Original Article

Symptoms and signs of dry eye in children with Graves' ophthalmopathy

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Abstract:

PURPOSE: The purpose of this study is to evaluate the tear secretion and ocular surface properties in children with Graves' ophthalmopathy (GO) and to compare the results with those of healthy children.

METHODS: This was a cross-sectional study. Forty-three patients with GO (Group 1) and 41 healthy children without any ocular and/or systemic disorder (Group 2) were examined clinically and underwent tests for dry eye. We performed analyses including the Ocular Surface Disease Index (OSDI) questionnaire, Schirmer's test under topical anesthesia (<5 mm was abnormal), slit-lamp biomicroscopy (corneal fluorescein staining and tear breakup time (TBUT) under blue-light illumination), and fundoscopic evaluation.

RESULTS: Dry eye symptoms and the mean OSDI score were significantly ($P < 0.02$) higher (15.6 ± 18.7) in patients with GO compared with controls (5.67 ± 3.6). The mean Schirmer's (basal tear secretion) tests value was significantly reduced in Group 1 (5.25 ± 3.1 mm) compared with Group 2 (17.1 ± 5.2), respectively. The difference was statistically significant ($p < 0.005$), suggesting inadequate tear production. The mean tear film breakup time in children was lower in patients with GO (8.3 ± 3.42 s,) compared with controls (13.2 ± 4.74 s), ($P < 0.001$) suggesting an unstable tear film. Decrease of corneal sensitivity (23.3%) was noted in patients with GO compared with controls. GO patients showed a significant increase of the frequency of corneal fluorescein staining (6.9%) in patients with GO compared with controls.

CONCLUSION: Patients with GO had a statistically significant higher incidence of dry eye symptoms and the increase of OSDI score. Significantly lower Schirmer's and TBUT tests results were seen in the study group when compared with the controls. These findings may indicate a tendency for dry eye in pediatric GO patients.

Keywords:

Children, dry eye, Graves' ophthalmopathy, ocular surface, tear secretion

Introduction

Graves' ophthalmopathy (GO) also known as thyroid eye disease, thyroid-related orbitopathy, thyroid-associated orbitopathy, or GO, is an autoimmune disorder in which autoantibodies to thyroid-stimulating hormone receptors cause an excess of thyroid hormones in orbital tissues, extraocular muscles, and lacrimal gland.[1-4] Dry eye is more common in patients with Graves' disease (GD). Rarely, it may be in patients with hypothyroidism and euthyroidism.[5-7]

The clinical picture of GO includes eyelid retraction in 80%–90% of patients, lagophthalmos, exophthalmos, eye movement restriction, and diplopia.[8-11]

GD and GO are unusual disorders in children as well as in adults.

In children with GO has a similar gender relationship, but the clinical picture is milder than in adults.

Jarusaitiene *et al*.[12] noted that the main symptoms of juvenile GO were eyelid retraction (73.7%), exophthalmos (65.8%), redness of conjunctiva (42.1%), and restriction of eye mobility (21.1%).

GO usually occurs within 1 year to 18 months of the onset of systemic GD symptoms with an active phase followed by spontaneous

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remission. However, for some patients, the active phase may return later.

Little is known about eye surface changes in children with GO.

The relationship between thyroid diseases and dry eye syndrome has long been known. Previous studies have assessed that Graves' ophthalmopathy increases the risk of dry eyes.[13-17]

GO in adults is most commonly associated with dry eyes.[16,18-20] GO patients suffer from eye discomfort, redness, and foreign body sensation.

Symptoms of dry eye can significantly impair the quality of life and affect the psychological condition of patients with thyroid disease and GO.[21] To improve the quality of life of patients with GO, doctors need to identify the cause of dry eye.

The mechanism of the relation between GO and dry eye is unknown. Internal and external causes can accelerate tear deficiency or decreased tear formation, increased evaporation, and abnormal tear film that alters the surface of the eye.[22,23] This is characterized by increased osmolarity of the tear film and subsequent inflammation of the surface of the eye.[24]

Studies suggest that the lacrimal gland may be directly involved in the pathogenesis of dry eye disease.[25] Decreased tear production is also due to the inflammatory process in GO.[26] Such mechanisms involved may be synergistic.

The thyroid and tear glands stimulate a specific thyroid-stimulating hormone receptor antigen that elicits an autoimmune thyroid and orbital response.[3,18,27,28] Thyroid hormone receptor autoantibodies expressed by the lacrimal gland disrupt the function of this gland, leading to deficiency of tears and eye dehydration which are signs of dry eye in patients with GO.[18] Computed tomography and magnetic resonance imaging show an increase in the lacrimal gland in patients with GO. Patients with GO also have an abnormal tear protein composition that is associated with tear dysfunction.[18]

Wide palpebral fissure, lagophthalmos, proptosis, decreased blink rate, lack of tear production, and tear evaporation are the main causes of dry eye in patients with GO.[29-33]

Many published works have shown that approximately 45%–85% of patients with GO may experience dry eye symptoms.[10,13,20,34,35]

Gupta *et al*. indicated that GO is a common cause of ocular surface lesions.[30] Eckstein *et al*. and[18] Iskeleli *et al*.[36] reported that patients with GO often have significant ocular surface disorders and dry eye symptoms compared with healthy individuals.

Studies have reported dysfunction of the meibomian gland in patients with thyroid disease and GO.[4,37,38]

Bruscolini *et al*.[39] showed that patients with GD have a tear film and cornea damage even in the absence of proptosis.

Achtsidis *et al*.[20] showed decreased corneal sensitivity in patients with early active GO and no exophthalmos. Kan *et al*.[40] have assessed dry eye symptoms in adults with Hashimoto's thyroiditis and proptosis, and shorter Schirmer's and tear film rupture time test results compared to controls. Pathogenetic factors of dry eye in children are not well defined as in adults.[41-43]

Studies have shown that T lymphocyte-dependent inflammation is associated with tear dysfunction, increased tear film evaporation, and osmolarity due to exophthalmos and eyelid retardation, this may contribute to dry eye symptoms.[18,32,36] T cells penetrate orbital tissues and the external muscles of the eye in response to this antigen present in thyroid tissue.[2] The inflammation often results in glycosaminoglycan deposition, extraocular muscle fibrosis, and adipogenesis around the orbit.[3,44]

Dysfunction of the meibomian gland is reported to be an important cause of tear film evaporation and dry eye.[45,46]

Mrugacz *et al*.[47] showed signs of dry eye in children with ocular superficial cystic fibrosis. Studies have shown lower Schirmer's test and tear film rupture time scores.

There is a lack of research on ocular surface studies in children with GD and GO. Diagnosing children with GO and dry eye can be particularly challenging because they have difficulty articulating the symptoms and manifestations of the disease. There are several publications on these studies of pediatric Hashimoto's thyroiditis.[48]

Gunay *et al*.[48] study shows several ocular surface changes in children with Hashimoto's thyroiditis without clinical signs of thyroid-related ophthalmopathy.

The most common dry eye questionnaire is the Ocular Surface Disease Index (OSDI).[49] Other tests should be used in conjunction with dry eye questionnaires, as there is no single test that can diagnose dry eye status in GO.[50,51]

Children may need to adapt to specific tests depending on the patient's age. Most tests for the diagnosis and monitoring of dry eye in children are the Schirmer's test, fluorescein-stained biomicroscopy, and tear breakup time (TBUT) tests.[22,52]

In this study, we aimed to evaluate symptoms of dry eye, the tear secretion and ocular surface properties in children with GO, and to compare the results with healthy subjects.

Methods

A cross-sectional study was conducted at the Lithuanian University of Health Sciences Hospital, Kaunas. The study included two groups: Group 1 included 43 children with GO and group 2 (control group) - 41 healthy children.

Before the study, all patients and control persons or their parents signed written informed consent. Our study was done in accordance with the Declaration of Helsinki and approved by the Lithuanian Health University ethics committee.

All measurements were carried out by the same examiner under normal conditions.

The patient was assigned to the GO group when two or more of the following criteria were met:[1] abnormal thyroid function and[2] any sign or symptom, including exophthalmos, lid retraction (upper eyelid margin at or above the limbus), and lid lag (immobility of the upper eyelid during downward gaze).

Patients were aged 13–18 years and TSH, free T3 and T4 levels were within the normal ranges (euthyroid) before the ophthalmological investigation.

Those in the control group were without any ocular and/or systemic disorders. Patients who had ages <13 years, and used contact lenses were excluded from the study. Patients with the GO group and healthy children underwent a routine complete ophthalmic examination, including visual acuity testing determined with standard Snellen's chart. We performed analyses including the OSDI with 12-item questionnaire, Schirmer's tests under topical anesthesia (<5 mm was abnormal), corneal sensitivity testing, slit-lamp biomicroscopy, corneal fluorescein staining, TBUT under blue-light illumination, and fundoscopic evaluation.

Statistics

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp. The study data were described as the mean and standard deviation (M ± SD) and percentage. Student's *t*-test and Mann–Whitney test were used to analyze differences between the values obtained from the data of two groups. A *P* was considered statistically significant at 0.05 or < 0.05.

Results

A total of 43 patients with GO (Group 1) patients (11 boys and 32 girls), aged 13–18 years 15.4 ± 5.2 years) and an age-matched control (Group 2) consisted of 41 children of 12 males and 29 females ranging in age from 14 to 18 years participated in the study. The mean age of the control group was 14.9 ± 4.8 years.

The mean duration of GO was 6.59 ± 7.52 months (range 0.5–36 months).

Twenty-two patients (51.2%) were hyperthyroid, 8 (18.6%) had hypothyroidism, and 13 (30.2%) had normal thyroid function when included in the study. The mean ± SD values of the OSDI, Schirmer's test, TBUT scores of GO patients, and normal controls are presented in Table 1.

Dry eye symptoms were significantly higher in the patient group when compared to the controls. The average score of OSDI was significantly higher 15.6 ± 18.7 ($P < 0.02$) within the GO group, while the mean score of OSDI was 5.67 ± 3.6 in the control group. The mean Schirmer's (basal tear secretion) tests value was significantly reduced in Group 1 (5.25 ± 3.1 mm) compared with Group 2 (17.1 ± 5.2), respectively. The difference was statistically significant ($p < 0.005$), suggesting inadequate tear production. The mean tear film breakup time in children was lower in Group 1 (8.3 ± 3.42 s) compared with Group 2 (13.2 ± 4.74 s), ($P < 0.001$) suggesting an unstable tear film. Decrease of corneal sensitivity (23.3%) was noted in patients with GO compared with controls. GO patients showed a significant increase of the frequency of corneal fluorescein staining (6.9%) in patients with GO compared with controls.

Table 1: Clinical characteristics of the Graves' ophthalmopathy and control groups

	GO group ($n=43$)	Control group ($n=41$)	*P*
Age (year), mean±SD	15.4±5.2	14.9±4.8	0.49
Male, *n* (%)	11 (25.6)	12 (29.3)	0.61
Female, *n* (%)	32 (74.4)	29 (67.4)	
Duration of GO (months), mean±SD	6.59±7.52		
Hyperthyroidism, *n* (%)	22 (51.2)		
Hypothyroidism, *n* (%)	8 (18.6)		
Euthyroidism, *n* (%)	13 (30.2)		
OSDI, mean±SD	15.6±18.7	5.67±3.6	<0.02
TBUT (s), mean±SD	8.3±3.42	13.2±4.74	<0.01
Schirmer's test (mm), mean±SD	5.25±3.1	17.1±5.2	<0.005
Decrease of corneal sensitivity, *n* (%)	10 (23.3)		
Ocular surface fluorescein staining, *n* (%)	3 (6.9)		

GO: Graves' ophthalmopathy, SD: Standard deviation, OSDI: Ocular Surface Disease Index, TBUT: Tear breakup time

Discussion

The relation between GO and dry eye has long been established in the literature.

Dry eye is a common disease and is increasingly occurring in people with autoimmune diseases and thyroid disorders.[22,23,53]

Studies have revealed that dry eyes in young people cause eye discomfort and can lead to depression and anxiety.[54-56] There was confirmed that ocular inflammation is caused by T lymphocytes and this influences the pathogenesis of dry eye syndrome by reducing the formation of tears.[26]

Several studies have shown that patients suffered from thyroid diseases have signs of dry eyes. Abusharaha *et al*.[33] reported that individuals with hypothyroidism had higher mean phenol red test scores compared with hyperthyroidism. The mean OSDI score was found to be much higher in patients with hyperthyroidism (31.0 ± 28.0) compared to subjects with hypothyroidism (11.2 ± 11.0).[33]

The results obtained by Turkyilmaz *et al*.[31] revealed that adult patients with thyroid disorders had dry eye signs compared with healthy people. A higher mean OSDI score (29.0 ± 20.8) was in patients with thyroid disease compared with healthy subjects (13.2 ± 7.8). The mean TBUT test score in the study group with thyroid disease was significantly lower in both eyes (4.9 ± 1.6 and 4.2 ± 1.9 s) in comparison with the control healthy people group (13.2 ± 2.6 and 12.3 ± 2, 2 s). The mean Schirmer's test score was lower in patients with thyroid disorders than in healthy subjects.[31]

Another study showed that the mean Schirmer's test score was significantly reduced by 14 ± 8 mm in patients with thyroid disorders compared with normal humans (24.9 ± 3.6 mm).[16]

Reduced tear leakage or evaporation of the cornea and the instability of the tear film cause discomfort in the eyes and impaire vision. There were noted that corneal sensitivity decreased in the early stages of thyroid disease.[1]

Patients with GO experience changes in the surface of the eye that result in dry eyes.[16,20,32,57] Sixty-five percent of patients with GO were studied in a cohort study, and 97% of patients had one or more symptoms of dry eye: 65% of patients suffered from excessive tearing, 70% from sanding and irritation, and 55% from photophobia.[58]

Gupta *et al*.[30] showed that patients with GO do not generally have poor water production. Normal Schirmer's studies were performed in 81% of patients. Schirmer's values were reduced (approximately 8.5 mm) in 43% of GO patients in the control group. Authors suggest that Schirmer's values <8 mm may be classified as pathological in patients with GO.

Fluorescein staining showed significantly greater corneal damage in adult patients with GO and dry eye compared with healthy subjects.[18]

Patients with early signs of GO also have decreased corneal sensitivity.[20]

Eckstein *et al*.[18] reported that in patients with GO, there is an association between eye surface dryness and damage to the surface of the eye and a decrease in tear production and disorder of the lacrimal glands.

Villani *et al*.[19] described that confocal microscopy showed that patients with GO had lower levels of corneal nerve fibers than healthy people. One study found that dry eye symptoms were found in 70.4% of students and were associated with risk factors such as gender, smoking, and eye drops.[59] Other studies have shown that OSDI scores show fewer dry eye symptoms and mild eye surface changes in children compared to adults.[39] OSDI assessment may have limited benefit in detecting dry eyes in children due to poor compliance and difficulty in understanding instructions.[60-62]

We could objectify the symptoms of dry eyes as a common feature of GO. Our study showed that GO children patients had a higher mean OSDI score (15.6 ± 18.7) compared with controls (5.67 ± 3.6).

Gunay *et al*.[48] conducted that the mean Schirmer's test and tear film breakup time scores were lower in children with Hashimoto's thyroiditis than in healthy subjects (14.91 ± 6.27).

In our study, the results of the Schirmer's test show a significant difference between the GO and control groups. Tear secretion was significantly ($p < 0.005$) lower compared to the healthy group (Schirmer's test 5.25 ± 3.1 mm vs. 17.1 ± 5.2 mm).

Inflammation of the eyes caused by these problems also contributes to damage to the surface of the eye. The mean TBUT score in our patients with GO was significantly ($P < 0.001$) lower (8.3 ± 3.42 s) than in controls (13.2 ± 4.74 s). Tear film instability can dry out because the stability of the tear film depends on several factors, such as the tear interval, proper blinking, normal tear function, and maintenance of a normal eye surface. In our 23.3% and 6.9% of patients with GO, a decrease of corneal sensitivity and corneal fluorescein staining was established, respectively. This result suggests the severity of dry eye in these patients with GO and may be due to insufficient tear secretion, high tear evaporation, and tear film instability.

The evaluation of dry eyes, including ocular surface assessment, tear secretion, and TBUT, should be evaluated to properly treat GO patients.

This study has several limitations: A relatively small number of patients, not all children were able to name dry eye symptoms. Specific dry eye tests have been difficult to perform due to the low age of the patient. Further and more detailed studies are needed to better determine dry eye symptoms, tear secretion, and ocular surface results.

Conclusion

Patients with GO had a statistically significant higher incidence of dry eye symptoms and the increase of OSDI score. Significantly lower Schirmer's and TBUT tests results were seen in the study group when compared with the controls. The study demonstrates several tear secretion and ocular surface changes in children with GO. These findings may indicate a tendency for dry eye in pediatric GO patients.

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Conflicts of interest

There are no conflicts of interest.

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