anti-TNF monoclonal antibodies (infliximab, adalimumab, etanercept). Efficacy and safety of administration of these drugs in pediatric patients is still unclear. In adults, effects of therapy seem promising [56–58], but further trials are needed.

Retrobulbar irradiation, widely used in adults, is not recommended in children and adolescents with TAO in view of the tumor-induction risk [59]. In rare conditions surgery may be recommended in children and adolescents with ophthalmopathy. Urgent tarsorrhaphy or

orbital decompression is necessary in sight-threatening exposure keratopathy or DON [29, 33]. Except urgent conditions, orbital decompression in order to correct proptosis, eyelid position correction surgery, or restrictive strabismus surgery should be performed not earlier than 6–8 months after conversion of ophthalmopathy into inactive phase and in stable endocrinological and ophthalmic clinical picture.

Conclusions

Thyroid eye disease in children and adolescents has been investigated for many years. Studies show that in most cases ocular symptoms are mild with predominant soft tissue involvement, eyelid retraction and proptosis. Restoring euthyroidism usually causes improvement in ocular condition. Until a few years ago, sight-threatening complications were almost never observed in the pediatric population with TAO, but latest data reveal that DON or exposure keratopathy may occur in children, and in this case an urgent surgical intervention is crucial. All children and adolescents with thyroid dysfunction should be under regular ophthalmologists' supervision for early identification of conditions that may lead to severe ocular and vision complications. Proptosis, eyelid retraction and soft tissue involvement may worsen quality of life in pediatric patients and negatively influence their self-confidence due to the change in their appearance. TAO accompanies not only hyperthyroidism (Graves' disease), but may develop in course of hypothyroidism (chronic lymphocytic thyroiditis, Hashimoto's disease) and in euthyroid state. Therefore, we suggest using terms generally describing this condition as thyroid eye disease, TAO, most often, instead of Graves' ophthalmopathy. Further, prospective studies regarding pediatric TAO on larger groups of patients should be performed in order to ensure the best care of children and adolescents.

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