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Research Article

Evaluation of the Features of Graves' Ophthalmopathy in Juvenile Graves' Disease

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Abstract

The aim of our study was to evaluate the features of Graves' ophthalmopathy in juvenile Graves disease.

Objectives: To identify the signs of Graves' ophthalmopathy in juvenile patients with Graves' disease.

Methods: The retrospective study was done at the Lithuanian University of Health science Kaunas Clinic of Eye diseases outpatient department. We reviewed the electronic medical records of all patients with Graves' Disease (GD) seen at the Clinic of Eye diseases, selecting 130 total patients, the age at diagnosis of GD, patients age was 17 (4.4-29.3) years. All patients had undergone a full ophthalmologic exam, including visual acuity, CAS, exophthalmometry with Hertel mirror exophthalmometer, biomicroscopy and ophthalmoscopy.

The statistical analysis was performed using the following softtware program package „SPSS for Windows" (SPSS Inc., Chicago, IL, USA). The level of statistical significance was set at $p<0.05$ for all the tests.

Results: Of the total 130 patients with GD, 92 had no evidence of Graves' Ophthalmopathy (GO-) and 38 had Graves' Ophthalmopathy (GO+). When comparing the development of Graves' Ophthalmopathy in patients with Graves' disease by gender, we found that in both (GO+ and GO-) groups, there were statistically significantly more females than males (76.3/23.7% in the GO +group and 91.3/8.7% in the GO- group, $p < 0.05$). The study found that 38 patients with Graves' disease had ocular changes characteristic of Graves' Ophthalmopathy. The most common patient's complaints were bulging of eyes (76.3%) and symptoms which are characteristic of dry eye syndrome (eye grittiness - 42.1%, tearing - 42.1% and photophobia - 31.6%). In the Graves' ophthalmopathy group, the most common specific signs were upper eyelid retraction (73.7%) and Graefe's symptom (47.4%). As non-specific, clinical symptoms of activity, showing 42.1 % of cases, hyperemia of conjunctivae (42.1%), caruncular redness (23.7%) were observed. The clinically active form (CAS was more than 3 points out of 7) was observed in 8 (21.1%) GO+ patients. 8 (21.1%} patients had impaired eye movements, but eye movements were limited only to the lateral side. There were no color sensitivity disorders in GO+ patients.

Conclusion: The most common patient's with Graves' Ophthalmopathy complaints were bulging of eyes and symptoms which are characteristic of dry eye syndrome (eye grittiness, tearing and photophobia). In this group of patients the most common specific signs were upper eyelid retraction and Graefe's symptom. As non-specific, clinical symptoms of Graves' Ophthalmopathy activity were hyperemia of conjunctivae, caruncular redness.

Keywords: Juvenile Graves Disease; Juvenile Graves' Ophthalmopathy; Ocular Signs

Introduction

Graves' Disease (GD) is an autoimmune process that affects the thyroid gland, microtissues of the orbit, extraocular muscles,

and, rarely, the skin. Graves' Ophthalmopathy (GO) is the most common inflammatory condition that presents as an extrathyroidal form of Graves' disease in adults (usually aged 40-50 years). Graves' Ophthalmopathy most commonly develops in hyperthyroidism, but can also occur in Hashimoto's autoimmune thyroiditis and euthyroidism [1-3]. Ophthalmopathy occurs in approximately 50% of patients with Graves' disease, but GO in children and young adults is rare and has not been extensively studied [4]. Antibodies to thyrotropin receptor (TSH-R Ab) play a crucial role in the pathogenesis of GD and GO, they stimulate TSH receptors on thyrocytes and fibroblasts of the orbit. The proliferation of lymphocytic cells and fibroblasts triggers an inflammatory reaction at the level of orbital fibroblasts, leading to the production of cytokines and glycosaminoglycans. These mechanisms lead to edema of the orbital soft tissues and extraocular muscles, leading to swelling of microsoft tissues, proptosis, limitation of eye movements and, in severe cases, even corneal ulceration and dysthyroid optic neuropathy [5-9]. It is now clear that the disease has many etiological factors and they may influence its development [6,7].

Since GD and GO affect different organ systems, a common approach has been developed in the areas of diagnosis and treatment of these diseases. In order to unify the interdisciplinary research of GO, the European Graves' Orbitopathy Group was established. The EUGOGO was recommended as a form of GO assessment [10]. In order to clarify the possible occurrence of Graves' disease, we selected a young cohort, assuming that they spent less time in the combination of risk factors. It has been noted that in children Graves' disease in European countries increased [2,11].

GD is much rarer in children than in adults with an estimated incidence rate of 4.58 to 100 000 population per year, accounting for almost 15% of all paediatric thyroid diseases. Graves' disease is much less common in children than in adults, the incidence rate per year of this disease is 4.58 to 100000 population. It accounts 15 percent of all thyroid diseases in children [1,2,12]. As children are diagnosed with Graves' disease their risk of developing Graves' ophthalmopathy is about the same as adults and the incidence is similar to that of women [2,13,14]. GO diagnosed in children manifests in milder forms than in adults, mainly manifested by microsoft tissue changes. Severe GO, with restrictions in eye movements, dysthyroid optic neuropathy and exposure keratopathy, is more common in adult patients [2,13-16].

Both Graves' disease and Graves' Ophthalmopathy in children require new diagnostic methods and treatment [4]. Most cases of GD can be successfully treated, GO can cause both cosmetic and functional consequences, such as eyelid retraction, ectropion, corneal ulceration, optic neuropathy and difficulty with eye movements. International scientific literature reviews show that there are many studies of Graves' Ophthalmopathy and its clinical manifestations in adults. Since Graves' Ophthalmopathy occurs relatively rarely in children and adolescents compared to adults, there is a lack of research in this area. Graves' Ophthalmopathy may significantly influence the quality of life of patients. It has been found that children, adolescents and young adults with Graves' ophthalmopathy have psychological problems, difficulties in learning, working. This may change patients emotional, social, physical activities [6,7,16,17].

The disease, if the cornea or optic nerve is not damaged, does not cause vision loss, but it can disrupt the patient's quality of social life and patients may become socially withdrawn. In children, exophthalmos, strabismus and other eye symptoms (double vision, limited eye movements) cause negative emotional reactions, sleep disorders, mood swings and depression, especially during puberty [15,18]. Since Graves' Ophthalmopathy (GO) is rare in children, its symptoms are rarely present, which means there is a risk of late detection of the disease. Changes in Graves' Ophthalmopathy in children and young patients have not been sufficiently studied in Lithuania.

Aim and Objectives

The aim of the present study was to evaluate the features of Graves' ophthalmopathy in juvenile Graves disease.

The objectives of the study were as follows:

to identify the signs of Graves' Ophthalmopathy in juvenile patients with Graves' disease.

We identified the most significant changes in patients with GO compared with the GD group without pronounced ophthalmopathy.

Ethical Approval

The study protocol was approved by the Kaunas Regional Biomedical Research Ethics Committee.

Materials and Methods

The retrospective study was done at the Lithuanian University of Health science Kaunas Clinic of Eye diseases outpatient department. We reviewed the electronic medical records of patients who were newly diagnosed with Graves' Disease (GD) at the age of less than 30 years. There were studied 130 patients, 92 of them were without Graves' Ophthalmopathy (GO-) signs and 38 - with Graves' Ophthalmopathy (GO+). When comparing the development of Graves' Ophthalmopathy in patients with Graves' Disease by gender, we found that in both (GO+ and GO-) groups, there were statistically significantly more females than males (76.3/23.7% in the GO +group and 91.3/8.7% in the GO- group, $p < 0.05$).

The diagnosis of GD was made by an endocrinologist based on generally accepted clinical and laboratory criteria: clinical symptoms of hyperthyroidism, increased serum Free Thyroxine (FT4), Free Triiodothyronine (FT3), decreased Thyrotropin (TSH), increased serum TSH Receptor Antibodies (TSHR Ab) and diffuse goiter detected by palpation and ultrasound. All patients had undergone a full ophthalmologic exam, including visual acuity, Clinical activity score (the clinically active form when CAS was more than 3 points out of 7), exophthalmometry with Hertel mirror exophthalmometer, biomicroscopy and ophthalmoscopy.

Exclusion criteria were as follows: previous history of autoimmune, neurological, oncological, infectious eye diseases, orbital, retinal and corneal diseases, glaucoma, ocular trauma, surgical procedures on extraocular muscles, eyeball and orbit; amblyopia; keratoconus, pregnant women.

The study was performed according Helsinki Declaration and approved by the medical ethics committee of Lithuanian University of Health.

Statistical Analysis

The statistical analysis was performed using the following softtware program package „SPSS for Windows" (SPSS Inc., Chicago, IL, USA). The level of statistical significance was set at $p<0.05$ for all the tests.

Results

According to the age at diagnosis of GD, patients age was 17 (4.4-29.3) years. Patients were divided into two groups children (up to 18 years) and young adults (18-30 years). The critical age for the development of GD in children is about 14 years and in young adults - about 21 years. Age at diagnosis and the development of Graves' ophthalmopathy were not associated in these two patient subgroups ($p > 0.05$) (Table 1).

Age (year)	**Median (25-75 percentiles)**			**p**
	All sample	**GO-**	**GO+**	
	(n = 130)	**(n = 92)**	**(n = 38)**	
Age at diagnosis	17 (4.4-29.3)	17 (14-21)	18.15 (12.85-20.08)	0.57
Children age at diagnosis (n = 67)	14 (12-16)	14.1 (12.1-16)	13 (10-16)	0.42
Young adults age at diagnosis (n = 63)	21 (19.4-24)	21 (20-25.8)	20 (19.1-21)	0.165
GO - Graves' disease patients who did not develop ophthalmopathy GO+ Graves' disease patients who developed ophthalmopathy				

Table 1: Comparison of age of study patient groups.

Ophthalmological examination data were obtained in juvenile Graves' Ophthalmopathy and Graves' Disease and these data were compared between groups. The study found that 38 patients with Graves' Disease had ocular changes characteristic of Graves' Ophthalmopathy (Table 2).

Complaints % (n)	GO+	GO-	p
Bulging eyes	76.3 (29)	1.1 (1)	< 0.001
Photophobia	31.6 (12)	3.3 (3)	< 0.001
Eye grittiness	42.1 (16)	3.3 (3)	< 0.001
Tearing	42.1 (16)	5.4 (5)	< 0.001
Intermittent double vision	10.4 (4)	0.0 (0)	< 0.001
Pushing of the eyeball	15.8(6)	0.0 (0)	< 0.001
Eyelid swelling	18.4 (7)	5.4 (5)	< 0.04

Table 2: Ophthalmological complaints in patients with Graves' Ophthalmopathy.

The most common patient's complaints were bulging of eyes and symp¬toms which are characteristic of dry eye syndrome (eye grittiness, tearing and photophobia).

In the GO+ group, the most common specific signs were upper eyelid retraction and Graefe's symptom. As non-specific, clinical symptoms of activity, showing 42.1 percent of cases, hyperemia of conjunctivae, caruncular redness (23.7%) were observed. The clinically active form (CAS was more than 3 points out of 7) was observed in 8 (21.1%) GO+ patients. 8 patients had impaired eye movements, but eye movements were limited only to the lateral side. There were no color sensitivity disorders in GO+ patients (Table 3).

Features, % (n)	GO+	GO-	p
Corneal fluorescein staining	5.3 (2)	0.0 (0)	< 0.001
Caruncular redness	23.7 (9)	0.0 (0)	< 0.001
Conjunctival hyperemia	42.1(16)	8.7(8)	< 0.001
Chemosis	10.5 (4)	0.0 (0)	< 0.006
Eyelid redness Eyelid swelling	10.5 (4); 28.9 (11)	0.0 (0)	< 0.006
Disorder of ocular motility	21.1 (8)	0.0 (0)	< 0.001
Disorder of color sensitivity	0.0 (0)	1.1 (1)	0.72
Head forced position	13.2 (5)	0.0 (0)	< 0.001
Lower lid retraction	47.4 (18)	0.0 (0)	< 0.001
Upper eyelid retraction	73.7 (28)	0.0 (0)	< 0.001
Graefe's symptom	47.4 (18)	0.0 (0)	< 0.001
CAS	21.1 (8)	0.0 (0)	< 0.001

Table 3: Ophthalmological examination assessment comparison between GO+ and GO- groups.

Discussion

Because Graves' ophthalmopathy is rare in childhood, it is often thought to be a less severe disease than in adults. Our study represents a large study of children with GO. The gender distribution of our patients is similar to that of most other authors of children with GO studied, with a lower predominance of male [11,19]. In our study were statistically significantly more women than men similar to the other studies (1,2,4,11].

Ionescu, et al., founded that the clinical presentation of soft tissue damage and proptosis in the pediatric GO population is similar to adults [11]. They found that proptosis was present in the majority of children (84.3%), eyelid retraction was in 67%, eyelid swelling in 27% and diplopia in 11.3% of children. Authors found conjunctival hyperemia in 12.1%, punctate epithelial keratopathy in 13.9%, chemosis in 5.2% and caruncular swelling in 3%, 2.6% pf patients. Other authors also showed that proptosis was the most common clinical sign of GO in children, followed by eyelid retraction and eyelid swelling [19].

Durairaj, et al., noted that eyelid retraction was the most common symptom, followed by proptosis. Ocular movement restriction was found in 11% of their patients, which is consistent with our results [20]. In our study the in Graves' Ophthalmopathy group, the most common specific signs were upper eyelid retraction and Graefe's symptom, which is similar to data published by other authors. Also, there were clinical symptoms of process activity, as redness of conjunctivae, caruncular redness, CAS more than 3 points was in 21.1%. There were no optic neuropathy signs.

Analyzing many articles that deal with pediatric GO, it can be concluded that GO in children has a milder form of the disease than in adults with this disease. Approximately 5-7% of patients with GO may develop dysthyroid optic neuropathy [15,21,22]. Our patients had no signs of optic neuropathy. According to Jankauskiene, Jarushaitiene study, in patients with GO wide eyelid fissure, lagophthalmos, proptosis, lack of tear production, decreased blink rate and corneal evaporation can cause dry eye symptoms [23].

Restrictive myopathy in adult patients can range from 20% to 43% [8,10,22]. In our study the limitation of ocular movements to the lateral side was in 21.1% of patients with Graves ' Ophthalmopathy. We think that juvenile patients with GD and GO have a shorter duration of illness than adults and have less muscle fibrosis due to less inflammation of the ocular tissues and extraocular muscles.

Conclusion

The most common patient's with juvenile Graves' Ophthalmopathy complaints were bulging of eyes and symptoms which are characteristic of dry eye syndrome (eye grittiness, tearing and photophobia). In this group of patients the most common specific signs were upper eyelid retraction and Graefe's symptom. As non-specific, clinical symptoms of Graves' Ophthalmopathy activity were hyperemia of conjunctivae, caruncular redness. The results of this study allow us to predict the risk of developing juvenile Graves' ophthalmopathy and to determine the severity and progression of Graves' disease.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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