

Clinical Ocular Features in Children and Young Adults with Thyroid Diseases

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Abstract

The study of clinical ocular manifestations recruited 105 patients who presented to the Endocrine and Eye clinics of Lithuanian University of Medical Sciences with a history of thyroid diseases. The study comprised two groups of patients: the group I included 36 patients (under 18 years) and the group II-69 (from 18 to 34 years). As the control group, 25 children and 30 young adults of similar age without thyroid, eye and systemic diseases were selected.

A comprehensive ophthalmic assessment including patient's complaints, best-corrected Snellen visual acuity, ocular motility, proptosis measurements, intraocular pressure (IOP), eyelid signs (lid aperture, lid retraction), slit lamp and fundus investigation was performed.

Our investigation confirms that in children with thyroid diseases ocular symptoms and signs such as upper eyelid retraction, stare and mild proptosis were predominant. Young adults with thyroid diseases complained of foreign body sensation, photosensitivity and pain. There was manifestation of eyelid retraction, eyelid oedema and redness, conjunctival redness and chemosis, eyelid retraction, proptosis and widened palpebral fissure. A small number of young adults with thyroid diseases suffered from severe ocular complications as keratopathy, diplopia.

This examination may be useful in early diagnosis of ocular changes in children and young adults with thyroid diseases.

Keywords: Graves' disease; Thyroid disease; Graves' ophthalmopathy

Introduction

Patients with thyroid disease (thyrotoxicosis, hypothyroidism and thyroiditis) can manifest different eye symptoms and signs: proptosis of eyeball, lid retraction, corneal, extraocular muscles and optic nerve damage. The clinical features of Graves' ophthalmopathy may be one of the most common manifestations of Graves' disease (GD).

Graves' ophthalmopathy (GO) is an autoimmune inflammatory orbital disease linked to autoimmune hyperthyroidism and rarely be seen in patients with Hashimoto's thyroiditis, or in euthyroid patients. GO affects females six times more frequently than males (86% females and 14% males), in severe forms of Graves' ophthalmopathy the female: male ratio may be reduced to 4:1 [1].

Recent epidemiological data about the incidence of Graves' disease during children and adolescence are limited, thus the information about its clinical picture is less well established in children in comparison with adults.

The onset of the Graves' ophthalmopathy and hyperthyroidism develop simultaneously in most cases but ocular changes may precede or follow hyperthyroidism.

The incidence of Graves' disease in adults has been reported to be between 15 and 20 per 100 000 a year but in children it is much less common; it has been reported 0.79 and 6.5 per 100 000 children, the female-to-male ratio being about 3:1 up to 5:1 [2]. The low incidence of childhood GO might be related to the low incidence of Graves' disease during childhood. Most of the serious conditions described in the adult series were only occasionally reported in pediatric age group [3].

Wong and Cheng study confirms the high incidence of childhood Graves' disease in Hong Kong population and documents an increasing trend for girls [4].

There was noted that Graves' ophthalmopathy is more benign in children [5].

In juvenile Graves' disease ocular changes were reported in two-third of patients 11-18 years old and one third of cases less than 10 years old [6].

Although the pediatric population has similar clinical manifestations of GO as in adults, the disorder is less severe in children [2,7,8].

In Denmark, about 95% of children with thyrotoxicosis have GD. In Iceland, the incidence of GD as the cause of thyrotoxicosis is 83%. Graves' ophthalmopathy in juvenile GD is more common but less severe and more likely to remit completely [9].

The female preponderance is similar between children (87%) and adults (83%) with Graves' hyperthyroidism. Teenage girls were most affected by Graves' ophthalmopathy [10].

None of children with GD developed vision-threatening complications and required surgical intervention [11].

Children have about the same (or slightly increased) risk of developing Graves' ophthalmopathy in hyperthyroidism as adults [12]. GO occurs in the same proportion between sexes as GD but with a milder clinical presentation compared with adults.

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Eyelid retraction and proptosis in Eha et al. study were the predominant signs in 10 of 11 investigated patients under the age of 18 years [13].

The complete constellation of typical features (hyperthyroidism, eyelid retraction, exophthalmos, restrictive extraocular myopathy, and optic nerve dysfunction) in children occur relatively infrequently [14].

The diagnosis of GD is based on clinical signs of hyperthyroidism, laboratory thyroid function testing, and the presence of thyroid-stimulation autoantibodies [2,7,15,16].

The major symptoms include one or more of the following: sense of irritation in the eyes; excessive tearing that is often made worse by exposure to cold air, wind, or bright lights, eye or retroorbital discomfort or pain, blurred vision, binocular diplopia and occasionally loss of vision. These signs are less frequent or absent in children [2,9].

Proptosis may be the main sign in Graves' ophthalmopathy [17]. Krassas et al. showed that values of proptosis depended on the subject age and gender [14].

Severe Graves' ophthalmopathy may be associated with excessive proptosis of eye-ball, globe subluxation, and corneal ulceration from exposure keratopathy, orbital congestion, optic disc swelling, choroidal folds, and optic neuropathy.

Most studies of children and young adults with Graves' disease were retrospective.

The primary objectives of our study were to study the clinical ocular features in children and young adults with thyroid diseases.

Material and Methods

The study of clinical ocular manifestations recruited 105 patients who presented to the Endocrine and Eye clinics of Lithuanian University of Medical Sciences with a history of thyroid diseases. The group under 18 years included 36 patients, and the group from 18 to 34 years. There were evaluated data on the pediatric group separately from those of the adult cases group, followed by a comparison of the groups. As the control group, 25 children and 30 young adults of similar age without thyroid, eye and systemic diseases were selected.

The diagnosis of thyroid disease is based on clinical signs of thyroid disease and findings of laboratory thyroid function testing. We recorded patient's data: age, sex, family history (thyroid disorders), smoking (active, passive). There was done a comprehensive ophthalmic assessment including best-corrected Snellen visual acuity, ocular motility, intraocular pressure (IOP), eyelid signs (lid aperture, upper lid retraction, lid lag) and ocular complaints (periocular pain, photosensitivity, foreign body sensation and lacrimation). Retraction of the upper eyelid was defined as any exposed superior sclera beyond the limbus in the primary gaze. Lid lag was defined as the static situation in which the eyelid is higher than normal with the globe in downgaze; lagophthalmos was defined as the inability to close the eyelids completely.

Slit lamp (conjunctival injection, chemosis, corneal staining) and fundus (evidence of optic neuropathy) investigation were performed. Proptosis was measured by digital image processing system consisting of Hertel's exophthalmometer, video camera and personal computer [18,19].

Statistical analysis was performed using statistical SPSS software package (Version 20.0). The following statistical characteristics were

expressed as mean value and standard deviation (SD). Independent sample *t*-test was used for comparing the means between the two groups, and χ^2 -test was used to compare the non-parametric variables in the two groups. The level of statistical significance was set at $p < 0.05$.

Results

The mean age of children with thyroid dysfunction (group I) was 13.3 (SD 3.8) years, range from 3 to 18 years, 30 girls and 6 boys (Table 1). The mean age of young adults (group II) was 24.6 (SD 2.7) years, range from 18 to 34 years, females were 60, males-9. The age of the control group of children was 13.1 (SD 2.9) years, young adults-25.2 (SD 3.1) years.

The majority of patients were with thyrotoxicosis (hyperthyroidism) at the time of ophthalmological examination - 92 (87.6%), 3 (2.9%) of patients were hypothyroid and 10 (9.5%)-euthyroid. 33 (91.7%) children were hyperthyroid and 3 (8.3%)-euthyroid. 59 (85.5%) young adults were hyperthyroid, 3 (4.4%) -hypothyroid and 7 (10.1%)-euthyroid. None of the patients had associated systemic diseases.

Median duration of thyroid disease in young adult was 3.6 times longer than that of in the children group.

Four children (11.1%) reported that family members had thyroid diseases, 13 (18.8%) of young adults had a family history of thyroid dysfunction, 10 (14.5%) of them reported associated thyroid eye problem.

Three patients under 18 years old (8.3%) were active smokers, 4 patients (11.1%) had household members who smoked currently. Being active smokers was reported by 17 adult patients (24.6%), five patients (7.2%) were an ex-smokers, and 11 (15.9%) were passive smokers.

The frequency of ophthalmic complaints is listed in Table 2. Among 36 children patients, 2.0 to 11.1% of patients reported ocular complaints. The most common complaints of our young adult patients were foreign body sensation (30.4%), photosensitivity (34.8%), and ocular and periocular pain (37.7%), tearing (42.0%). Decreased visual acuity caused by keratopathy was in 10.1% of patients and refractive errors were found in less than 1.0% of cases. Five of the young adult patients (7.2%) complained of binocular double vision.

Patients	Children (36)	Young adults (69)
Mean age (years) Mean \pm SD	13.3 \pm 3.8	24.6 \pm 2.7
Median duration of the disease (years) Mean \pm SD	1.3 \pm 0.4	4.7 \pm 1.2
Female: male ratio	5:1	7:1
Family history (positive)	4(11.1%)	13(18.8%)
Smoking:		
Active	3(8.3%)	17(24.6%)
Ex-smoking	0	5(7.2%)
Passive	4(11.1%)	11(15.9%)

Table 1: Distribution of patients with thyroid dysfunction according to age, disease duration, sex and risk factors.

Symptom	Children n(%)	Young adults n(%)
Foreign body sensation	2(5.6)	21(30.4)
Photosensitivity	3(8.3)	24(34.8)
Pain	3(8.3)	26(37.7)
Tearing	4(11.1)	29(42.0)
Diplopia	0	5(7.2)
Decreased visual acuity	1(2.8)	7(10.1)

Table 2: The frequency of ophthalmic complaints in children and young adults with thyroid dysfunction.

The frequency of clinical features is presented in Table 3. The majority of ocular signs among children patients with thyroid dysfunction was eyelid retraction (36.1%) and stare (47.2 %). A higher proptosis was detected in 25.0% of children with thyroid diseases than in the control group. The mean of proptosis measurements in the children group was 16.3 ± 2.2 mm ($p < 0.01$) comparing with the control group and ranged from 14.5 to 20.5 mm. Mean of proptosis in the control group under the age of 18 years was 14.2 ± 1.8 mm.

Most of the young adult patients had eyelid position signs and edema. Eyelid retraction was observed in 49.3% of patients, lid lag in 42.0 % and eyelid edema in 56.5%. More patients with proptosis (60.9%) and stare (66.7%) than in the control group were found. Mean proptosis in young patients was 18.04 ± 1.7 mm ($p < 0.005$), measurements ranged from 15.5 mm to 23.5 mm. Mean proptosis in the control group of young adults was 15.3 ± 1.2 mm.

Clinical sign	Children n(%)	Young adults n(%)
Eyelid retraction	13(36.1)	34(49.3)
Stare	17(47.2)	46(66.7)
Lid lag	8(22.2)	29(42.0)
Lagophthalmos	2(5.6)	14(20.3)
Proptosis	9(25.0)	42(60.9)
Conjunctival redness	4(11.1)	31(44.9)
Eyelid redness	7(19.4)	41(59.4)
Chemosis	5(13.9)	28(40.6)
Eyelid edema	6(16.7)	39(56.5)
Corneal fluorescein staining	1(2.8)	7(10.1)
Punctate corneal epithelial erosions	1(2.8)	7(10.1)
Corneal ulceration	0	2(2.9)
Limited extraocular motility	1(2.8)	8(11.6)
Restrictive strabismus	0	3(4.3)

Table 3: The frequency of clinical features in children and young adults with thyroid dysfunction.

Complaints	Hyperthyroidism		Hypothyroidism		Euthyroidism	
	Children	Young adults	Children	Young adults	Children	Young adults
Foreign body sensation n (%)	2(6.1)	15(25.4)		2(6.7)	1(33.3)	4(57.1)
Photosensitivity n (%)	2(6.1)	20(33.9)		1(33.3)	1(33.3)	3(42.9)
Pain n (%)	2(6.1)	23(39.0)		1(33.3)	1(33.3)	2(28.6)
Tearing n (%)	3(9.1)	24(40.7)		2(66.7)	1(33.3)	3(42.9)
Diplopia n (%)	0	5(8.5)		0		0
Decreased visual acuity n (%)	1(3.0)	5(8.5)		1(33.3)		1(14.3)

Table 4: The frequency of ophthalmic complaints in children and young adults according to the thyroid state.

Clinical sign	Hyperthyroidism		Hypothyroidism		Euthyroidism	
	Children	Young adults	Children	Young adults	Children	Young adults
Eyelid retraction n (%)	12(36.4)	29(49.2)		1(33.3)	1(33.3)	4(57.1)
Stare n (%)	15(45.5)	42(71.2)		1(33.3)	2 (66.7)	3(42.9)
Lid lag n (%)	6(18.2)	26(44.1)		1(33.3)	2 (66.7)	2(28.6)
Lagophthalmos n (%)	2(6.1)	12(20.3)				2(28.6)
Proptosis n (%)	8(24.2)	37(62.7)		1(33.3)	1(33.3)	4(57.1)
Conjunctival redness n (%)	4(12.1)	28(47.5)		1(33.3)		2(28.6)
Eyelid redness n (%)	7(21.2)	37(62.7)		1(33.3)		3(42.9)
Chemosis n (%)	5(15.2)	26 (44.1)				2(28.6)
Eyelid edema n (%)	5(15.2)	34(57.6)		1(33.3)	1(33.3)	4(57.1)
Corneal fluorescein staining n (%)	1(3.0)	7(11.9)				
Punctate corneal epithelial erosions n (%)	1(3.0)	7(11.9)				
Corneal ulceration n (%)	0	2(3.4)				
Limited extraocular motility n (%)	1(3.0)	8(13.6)				
Restrictive strabismus n (%)	0	3(5.1)				

Table 5: The frequency of clinical features in children and young adults according to the thyroid state.

Palpebral fissure in children with thyroid diseases was 9.2 ± 2.3 mm ($p > 0.05$) and in young adults it was widened (15.3 ± 1.8 mm, $p = 0.02$), in the control groups of patients the aperture of eyelids were 8.5 ± 1.9 mm and 9.1 ± 2.1 mm respectively.

The frequency of corneal staining and punctate epithelial erosions in children with thyroid diseases was very low, found only in one patient (2.8%). Seven young adult patients (10.1%) who had their corneas stained positive with fluorescein had a clinical picture of epithelial erosions, 2 young patients had corneal ulcerations in lower part of cornea.

Only one patient under 18 years (2.8%) had limited extraocular motility in extreme gaze to lateral side. Eight young adults (11.6%) had limitation of extraocular motility in upward and lateral gaze. There was no instance of optic disc abnormality (swollen or pale) in children and young adults. Our study shows that most patients with hyperthyroidism had complaints (Table 4). The majority of patients with hyperthyroidism had ocular symptoms and signs (Table 5). Only several euthyroid young adults had complaints and ocular signs.

Discussion

Ocular changes are rare in children with thyroid diseases and this is the largest and the first study of assessment of eye disorders in children and young adults with thyroid dysfunction in Lithuania.

Our group of patients presented with features typically noted among children with Graves' ophthalmopathy, that is, eyelid retraction, stare and proptosis.

Investigators reported the presence or absence of milder manifestations of Graves' ophthalmopathy in pediatric patients [7].

Our ocular investigations of juvenile patients with thyroid diseases

may be compared with other similar previously reported studies. Eye manifestations were found to be more common among females. However, in other studies the children with Graves' ophthalmopathy female:male ratio was 7:1 or 9:1 [2,4], whereas our study group of children included slightly less female : male ratio (5:1). Distribution of adult patients by sex in other studies [1,20] was similar to our distribution of young adults.

Among our studied children, family history of thyroid diseases was positive in 14 (11.1%), and in the group of young adults-in 13 (18.8%) subjects. In Holt et al. study 59% of pediatric patients had a positive family history of autoimmune thyroid disease [21].

Three patients (8.3%) under the age of 18 years were active smokers, and 4 (11.1%) - passive. Smoking, as a risk factor, has the role in the development and progression of Graves' ophthalmopathy [1,6]. Our study showed that in the young adult group 17 were active smokers (24.6%) and 11-passive smokers (15.9%).

The frequent complaints of our young adult patients were foreign body sensation, photosensitivity, ocular and periocular pain, tearing.

Few studies showed that eye clinical picture in children is less well defined than in adults [2,6,7,11,14].

Eyelid abnormalities were the most common in children and young patients with thyroid pathology in our study. Eyelid retraction (36.1%) and stare (47.2%), lid lag (22.2 %) were the most frequent clinical signs of our studied children. It was similar to other studies [21,22]. The rate of lid retraction and lid lag in our children with thyroid pathology was lower than the rates from 50 to 100% reported by other authors [2,7,13]. In Acuna et al. study lid lag was in 2% children with Graves' disease [11].

The majority of clinical features in our young adults were as follows: proptosis (60.9%), eyelid redness (59.4%), lid edema (56.5%), lid retraction-in 49.3%. These findings are in agreement with previous Gaddipati and Meyer (2008) reports [23]. They showed that in adult eyelid retraction was present in 38%, lagophthalmos-in 16%. Relatively low frequency of lid lag suggests that factors other than restriction/fibrosis are probably responsible for the etiology of lid retraction in many patients [23]. Kozaki et al. (2010) showed lid retraction in 57.7% of adult patients [24]. Eyelid retraction may be of thyroid hormone excess, an increased stimulation of the eyelid retractors or innervation of the superior rectus/levator muscles and contracture, overactivity of Muller's muscle, contracture of inferior rectus muscle [23,24].

The data of proptosis in children are very different. Proptosis in children with thyroid diseases in other studies was from 12 to 100 % [2,7,11,13,21,22] in our study-proptosis was in 25.0% of patients under 18 years old. Eha et al. noted that in patients aged 11 years and older, values of proptosis 19 mm were considered as pathological [13]. Exophthalmos presented in our children age group was lower than this value. As in our previous study children were found to have mild proptosis [25]. Proptosis was found in 60.9% of our young adult patients and stare in-66.7%. Kozaki et al. noted clinically significant proptosis (>=15 mm) in 74.2% of adult patients. The average exophthalmometer reading was 17.2 +/- 3.2 mm, with proptosis less pronounced with age [24].

The cause of low frequency of extraocular myopathy in the pediatric group remains unknown. Only one patient (2.8%) had limitation of extraocular movements. Limitation of ocular motility in Acuna et al. study (2.0%) was similar to our study [11]. Our study bears a resemblance to Eha et al. (2010) and Goldstein et al. studies; none of children had restrictive strabismus (13.22). Other investigators noted restrictive strabismus from 1 to 3% [2,7,21]. Previous studies on

dysthyroid ophthalmopathy in children also suggested that the degree of ophthalmopathy appears to be substantially more benign than that found in adults. Limitation of extraocular movements was in 8 our young adult patients (11.67%). It was showed that the semi-quantitative rectus extraocular muscle parameters of magnetic resonance imaging can show the clinical activity and the course of Graves' ophthalmopathy [26]. Three (4.3%) our patients developed restrictive strabismus.

Only one patient of this group under the age of 18 years had mild punctate epithelial corneal erosions and fluorescein staining. In Acuna et al. (2007) study exposure keratopathy was noted in 4% of patients [11]. It should be noted that none of the children in our study who exhibited exophthalmos had severe corneal exposure keratopathy with corneal ulceration. Fluorescein corneal staining and punctate epithelial erosions were in 7 patients (10.1%). This might be related to the high incidence of lid retraction and lagophthalmos as the lesions were located at the lower sector of the cornea.

The optic disc of all our patients with thyroid diseases appeared normal, and no patient had clinical evidence of optic neuropathy. This is similar with previous studies [2,7,8,13]. These corneal and extraocular muscle findings may be associated with advanced eye changes in young patients with thyroid diseases.

Our study shows that eye symptoms and signs occurred more often in hyperthyroid patients. Eye changes are rarely found in children with thyroid diseases and often incorrect diagnosis may be done by a family doctor, endocrinologist or pediatrician. In our study the young adult patients with hyperthyroidism were more severely affected than children. The absence of restrictive strabismus and optic neuropathy in the children group, and presence of corneal epithelial erosions and restrictive strabismus in the young adult group in patients with hyperthyroidism seem to be clinically important.

Conclusion

Our study confirms that ocular changes are much milder when they are present in children than in young people with thyroid diseases. Eye symptoms and signs occurred more often in hyperthyroid patients. This ocular examination is useful in early diagnosis of Graves' ophthalmopathy in children and young people with thyroid dysfunction. As eye changes in children with thyroid diseases have an increased risk of developing ocular disorders, they must be examined periodically. We propose a detailed eye examination for all subjects who are diagnosed with thyroid or Graves' diseases. This may allow an earlier diagnosis and treatment of complications such as exposure keratopathy, optic neuropathy and restrictive strabismus.

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