

Thyroid-associated orbitopathy characteristics and surgery requirement rate

Características de orbitopatía asociada al tiroides y tasa de requerimiento de cirugía

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ABSTRACT

Objective. To know the demographic and clinical characteristics of Thyroid Associated Orbitopathy (TAO), as well as the requirement rate of orbital surgery in patients of the Orbit Service in the National Medical Center of the West, IMSS. **Methods.** Observational, cross-cutting, descriptive and retrospective study carried out analyzing the records of patients diagnosed with TAO and treated at a third-level care center from January 2005 to July 2016. **Results.** A total of 236 orbits of 118 patients were valued, with an average age of 47.3 ± 13.2 years, 74.6% were female and 25.4% male. 4.2% of patients were treated with hypothyroidism, 94.1% with hyperthyroidism and 1.7% with diffuse toxic goiter. 44.9% of patients studied had eye movement restriction, 10.2% exposure keratopathy and 51.7% intraocular hypertension. 34.7% of patients valued in the service required orbital decompression, 16.1% palpebral surgery and 8.5% strabism correction. In the conservative management of these patients 48.3% required the use of topical eye lubricants, while 52.5% required the use of eye hypotensives in variable numbers. **Conclusions.** TAO was mainly associated with hyperthyroidism, being more common in female patients between the age of 40 and 59; more than 50% of patients required the use of eye hypotensives. Likewise, surgical management was performed in more than 50% of patients, with orbital decompression being the most frequent intervention.

Keywords: Thyroid orbitopathy; Exophthalmos; Orbital decompression

RESUMO

Objetivo: Conheça as características demográficas e clínicas da Órbita Associada da Tireoide (OAT), bem como a taxa de exigência da cirurgia orbital em pacientes do Centro Médico Nacional do Oeste. **Métodos.** Estudo observacional, transversal, descritivo e retrospectivo realizado analisando os registros de pacientes diagnosticados com OAT tratados num centro de cuidados de terceiro nível de janeiro de 2005 a julho de 2016. Os resultados. Um total de 236 órbitas de 118 pacientes foram avaliados, com uma idade média de 47,3 (13,2 anos, 74,6% eram do sexo feminino e 25,4% masculinos. 4,2% dos doentes foram tratados com hipotireoidismo, 94,1% com hipertireoidismo e 1,7% com goiter tóxico difuso. 44,9% dos doentes estudados com restrição de movimento ocular, 10,2% com queratopatia de exposição e 51,7% com hipertensão intraocular. 34,7% dos doentes avaliados no serviço necessitaram de descompressão orbital, 16,1% de cirurgia palpebral e 8,5% de correção do hatrabisma. Na gestão conservadora destes doentes, 48,3% exigiam o uso de lubrificantes tópicos dos olhos, enquanto 52,5% dos pacientes necessitavam do uso de hipotensivos oculares em número variável. **As conclusões.** A OAT foi associada principalmente ao hipotireoidismo, sendo mais comum em pacientes do sexo feminino entre os 40 e os 59 anos; mais de 50% dos pacientes necessitaram do uso de hipotensivos oculares. Da mesma forma, a gestão cirúrgica foi realizada em mais de 50% dos pacientes, sendo a descompressão orbital a intervenção mais frequente.

Descritores: Orbitopatia da tireoide; Exofátalmo; Descompressão orbital

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INTRODUCTION

Thyroid-associated orbitopathy (TAO) is the leading cause of orbital pathology; it accounts for 50%-60% of orbital surgeon's consultations.⁽¹⁾

Although TAO is the most common extrathyroidal manifestation of Graves' disease, it can also emerge in patients without past or present history of hyperthyroidism (euthyroid), in patients with hypothyroidism, or it can even be associated with Hashimoto's thyroiditis.⁽¹⁾

TAO-emergence age presents bimodal incidence peak: at 40-44 and 60-64 years in women, and at 45-49 and 65-69 years in men.⁽¹⁾

The disease is often bilateral (85-95%), but it can also manifest itself unilaterally (5-15%). In addition, 5% of patients experience reactivation of orbital inflammatory disease once the initial episode has subsided.⁽¹⁾

The most frequent and useful signs and symptoms to be taken into consideration for early diagnosis purposes are:

Signs: eyelid edema, periorbital edema, chemosis, hyperemia, keratopathy, chronic conjunctivitis.⁽¹⁾

Symptoms: Orbital pain or "sensation", tearing, photophobia, foreign body sensation, blurred vision, double vision (diplopia), and discomfort (pain) when moving one's eyes.⁽¹⁾

The course of the disease can be divided into active (dynamic) and inactive (static) stage; signs and symptoms of disease activity comprise exophthalmos, conjunctival injection, chemosis, diplopia, corneal ulceration and, most rarely, decreased visual acuity due to optic nerve compression. Corticosteroids are only effective during the dynamic stage.⁽¹⁾

According to Bartley, TAO is diagnosed when there is eyelid retraction (above the upper corneoscleral margin in primary position, without frontal muscle contraction) in association with thyroid dysfunction (increased free thyroxine or TSH level), exophthalmos (Krahn or Hertel higher than, or equal to, 20 mm), optic nerve dysfunction (changes in contrast, positive Marcus Gunn), abnormal campimetry (or dyschromatopsia not associated with another lesion), as well as extraocular muscle involvement.⁽²⁾

Classification

Disease activity can be determined based on the Clinical Activity Score (CAS), which is the most widely used scale nowadays due to its clinical use and simplicity.

Clinical determinants of disease activity based on CAS classification comprise:

First consultation (score 0/7):

- Spontaneous retrobulbar pain
- Pain while trying to look up and down
- Reddish eyelids
- Reddish conjunctiva
- Caruncular edema or folds
- Eyelid edema
- Conjunctival edema (chemosis)

Follow-up (3 additional points, score 0/10)

- Exophthalmos increase by 2 mm, or more, in the last 1-3 months
- Decreased visual acuity in the last 1-3 months
- Ocular motility decrease by 8°, or more, in the last 1-3 months

Clinical Activity Score (CAS) higher than 3/7 is suggestive of active TAO; likewise, the classification by EUGOGO (2016) also helps determining disease severity level.

Severe orbitopathy only affects 4%-5% of patients; it is more often observed in older, diabetic and male patients.⁽¹⁾ Smoking habit is one of the risk factors that mostly influence TAO. It is not only associated with the most aggressive forms of

the disease, but also with lower patients' response to treatment and longer disease duration. TAO-smoking association is clearly established in the literature.⁽¹⁾

TAO progression can lead to several complications such as exposure keratopathy, restrictive myopathy and optic neuropathy, which can lead to irreversible visual dysfunction in case of inappropriate management or diagnostic omission. Hence, the importance of investigating, featuring and making timely intervention in patients with TAO.⁽¹⁾

Aim

General aim

Understanding TAO features and surgery requirement rate in a reference medical center in Mexico.

1. Identifying patients' demographic features (age, sex, thyroidal diagnosis).

2. Describing the affected orbit, exophthalmometry results, as well as the frequency of restrictive pattern, optic neuropathy, exposure keratopathy and intraocular hypertension.

3. Determining the surgery requirement rate and surgical treatment features.

METHODS

Study design

Observational, cross-sectional, descriptive and retrospective study was carried out in cases of TAO patients treated at the CMNO High Specialty Medical Unit of the Mexican Institute of Social Security, in Guadalajara City, Jalisco, Mexico, from January 2005 to July 2016.

Patients were selected through intentional non-probability sampling - for convenience purposes. All patients diagnosed with TAO, who were treated at the service, were included in the study. For methodological purposes, sample size was calculated based on the infinite population formula, by taking into consideration the prevalence of thyroid-associated orbitopathy in patients with Graves' disease at 10%, 95% confidence interval and 6% margin of error (n = 96).

Selection criteria

Inclusion criteria

-Patients diagnosed with thyroid disease (hyperthyroidism, hypothyroidism or subclinical thyroid disease).

- Cases of patients diagnosed with TAO (based on the incidence of exophthalmos, palpebral retraction, restrictive strabismus, conjunctival injection, chemosis, periocular edema and tearing).

- Male and female individuals at any age group.

Exclusion criteria

- Previous diagnosis of glaucoma.

- Cases lacking information in the file.

Procedures

Retrospective review of electronic and physical files was carried out to extract the following information:

1. Patients' overall features: age, sex, thyroidal diagnosis and status.

2. Affected orbit, exophthalmometry value, as well as presence or absence of intraocular hypertension, restrictive pattern and optic neuropathy.

3. Surgery requirement rate and surgical treatment type.

Collected data were subjected to statistical analysis in the SPSS software v. 22.

Statistical analysis

Data were captured in the SPSS software v.22 for Mac, which was used to perform descriptive and inferential analysis of qualitative and quantitative data, whenever applicable.

Descriptive analysis applied to qualitative variables was carried out based on frequencies and percentages, whereas that applied to quantitative variables was based on mean and standard deviation. Surgery requirement rate was calculated based on 100 assessed patients.

Inferential analysis applied to qualitative variables was performed based on Chi-squared test, whereas that applied to quantitative variables was based on Student's t test (independent samples). Chi-square test and t-test for independent samples were used to investigate whether there were significant differences in clinical and paraclinical features between patients who required surgery and the ones who did not. Statistical significance was set at $p < 0.05$.

Ethical aspects

The study was evaluated and approved by the Local Health Research Committee (CLIES - Comité Local de Investigación en Salud), protocol n. R-2017-1301-30.

The current research was carried in compliance with the legal framework of the General Law on Health, which classifies it as risk-free.

The study has followed the ethical principles for medical research involving human subjects, which were established by the World Medical Association in the Declaration of Helsinki (1964) and ratified in Rio de Janeiro (2014).

RESULTS

Patients' overall features

The total number of 236 orbits from 118 TAO patients (mean age = 47.3 ± 13.2 years) were evaluated throughout 11 years of study (January 2005-July 2016). Patients' distribution based on age group is shown in Figure 1; 74.6% of them were women and 25.4% were men (Figure 2).

Hypothyroidism, hyperthyroidism and diffuse toxic goiter accounted for 4.2%, 94.1% and 1.7% of underlying thyroid diseases observed in the investigated patients, respectively (Figure 3)

Ophthalmopathy features and comorbidities

Patients with affected left eye accounted for 5.9% of cases, whereas the ones presenting affected right eye accounted for 8.5% and those whose both eyes were affected accounted for 85.6% of cases (Figure 4). Of the total number of patients ($n = 118$), 44.9% ($n = 53$) presented eye movement restriction, 10.2% had exposure keratopathy and 51.7% had ocular hypertension (Table 1) - a single patient could present one, or more, comorbidities.

Exophthalmometry results

Based on the exophthalmometry analysis applied to patients, mean eyeball protrusion reached 20.8 ± 3.1 mm in the right eye and 20.3 ± 3.3 mm, in the left eye (Figure 5; Tables 2 and 3).

Surgery requirement rate

In total, 34.7% of patients treated for TAO required orbital decompression, whereas 16.1% of patients underwent eyelid surgery and 8.5% underwent strabismus surgery (Figure 6). In other words, 59.3% of patients required surgery; 11.1% of them required more than one procedure type, whereas 48.2% of them only required one intervention type.

Conservative management features

In total, 48.3% of patients required eye lubricant due to

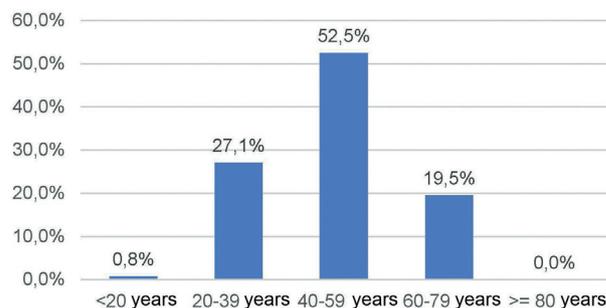


Figure 1: Patients' distribution based on age group

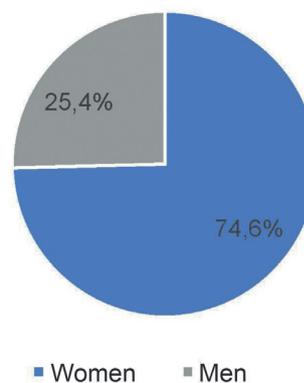


Figure 2: Sex of patients with thyroid-associated ophthalmopathy

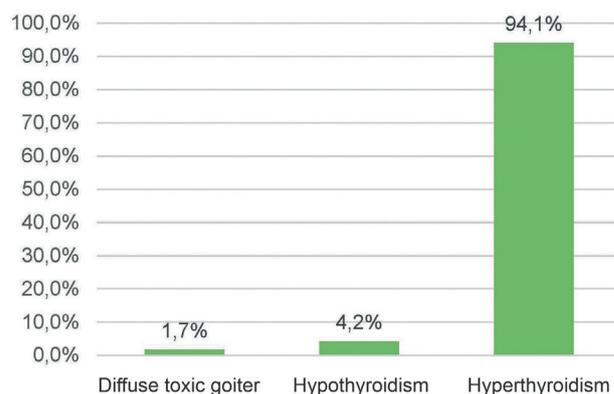


Figure 3: Underlying thyroid disease

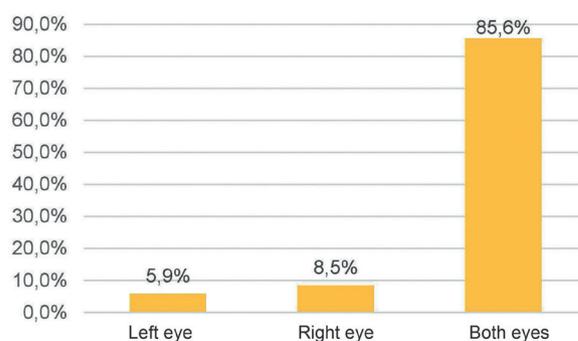


Figure 4: Laterality of the condition

Table 1
Frequency of clinical signs in 120 patients with a diagnosis of dysthyroid orbitopathy ²

Sign	Affected eye	Frequency
Eyelid retraction	-Right eye only.	10
	-Left eye only.	10
	-Both eyes	88
Exophthalmos	-Right eye	2
	-Left eye	8
	-Both eyes	63
Optic nerve dysfunction	-Right eye	2
	-Left eye	1
	-Both eyes	4
Restrictive myopathy	-Right eye only.	5
	-Left eye only.	8
	-Both eyes	38
Evidence of stretching the extraocular muscles	- Left eye only.	1
	-Both eyes	2
	-Both eyes	9
Clinical evidence of thyroid dysfunction		113

Table 2
Exophthalmos degree

Eye	Media ± DE, mm	Range
Right (RE)	20.8 ± 3.1	10 – 29
Left (LE)	20.3 ± 3.3	10 – 28

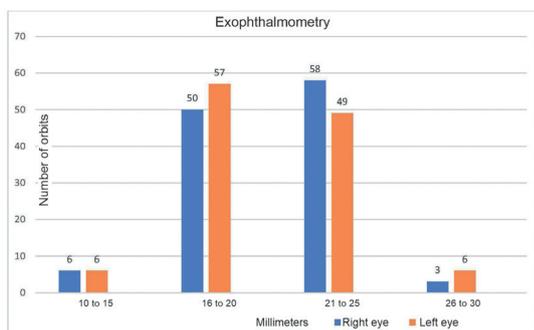


Figure 5: Orbit distribution based on exophthalmometry

Table 3
Patients' classification based on exophthalmos degree

Group	Orbits	Percentage
I (Exophthalmometry < 22mm)	138	58,05%
II (Exophthalmometry ranging from 22 mm to 25 mm)	89	37,71%
III (Exophthalmometry > 25 mm)	9	3,81%

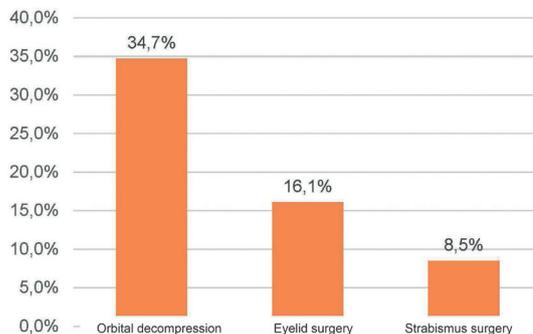


Figure 6: Type of surgical procedure performed on patients

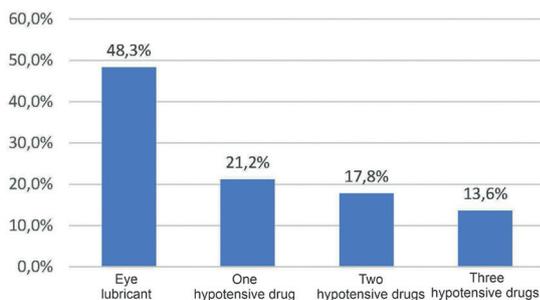


Figure 7: Percentage of patients

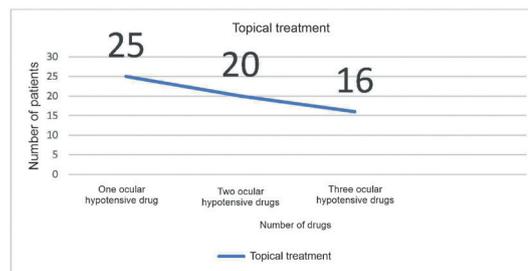


Figure 8: Number of patients who required ocular hypotensive drugs

Table 4
Patients' classification based on exophthalmos degree recorded by Galvis for 107 orbits

Grupo	Órbitas	Porcentaje
I (Exophthalmometry < 22mm)	15	14.02%
II (Exophthalmometry ranging from 22 mm to 25 mm)	64	59.81%
III. (Exophthalmometry > 25 mm)	28	26.17%

eye surface disorders, mainly dry eye, whereas 52.5% of patients required ocular hypotensive drugs; 21.2% of them used one ocular hypotensive drug, whereas 17.8% used two and 13.6% used three ocular hypotensive drugs (Figures 7 and 8).

DISCUSSION

An interesting casuistry of TAO patients has accumulated throughout the evaluated period (11 and a half years). The highest

Table 5
Comparison between TAO findings in the Mexican population and data available in the international literature.

	Similarities	Discrepancies
Patients' distribution based on sex- Female/Male	<ul style="list-style-type: none"> • Bartley y col 2.5-5:1 • CMNO: 3:1 	
Patients' distribution based on age	<ul style="list-style-type: none"> • Bartley et al: 41-50 years • CMNO: 40-59 years. 	
Basic diagnosis	<ul style="list-style-type: none"> • Pérez Moreiras Hyperthyroidism: 90% • CMNO. Hyperthyroidism: 92.22% 	<ul style="list-style-type: none"> • Pérez Moreiras Hyperthyroidism: 0.83% (n=1) DTG*: 0. Euthyroid. 5.8% (n=7) Hashimoto's thyroiditis: 3.3% • CMNO Hypothyroidism: 5.6% (n=5) DTG*: 2.54% TH*: 0%. Euthyroid: 0%
Laterality of the condition	<ul style="list-style-type: none"> • Pérez Moreiras Bilateral. 85-95% (n=110) Unilateral. 5-15% (n=10) Derecha 62.5% Izquierda 37.5% • CMNO Bilateral. 85.6% (n=102) Unilateral. 14.7% (n=16) Derecha 62.5% Izquierda 37.5% 	
Surgery requirement	<p>EYELID</p> <ul style="list-style-type: none"> • (Galvis et al.): 31.7% • CMNO: 16.1% <p>ORBITAL DECOMPRESSION</p> <ul style="list-style-type: none"> • (Lyons et al.) 6: 37.77% • CMNO: 34.7% 	<p>STRABISMUS</p> <ul style="list-style-type: none"> • (Galvis): 29.3% • CMNO: 8.5%
Muscle restrictive pattern	<ul style="list-style-type: none"> • (Bartley et al.) 42.5% • CMNO: 43.22% 	
Optic neuropathy		<ul style="list-style-type: none"> • (Neigel et al.) 8.6% • CMNO. 5.08%
Optic Neuropathy Management		<ul style="list-style-type: none"> • (Neigel et al.)⁷: • 5.2% Orbital decompression • CMNO: 83.4% Orbital decompression.
Ocular hypertension		<ul style="list-style-type: none"> • Bartley et al 25% • Palikhe Sabita et al. 11% • Saleha Sultana et al. 17.5% • CMNO: 52.5%

*TAO. Thyroid-associated orbitopathy; DTG: Diffuse Toxic Goiter; TH: Thyroiditis.

TAO incidence peak was observed in patients in the age group 40-59 years; it was extremely rare in patients younger than 20 years and there was no record of it among patients older than 80 years. The female/male patient ratio of 3:1 has corroborated previous reports.

Five (5) out of 10 patients presented high intraocular pressure. Consequently, they required supportive management based on ocular hypotensive drugs. This ocular hypertension figure is unusually high, since, despite reports on the association between glaucoma and thyroid disease (OR 1.38, 95% CI 1.08-1.76), glaucoma rates often reach 11.9% in patients with thyroid issues, based on Cross et al., in comparison to 52.5% of glaucoma cases observed in TAO patients treated in the CMNO.⁽³⁾

Surgical management was necessary in 6 out of 10 patients in the herein assessed population. Chu et al. reported that 52.8% of patients underwent orbital decompression in comparison to 34.7% of patients in the herein investigated population.⁽⁴⁾ Eyelid and strabismus surgeries were also more often required in the aforementioned report (49.1% and 26.4%, respectively) than in the current sample (16.1% and 8.5%, respectively).

Exophthalmos degree in the herein assessed population was < 22mm in 58.05% of investigated orbits (n = 138) in comparison to the exophthalmos degree reported by Galvis in a study conducted with 107 orbits, among which, 59.81% presented higher exophthalmos degree, within 22-25mm⁽⁵⁾, as shown in Table 4. The herein analyzed population has shown lower trend to exophthalmos > 22 mm.

Based on the current findings, 11.1% of patients required more than one surgery type in comparison to 13.2% of patients in the study by Chu.⁽⁴⁾ In other words, patients' requirement to perform two, or more, surgical procedures in the current study is similar to the one reported in the literature.

Table 5 summarizes clinical similarities and discrepancies in TAO findings observed for the herein assessed population and in previous reports.

CONCLUSION

Six⁽⁶⁾ out of 10 TAO patients assessed in the current population required surgical management. Orbital decompression was performed in 1 out of every 3 TAO patients, which is comparable to previous reports available in the literature. However, eyelid and strabismus surgery requirement rates were lower in the current population.

There was high prevalence of ocular hypertension in the herein assessed patients, and it was much higher than the prevalence reported in previous studies. The current protocol was developed within the framework of an institution of public interest. Thus, it is worth emphasizing that the monthly maintenance of patients with ocular hypertension requires high institutional expenditure, since, unlike what happens with other medications, ocular hypotensive drugs demand chronic using, which, in many cases, cannot be interrupted.

It is possible concluding that prevention is the aim of TAO management processes. Thus, keeping it in mind at the time to assess any dysthyroid patient enables taking effective and early actions to avoid surgery requirements, sequelae and chronic use of topical drugs.

The current sample was relatively small, but it worked as starting point to help better understanding the most frequent forms of TAO presentation in the herein assessed population. The present study opens room for other research branches to help identifying the causes of high ocular hypertension prevalence in the ophthalmology field, as well as patients' lower trend to present significant exophthalmos.

What does the present research add to the literature in this field?

- Understanding the clinical features of TAO in a tertiary healthcare center in Mexico.
- One out of every two TAO patients treated in the investigated institution presented ocular hypertension at some point in disease evolution.
- There was no case of unilateral disease as TAO manifestation secondary to hypothyroidism or diffuse toxic goiter.
- Although left unilateral orbital involvement was the least frequent disease pattern, it recorded higher severity index whenever it happened.
- There was lower incidence of TAO associated with Hashimoto's Thyroiditis and with Euthyroidism (Means Syndrome) in the herein analyzed population; as well as higher incidence of it in patients with Diffuse Toxic Goiter and Hypothyroidism.
- 1.69% of the assessed patients presented retinal detachment.

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