Acta Ophthalmologica

Acta Ophthalmologica 2021

Case Series

Pediatric Graves' orbitopathy: a multicentre study

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ABSTRACT.

Purpose: **Graves' orbitopathy (GO) is a rare condition in children often considered to be a less severe condition than at an older age. The aim of our study was to analyse if there are any factors that distinguish paediatric from adult GO in order to provide guidelines for assessing and managing paediatric GO.**

Methods: **Study design is a multicentre retrospective observational case series; 115 paediatric patients diagnosed with GO who visited our university medical centres in the Netherlands and Iran between 2003 and 2019 were submitted for complete ophthalmological examinations, serological testing and/or orbital imaging. Main outcome measures focussed on the natural course and clinical picture as well as medical and surgical treatment in paediatric GO.**

Results: **Clinical findings included proptosis (n = 97; 84.3%), eyelid retraction (n = 77; 67%) and diplopia (n = 13; 11.3%). Ninety-two patients (80%) presented with mild disease, 21 (18.3%) with moderate-severe disease and two (1.7%) with severe GO. Five patients (4.3%) underwent intravenous glucocorticoids and 25 patients underwent orbital decompression surgery. Strabismus surgery due to primary involvement of extraocular muscles was performed in two patients (1.7%). Overall, rehabilitative surgical treatment was planned in 31 patients (26.9%) with inactive disease. Two patients experienced reactivation of the disease.**

Conclusion: **Despite the fact that paediatric and adult GO are considered two separate entities, they might be the same disease with two different clinical phenotypes. Paediatric GO population presents with a comparable clinical picture regarding both soft tissue involvement and proptosis, which may require surgical intervention. Proptosis was present in the majority of paediatric GO patients. Orbital decompression was performed in 21.7% of patients.**

Key words: Graves' disease – Graves' orbitopathy – orbital decompression – paediatric – rehabilitative surgery – severity – thyroid eye disease

The authors would like to thank Shahzad Tavakoli Rad (Orbital Center, Department of Ophthalmology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands), Annikki de Niet (Orbital Center, Department of Ophthalmology, Amsterdam University Medical Centers , University of Amsterdam, Amsterdam, The Netherlands), Jacquelien Hillebrand (Laboratory for Endocrinology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands) and Ozlem Köse (Orbital Center, The Rotterdam Eye Hospital & Erasmus Medical Center Rotterdam), Rotterdam, The Netherlands) who have contributed in collecting part of data and adding their expertise to the manuscript.

Acta Ophthalmol.

doi: 10.1111/aos.15084

Introduction

Graves' orbitopathy (GO) is an autoimmune orbital inflammatory condition most often associated with Graves' disease (GD), although it can also develop in patients with Hashimoto's disease or even in euthyroid patients (Krassas et al. 2005). In the pathogenesis of GD and also GO, anti-thyrotropin receptor antibodies (TSH-R Ab) play an essential role, stimulating the TSH-receptors expressed in the thyrocytes and orbital fibroblasts. Subsequently, an inflammatory response at the level of the orbital fibroblasts with production of cytokines and glycosaminoglycans is triggered by proliferation of lymphocytic cells and myofibroblasts. These mechanisms cause oedema of the orbital soft tissues and extraocular muscles (EOM) resulting in peribulbar swelling, proptosis, eye movement restriction and even dysthyroid optic neuropathy in severe cases (Szczapa-Jagustyn et al. 2016). GD is much rarer in children than in adults with an estimated incidence rate of 4.58/100 000 population per year, accounting for almost 15% of all paediatric thyroid diseases (Krassas et al. 2005; Jarusaitiene et al. 2016b; Simon et al. 2018). Paediatric GO occurs in approximately one third of cases of paediatric GD, occurring more frequently in children with a family history of autoimmune thyroid disease (up to 60%; Bettendorf 2002) and in countries with a higher prevalence of smoking (Krassas et al. 2005). Once paediatric patients have been diagnosed with GD, they have about the same risk to develop GO as adults, with a similar preponderance to females (Gogakos et al. 2010; Szczapa-Jagustyn et al. 2016). However, paediatric GO has been reported to be milder than in adults, with mainly soft-tissue involvement. Severe symptoms like ocular motility restriction, compressive optic neuropathy, exposure keratopathy or preorbital fat pad expansion are reported to be more common in adults (Bartley et al. 1996). Since smoking represents a risk factor for exacerbation of GO and the smoking prevalence in children is 4% compared to 47% in adults, it is hypothesised that the main reason for these clinical differences is the lack of smoking during childhood (Krassas et al. 2005). Racial factors predisposing to severe GO in young patients have been implicated, but no definite conclusions could be drawn (Papp et al. 2016). The aim of our retrospective study was to analyse the characteristics of paediatric GO population in order to provide guidelines for assessing and managing paediatric GO. A comparison was made between our paediatric GO cohort and adult GO patients as published in the recent literature.

Methods

Study population

A retrospective medical chart review was performed including paediatric GO patients that were seen in university medical orbital centres in the Netherlands (Amsterdam, Rotterdam, Utrecht and Leiden) or Iran (Tehran) between 2003 and 2019. A total of 115 paediatric patients with GO selected from Amsterdam (n = 32), Rotterdam (n = 28), Utrecht (n = 21), Leiden (n = 14) and Tehran (n = 20) were included in this study. Institutional Review Board/Ethics Committee ruled that approval was not required for this study. Data accumulation was in conformity with all state laws and the study is in adherence to the tenets of the Declaration of Helsinki. All paediatric patients were younger than 18 years and were diagnosed with GO based on clinical, laboratory and/or imaging findings according to the criteria suggested by Bartley and Gorman (1995): eyelid retraction in association with thyroid dysfunction, proptosis, optic nerve dysfunction or EOM involvement. For each patient, a paediatric endocrinologist confirmed the diagnosis of GD based on a complete clinical and serological investigation. Orbital specialists collected the following ophthalmological findings: best-corrected visual acuity, slit-lamp examination, intraocular pressure measured by Goldmann applanation tonometry in primary position and upgaze and funduscopy. Collected clinical features included palpebral aperture, upper and lower lid retraction and lid lag, proptosis in mm measured by Hertel's exophthalmometry as well as monocular ductions documented by orthoptic examination. Upper eyelid was defined as normal when the margin was at 1–1.5 mm below the superior limbus while a lower eyelid was considered normal when the margin was at the level of the inferior limbus. We assessed proptosis based on studies of exophthalmometry in different ethnicities as well as on the criteria of Jarusaitiene that defines proptosis as a difference of >2 mm between the two eyes (Kashkouli et al. 2008; Dijkstal et al. 2012; Jarusaitiene et al. 2016a). We assessed the activity stage based on clinical activity score (CAS; Mourits et al. 1997) as well the severity of GO according to the European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy (EUGOGO). These guidelines categorise severity into three groups: mild GO with minor soft tissue involvement, moderate-to-severe GO with moderate soft tissue involvement, constant or inconstant diplopia and sight-threatening GO with visual impairment (dysthyroid optic neuropathy) or severe corneal involvement (Bartalena et al. 2016). Experienced radiologists assessed the imaging studies (computed tomography scan or magnetic resonance imaging). Our primary outcome was documentation of natural course and clinical presentation of paediatric GO. As for the secondary outcomes, we focussed on the treatment protocol of thyroid dysfunction as well as the management of GO ('wait and see,' medical or surgical).

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 26.0 (SPSS Inc., IL, USA). Continuous variables are described as mean with standard deviation or median with interquartile ranges where appropriate. Categorical variables are described as numbers with percentages. In order to test the normality of distribution, the Shapiro-Wilk test was used. Statistical analysis of continuous variables that were not normally distributed was performed using nonparametric tests. For the comparison between two independent groups with continuous variables, the independent samples Mann-Whitney U test was used, and Spearman correlation was calculated for continuous indicators. Kruskal-Wallis tests were performed for the comparison between more than two independent groups. We used Fisher exact test when comparing proportions. Person

Table 1. Demographic data, clinical characteristics and treatment methods of paediatric patients with GO.

	N (%)
Total patients	115
Sex	
Female	93 (80.9)
Male	22 (19.1)
Age at onset thyroid dysfunction (median, interquartile range)	13 (6)
Age at onset eye symptoms (median, interquartile range)	14 (6)
Age at presentation (median, interquartile range)	15 (5)
Ethnicity	115
Caucasian	99 (86.1)
African	11 (9.6)
Asian	5 (4.3)
Family history of GO or thyroid dysfunction	99
Positive	64 (64.6)
Negative	35 (35.4)
Smoking information; available in 82 patients	82
No smoking	71 (86.6)
Current smoker	7 (8.5)
Ex-smoker	2 (2.4)
Passive smoker	2 (2.4)
Thyroid status at presentation; available in 106 patients	106
Hyperthyroid	94 (88.7)
Hypothyroid	2 (1.9)
Euthyroid	10 (9.4)
CAS	
0	61 (53)
1	31 (27)
2	19 (16.5)
3	2 (1.7)
4	0
5	1 (0.9)
6	1 (0.9)
GO severity	
Mild-moderate	92 (80)
Moderate-severe	21 (18.3)
Severe	2 (1.7)
Signs of GO	
Proptosis	97 (84.3)
Eyelid retraction	77 (67)
Von Graefe's sign	60 (52.1)
Eyelid swelling	31 (27)
Lagophthalmos	16 (13.9)
Diplopia	13 (11.3)
Punctate epithelial keratopathy	16 (13.9)
Optic neuropathy	2 (1.7)
Orbital imaging available (CT or MRI)	83 (72.1)
Orbital fat expansion	40 (48.2)
EOM enlargement	47 (55.3)
Treatment of thyroid disease	94 (81.7)
None	6 (6.9)
ATD treatment (block and replace strategy)	68 (72.3)
RAI treatment	15 (15.9)
Block and replace followed by thyroidectomy	3 (3.1)
Levothyroxine	2 (2.1)
TSH (median, interquartile range)	0.06 mU/l (2.49)
FT4 (median, interquartile range)	16 pmol/l (12)
Hertel (mean, ±SD)	
OD	19.79 mm (±3.27)
OS	19.72 mm (±3.39)
Lid aperture (mean, ±SD)	
OD	11.45 mm (±2.25)
OS	11.72 mm (±2.54)

CAS = clinical activity score, GO = Graves' orbitopathy, *N* = number, OD = right eye, OS = left eye, SD = standard deviation, TSH-R Ab = anti-thyrotropin receptor antibodies.

Chi-square test was performed when comparing two categorical variables. For testing if linear relationship between variables exists, we chose the univariate analysis of variance. For all the tests performed in this study, the level of statistical significance was $p < 0.05$.

Results

Demographic data, clinical characteristics and the applied treatments of the 115 paediatric patients with GO are shown in Table 1 and Fig. 1. The median age at diagnosis and first presentation was 15 years (range 0–18) and 81% of the patients' population were girls. From our population, 8.2% of GO occurred before hyperthyroidism, 67.3% at the same time and 24.5% after the occurrence of Graves' disease. Considering the age of GO onset, we did not find significant differences in age distribution between CAS categories ($p = 0.328$), nor between severity groups ($p = 0.959$). Regarding ethnicity, 86.1% of the patients were Caucasian, 9.6% of African origin, 4.3% Asian. Starting from the premises that environmental factors may have an impact on disease evolution, we evaluated the severity across the Dutch and Iranian population. Fisher exact test showed no significant difference in severity status between these two groups ($p = 0.099$), nor in smoking status or CAS. Regarding smoking behaviour, we did not find any significant correlation between smoking and CAS nor between smoking and severity of the disease (Pearson Chi-square test, $p = 0.998$, respectively, $p = 0.421$).

Thyroid status and management

The family history for GO or thyroid dysfunction was positive in almost 65% of patients. At the time of presentation, almost 89% of patients were classified as hyperthyroid. TSH-R Ab was measured using automated competitive binding immunoassays, namely an elecrochemiluminescent immunoassay Elecsys Anti-TSH Receptor (TRAb) (Roche Diagnostics, Mannheim, Germany) with a reference range of 0.3–40 IU/l and a cut-off value of <1.8 IU and a third generation automatic fluorescence enzyme immunoassay (ThermoFischer Scientific, Uppsala, Sweden) with a reference range of 0–40 IU/l and a cut-off value of 3.3 IU/l. All measurements

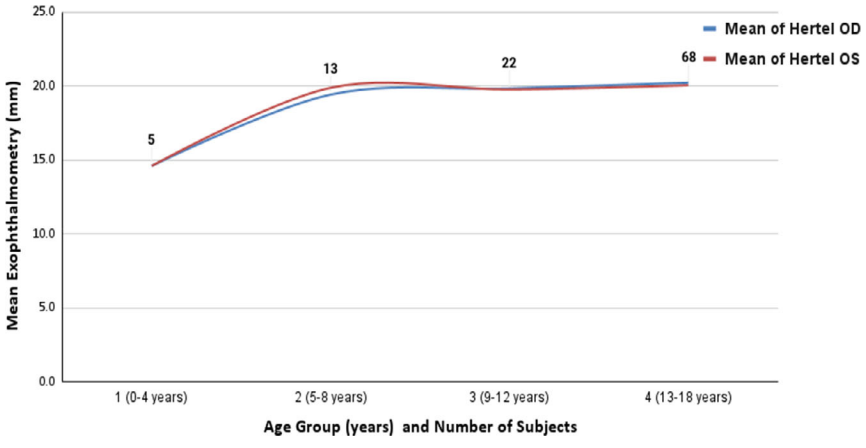

Fig. 1. Mean exophthalmometry and number of patients by age groups.

were performed at the time of the initial presentation before initiation of antithyroid drugs (ATD).

Serum TSH-R Ab measurement revealed positive antibodies in the vast majority of patients (n = 66 out of 75; 88%). All hyperthyroid patients were treated with ATD using a block and replace treatment strategy, 15 patients (15.9%) received definitive treatment with radioactive iodine (RAI; ^{131}I), and three patients (3.1%) eventually underwent thyroidectomy.

Clinical signs and imaging findings

Clinical findings included proptosis (n = 97, 84.3%), eyelid retraction (n = 77, 67%), eyelid swelling (n = 31, 27%) and diplopia (n = 13, 11.3%; Fig. 2). Diplopia was constant in primary gaze in two patients and inconstant in 11 patients. Slit-lamp examination identified conjunctival hyperemia (n = 14, 12.1%), punctate epithelial keratopathy (n = 16, 13.9%), chemosis (n = 6, 5.2%) and caruncular swelling (n = 3, 2.6%). Based on the clinical presentation, 92 patients (80%) were classified with mild GO, 21 patients (18.3%) with moderate-severe GO, while two patients (1.7%) had severe GO with signs of optic neuropathy such as decrease in visual acuity, colour vision impairment and/or visual field defect. Imaging showed muscle enlargement in 55.3% of patients, while orbital fat expansion was noted in 48.2% (Fig. 3).

GO management

Five patients with active GO, or with progressive proptosis were treated according to EUGOGO guidelines (Bartalena et al. 2016) with intermediate-dose intravenous methylprednisolone starting with 500 mg once weekly for the first 6 weeks followed by 250 mg once weekly for the next 6 weeks. Particularly, one 16-year-old girl from Leiden with a CAS of five who presented with dysthyroid optic neuropathy involving visual impairment and visual field defects received the high-dose glucocorticoids protocol consisting of three consecutive pulses of 1000 mg of methylprednisolone as first line therapy, repeated after 1 week. One year later, after treatment and stabilisation of the disease, the patient underwent orbital decompression because of asymmetric proptosis. At the age of 18 years, the patient presented again with active GO and progressive EOM restrictions, for which rituximab was started as second-line treatment with a favourable outcome, i.e., disease remission and no complications. Twenty-five patients (21.7%) with stable, inactive disease underwent orbital decompression surgery (2 or 3-wall decompression with or

Fig. 2. Clinical aspect of a 3-year-old girl with GO (A) Right eye hypoglobus with severe elevation and abduction restriction; (B) Postoperative appearance after strabismus surgery and lower eyelid retraction of the right eye; (C) Postoperative appearance after right lower eyelid lengthening with donor sclera. (Photos courtesy of Peerooz Saeed, MD, PhD).

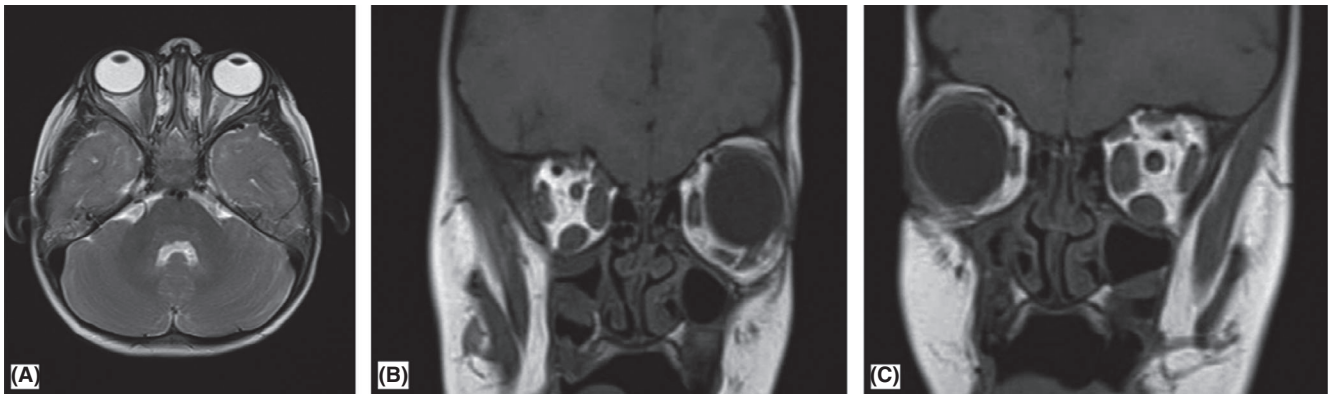

Fig. 3. MRI scan of the same patient (A) Axial T2 weighted image showing enlarged EOMs, especially medial rectus; (B and C) Coronal T1 weighted images showing enlarged medial and inferior rectus.

without fat removal) due to proptosis and its impact on the quality of life (QoL). Out of this group of 25 patients, 21 were female and only four male. Mean age at decompression was 18.2 years (range 15–24 years). Orbital decompression was performed in 17 mild, seven moderate-severe and one severe GO patients. Surgery was only indicated when the patients reached a minimum age of 15 years. Two female patients experienced reactivation of GO after orbital decompression. In the case of one 18-year-old smoking female patient with moderate-severe GO, 6 months after unilateral orbital decompression and strabismus surgery, clinical evidence of progressive proptosis on the same side and a CAS of four pointed towards reactivation of GO for which intravenous glucocorticoids were administered for 12 consecutive weeks. For the second patient, since she already underwent 2 years prior the pulsed intravenous glucocorticoids for sight-threatening GO, rituximab was indicated as second line treatment after reactivation of GO. Strabismus surgery was performed only in two out of 115 patients (1.7%) due to isolated muscle involvement and constant diplopia. Postoperative strabismus occurred in three out of 25 decompressed patients (12%) who required additional squint surgery. Regarding eyelid surgery, upper and lower lid lengthening procedures were performed in 18 patients (15.6%), specifically levator aponeurosis disinsertion and Müllerectomy for upper eyelid retraction and lengthening with donor sclera for lower eyelid retraction, respectively. Overall, rehabilitative surgical treatment was planned in 31 patients (26.9%) with inactive disease. Figure 4 depicts a patient who underwent orbital decompression and eyelid lengthening procedures.

Fig. 4. Top figures: Left proptosis and upper and lower eyelid retraction in a 13-year-old girl with inactive, mild GO. Bottom figures: 2 years later: final postoperative result in the same patient at the age of 15 years after rehabilitative surgery: left orbital decompression and levator disinsertion with Müllerectomy. Note a reduction in proptosis of 4 mm of the left eye and a symmetric eyelid position (Photos courtesy of Peerooz Saeed, MD, PhD).

Exophthalmometry registered weak positive correlations with lid aperture (Spearman's correlation = 0.243, p = 0.02 for OD; Spearman's correlation = 0.361, p = 0.0001 for OS) and with the age at GO onset (Spearman's correlation = 0.189, p = 0.05 only for OD), suggesting that Hertel values increase with age. As expected, the distribution of exophthalmometry differs significantly only between the mild and moderate-severe category ($p < 0.05$ using Kruskal-Wallis test), while no differences were seen between moderate-severe and severe GO (p = 0.842). In the decompression group, six out of 25 children (24%) underwent RAI prior to decompression surgery. From the 90 patients that did not undergo decompression, nine children (10%) required RAI. However, no significant relationship was found between the RAI treatment and the indication for orbital decompression (Fisher exact test, p = 0.091). No patient showed progression after RAI. Within the group of decompressed patients, preoperatively, exophthalmometry differed significantly

Table 2. Comparison of European and Middle Eastern mean exophthalmometry between paediatric healthy subjects (according to literature) and our paediatric GO patients

Ethnicity	Age category (years, number of children in our cohort versus literature)	Mean Hertel OD (mm) in our cohort ± SD;(95% CI)	Mean Hertel OS (mm) in our cohort ± SD (95% CI)	Mean Hertel (mm) (95% CI) in healthy children according to Dijkstal (12)
European	0–4 (4; 79)	15 ± 1.41 (12.7–17.2)	15 ± 1.41 (12.7–17.2)	13,2 (10.1–16.4)
	5–8 (11; 171)	19.09 ± 4.78 (15.8–22.3)	19.4 ± 4.57 (16.3–22.4)	14.4 (11.3–17.4)
	9–12 (11; 164)	19.45 ± 2.77 (17.5–21.3)	19.45 ± 2.94 917.4–21.4)	15.2 (11.9–18.6)
	13–18 (42; 181)	20.03 ± 2.92 (19.1–20.9)	19.7 ± 3.16 (18.7–20.6)	16.2 (12.8–19.5)

		Mean Hertel OD (mm) in our cohort ±SD)	Hertel OS (mm) in our cohort ±SD	Mean Hertel (mm), ±SD) in healthy children according to Kashkouli (11)
Middle Eastern	0–4 (3)	13.03 (±1.21)	13.11 (±1.20)	
	5–12 (6; 289)	20.58 (±2.72)	20.33 (±2.06)	14.2 (±1.8)
	13–18 (13; 319)	19.42 (±2.70)	19.46 (±2.87)	15.2 (±1.9)

OD = right eye, OS = left eye, SD = standard deviation.

between the patients with or without EOM enlargement ($p = 0.006$ for OD; $p = 0.011$ for OS), whereas no significant exophthalmometry differences were found between patients with or without fat volume increase ($p = 0.108$ for OD; $p = 0.388$ for OS). This finding might suggest that patients with muscle enlargement rather than the ones with orbital fat increase were submitted to orbital decompression surgery.

Discussion

Clinical and paraclinical findings

To our knowledge, this study represents the largest cohort of paediatric GO patients published to date. The gender distribution of our patients is similar to most of other studied cohort of paediatric GO patients, males being outnumbered (Goldstein et al. 2008; Lim et al. 2014; Chua et al. 2018). Comparable to adult GO patients from the literature, the female to male ratio in our study was 4:1 (Dolman 2018). We identified eyelid retraction, eyelid swelling and proptosis as main clinical signs, confirming previous results from other studies (Bartley et al. 1996; Krassas et al. 2005). Compared to two studies on exophthalmometry in USA and Iranian healthy paediatric populations, we report significantly higher Hertel values in our group, as highlighted in Table 2. Dijkstal et al. provided the normal distribution of Hertel exophthalmometry for the Caucasian paediatric population categorised in different age subgroups (Dijkstal et al. 2012). Comparing these data, children from our cohort had substantially higher exophthalmometry values in all subcategories. Likewise, according to Kashkouli et al. Iranian children and teenagers register a significantly lower mean exophthalmometry value compared to our cohort of Middle-Eastern GO patients (Table 2; Kashkouli et al. 2008). The fact that there are no solid guidelines for normal exophthalmometry values in a multiethnical paediatric population could be the reason for the discrepancies in proptosis prevalence among the studies. The results of our study showed that proptosis was the most frequent clinical sign of paediatric GO followed by eyelid retraction and eyelid swelling, which is in line with the data published by Chua et al. (2018). Durairaj et al. described eyelid retraction as the most common sign followed by proptosis. Restriction of eye movements was reported in 11% of their patients, comparable with our results (Durairaj et al. 2006). For the detection of TSH-R Ab there are currently two assays available: the competitive TSH-receptor binding inhibitory immunoglobulins (TBII) and the cell-based bioassays that can differentiate between stimulating (TSI) and blocking antibodies (Szczapa-Jagustyn et al. 2016; Kahaly et al. 2018). Recent studies have shown that third generation TBII assays, bridge assays and TSI bioassays are comparable regarding their diagnostic performance in terms of sensitivity/specificity and the predictive power of GO disease course (Villalta et al. 2018; Stohr et al. 2021). At the time of presentation, almost 89% of patients from our group had positive TBII. As expected, in accordance with previous reports, this study showed an increase of exophthalmometry values with age and normal orbital development (Nucci et al. 1989; Dijkstal et al. 2012). Two different adult cohorts from 2000, respectively, 2012 were compared with our paediatric cohort with regard to clinical nonophthalmological and ophthalmological characteristics (Table 3). We observed comparable clinical presentation among the three cohorts of patients with the exception of diplopia and optic nerve involvement. The incidence of performing rehabilitative surgery was almost 27% in our paediatric cohort and 33% in the study of Prummel et al. (2003; Perros et al. 2015).

Imaging

Analysis of neuroimaging from earlier studies revealed EOM enlargement without significant apical crowding, however orbital fat tended to be more enlarged compared to EOM (Holt et al. 2008; Chua et al. 2018). Nonetheless, Wu et al. reported three severe paediatric GO cases with compressive optic neuropathy which showed moderate to severe EOM enlargement and apical crowding on imaging (Wu et al. 2017). In our study, orbital imaging reported a predominance of muscle enlargement rather than orbital fat expansion. This observation might suggest that EOM enlargement contributes more to

Table 3. Comparative data between two different adult cohorts (2000 and 2012) and our present paediatric cohort on clinical characteristics

	2000 (Prummel et al. 2003)	2012 (Perros et al. 2015)	2020 (This study)
Mild GO	41.2%	60.5%	80%
Clinical signs			
Von Graefe's sign	84/143 (59%)	112/243 (46%)	60/115 (52.1%)
Lid aperture (mm)	13.3 ± 2.7	11.43 ± 2.55	11.72 ± 2.54
Lid swelling	113/144 (75%)	166/269 (62%)	31/115 (27%)
Proptosis (mm)	21.5 ± 4.0	20.7 ± 3.54	19.79 ± 3.27
Diplopia	71/145 (49%)	83/263 (31.5%)	13/115 (11.3%)
Corneal involvement	23/148 (16%)	37/266 (13.9%)	16/115 (13.9%)
Lagophthalmos	36/142 (25%)	46/265 (17.3%)	16/115 (13.9%)
Optic nerve involvement	29/149 (21%)	10/258 (3.9%)	2/115 (1.7%)
Thyroid status			
Hyperthyroidism	142/152 (93.4%)	253/269 (94.0%)	94/106 (88.7%)
Hypothyroidism	6/152 (4.0%)	8/269 (3.0%)	2/106 (1.9%)
No thyroid dysfunction	4/152 (2.6%)	8/269 (2.9%)	10/106 (9.4%)
Positive family history	46/139 (33%)	99/269 (38.6%)	64/99 (64.6%)
Treatment of thyroid disease			
Antithyroid drugs	72/141 (51.1%)	117/246 (47.6%)	68/94 (72.3%)
RAI	42/141 (29.8%)	47/246 (19.1%)	15/94 (15.9%)
Thyroidectomy	27/141 (19.1%)	59/246 (24.0%)	3 (3.1%)
Rehabilitative surgery (inactive disease)	33%		26.9%

proptosis development than orbital fat increase. A study hypothesised after a quantitative volumetric measurement of the orbital fat compartment that the enlargement of orbital fat is a rather a late phenomenon, whereas EOM enlargement is related to disease severity (Potgieser et al. 2015). As for apical crowding, this was visible on MRI/CT in three patients with inactive moderate-severe, two of whom underwent orbital decompression surgery.

Management of paediatric GO

The management of adult GO is currently based on the EUGOGO proposed guidelines. Intermediate or high-dose intravenous glucocorticoids are recommended as first-line treatment in the case of active moderate-severe orbitopathy, while sight-threatening orbitopathy should be managed with very high-dose intravenous glucocorticoids (Bartalena et al. 2016). For paediatric GO there is no clear specific therapeutic guideline, due to rare cases of severe disease. Nevertheless, in reserved cases with disease progression and worsening of eye changes, glucocorticoids should be initiated despite its adverse effects as immune suppression, weight gain and even growth failure. In our study, we had five children with active GO who underwent first-line treatment with cumulative doses of intravenous glucocorticoids. Two patients developed severe GO, for which both required intravenous glucocorticoids treatment. According to EUOGO, both were managed with very high-dose methylprednisolone course for three consecutive days repeated after 1 week. Future strategies in the management of adult GO are still being evaluated in clinical trials and interventional studies. Second line treatments with monoclonal antibodies are being constantly revised in adults and the results of the clinical trials are contradictory. While there is no data for use in paediatric patients, there are various monoclonal antibody treatments approved for treatment of GO after completion of randomized placebo-controlled trials, namely teprotumumab (Douglas et al. 2020). However, up to date there are no clinical trials focussing on the outcomes of teprotumumab compared to intravenous glucocorticoids. In addition, the durability of teprotumumab's effect after cessation of therapy is still under research. In phase III clinical trial (OPTIC), 46% of patients with initial proptosis response presented a durable effect in proptosis reduction and 39% presented improvement of diplopia at 72-weeks follow-up (Winn & Kersten 2021). Medications currently used off-label have been consistently shown to be of benefit in steroid-resistant GO, such as tocilizumab (Perez-Moreiras et al. 2018), for which there is safety data available in polyarticular-course juvenile idiopathic arthritis patients (Brunner et al. 2015). Two randomized controlled studies report contradictory results. While Stan et al. report no additional benefit over placebo; Salvi et al. conclude that rituximab could be effective and show clinical improvement when compared with intravenous methylprednisolone. Deltour et al. observed in a retrospective study the efficacy of rituximab in active and early stages of disease (Salvi et al. 2015; Stan et al. 2015; Deltour et al. 2020). Regardless, these are all studies on adults and controversial since many reports on various immunosuppressive therapies included patients previously treated with intravenous glucocorticoids. Recently, Cole et al. (2019) started a trial to investigate whether adjuvant rituximab in combination with ATD will facilitate remission in paediatric patients with GD. Although there are no conducted studies on rituximab in children with GO, in our study, one patient with a CAS of four was treated with rituximab as second line treatment after reactivation of the disease with good response to treatment and no complications. Worth mentioning is that all children from our cohort with indication for any type of immunosuppression were older than 15 years.

Besides medical treatment, a surgical approach can be considered in paediatric GO. Wu et al. (2017) previously highlighted the safety of orbital decompression surgery both in prepubertal and postpubertal patients. So far, studies conducted by Chua et al. (2018), Sherman et al. (2006) and Durairaj et al. (2006) reported rare cases of orbital decompression. The herein described group of paediatric GO patients contains the largest number of patients ($n = 25$) who underwent surgical decompression resulting in a favourable outcome. The normal reference for orbital volume and bone growth during childhood is still debated. While some researchers state that by the age of 8 years, the orbit and globe are up to 96% developed, others state that there is a linear increase in orbital volume throughout the first 15 years of life (Bentley et al. 2002; Escaravage & Dutton 2013). Therefore, since there is a lack of a reliable orbital

growth curve, all orbital decompressions were performed after the age of 15 years. The main indication for the surgery was physical disfigurement caused by proptosis and the profound impact on QoL. Postoperatively, two out of 25 patients (of whom one smoker) developed a reactivation of GO at 6 and 12 months postoperatively, and presented with progressive restrictive myopathy and proptosis. Following rehabilitative bony orbital decompression, Baldeschi et al. (2007) reported an incidence of 1.3% of delayed decompression-related reactivation, while Woo et al. (2017) observed this complication in 7.6% of patients. Although not well known, surgery itself might be a stimulus for the activation of antigen presenting cells with subsequent overexpression of inflammatory cytokines and fibroblasts' proliferation (Baldeschi et al. 2007).

Severity of paediatric GO

Most studies on paediatric GO conclude that the disease course is milder in childhood than in adulthood. Reviewing the frequencies of clinical signs and disease stages in the adult population from literature, we find that our cohort shows many similarities with adult GO. Approximately two thirds of adult GO patients present with mild disease, while one third have moderate-severe disease out of which 5%–7% might develop dysthyroid optic neuropathy (Dolman 2012; Saeed et al. 2018). Consistent with these percentages, in our cohort of paediatric GO patient, 80% of patients were classified as mild GO, 18.3% as moderate-severe, while 1.7% had severe GO. As for the clinical findings, the frequencies of eyelid retraction and periocular lid oedema in the adult population (70% and 25.6% respectively) are very similar to our paediatric cohort (67% respectively 27%), while proptosis was more common in our paediatric group, namely 84.3% compared to other studies that reported a percentage of 62% in adult GO patients (Bartley et al. 1996). Differences in proptosis prevalence could be due to subjective and variate definitions and guidelines. With regard to extraocular motility impairment, we found an important difference between adult and paediatric patients. While restrictive extraocular myopathy can vary between 20% and 43% in adult patients (Bartley et al. 1996; Khong et al. 2016), in our cohort diplopia was seen in only 11.3% of paediatric patients at initial examination. The discrepancy between the low percentage of patients with diplopia and the high percentage of imaging-confirmed EOM enlargement is still ambiguous. However, the authors lean towards the hypothesis of a lesser extend of intramuscular fibrosis in children due to a milder degree of tissue inflammation. The results of our study show that paediatric GO may not be milder than adult GO, as we reported a high incidence of proptosis and in contradiction with other results, a high percentage of paediatric patients that underwent orbital decompression (21.7%) and overall, a similar rate of patients submitted to rehabilitative surgery (26.9%) compared to adult cohorts. Still, some limitations could interfere with the accuracy of the reported data. First, given the fact that it is a retrospective study, we face with missing data especially concerning passive smoking, initial thyroid state as well as serially checked data on TSH-R Ab. Second, since it is a multicentre study, results might be biased due to differences in assessment and treatment protocols. The heterogeneity of immunoassays used for the measurement of TSH-R Ab made the analysis cumbersome. Further prospective studies are needed in order to determine the causative factors. Nevertheless, to our knowledge this study describes the largest cohort of paediatric GO patients to date, presenting valuable data on the clinical characteristics and treatment outcome in this specific population.

Conclusion

Paediatric and adult GO are often being treated as two different entities because of the presumption that the paediatric form is relatively mild in severity and in most cases does not require any medical or surgical treatment. Our study emphasises that paediatric and adult GO are rather two different clinical phenotypes of the same disease. We compared our paediatric GO population with the data on adult GO from the recent literature. Based on the results of this study, paediatric and adult GO patients present with a comparable clinical picture regarding both soft tissue involvement and proptosis, which may require surgical intervention. However, this study showed that EOM dysfunction is less severe; hence, the prevalence of diplopia is lower in children than in adults despite the high proptosis prevalence. Rehabilitative bony orbital decompression in children is indicated in cases with severe proptosis and significant impairment of the patient's QoL. Our data shows that orbital decompression in children older than 15 years is a safe procedure. In conclusion, given the results and favourable postoperative outcomes from our cohort of paediatric GO patients, we recommend performing rehabilitative surgery in patients with functional impairment and in patients with physical disfigurement associated with psychological or social problems.

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Received on April 21st, 2021.
Accepted on December 7th, 2021.

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