CLINICAL STUDY

Childhood Graves' ophthalmopathy: results of a European questionnaire study

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Abstract

Objective: Evaluation of the frequency of Graves' ophthalmopathy (GO) and its management in children and adolescents up to 18 years old with Graves' hyperthyroidism.

Study design: This was a questionnaire study (QS) among members of the European Thyroid Association and the European Society for Paediatric Endocrinology. Approximately 300 QS were sent to members with electronic addresses and 110 QS were returned from 25 countries: 52 respondents said they had no experience with Graves' disease in this age group, but 67 respondents (23 paediatric and 44 adult endocrinologists) completed the QS.

Results: Out of 1963 patients with juvenile Graves' hyperthyroidism seen by respondents in the last 10 years, 641 (33%) had GO; about one-third of GO cases were ≤ 10 years old, and two-thirds were 11–18 years old. The prevalences of GO among juvenile Graves' hyperthyroidism were 36.6, 27.3 and 25.9% in countries in which the smoking prevalence among teenagers was ≥ 25 , 20–25 and $< 20\%$ respectively ($P < 0.0001$ by χ^2 test). When confronted with the standard case of a 13-year-old girl with Graves' hyperthyroidism and moderately severe active GO, the diagnostic approach included on average 4.9 biochemical tests (TSH, free thyroxine (FT₄) and TSH.R-Ab, 100–88% of respondents) and 2.4 specific investigations (thyroid ultrasound by 69%, orthopsy/visual fields/visual acuity by 64% and orbital magnetic resonance imaging or computed tomography by 63%). Antithyroid drugs were the treatment of choice for 94% of respondents; 70% recommended a wait-and-see policy and 28% corticosteroids for the co-existing GO. In variants of the standard case, a younger age did not affect therapeutic approach very much. Recurrent hyperthyroidism would still be treated with antithyroid drugs by 66%, and with ¹³¹I by 25%. Worsening of GO or active GO when euthyroid would convince about two-thirds of respondents to initiate treatment of GO, preferably with steroids.

Conclusion: GO occurs in 33% of patients with juvenile Graves' hyperthyroidism; its prevalence is higher in countries with a higher prevalence of smoking among teenagers. The diagnostic approach to the standard case of a 13-year-old with Graves' hyperthyroidism and moderately severe active GO involves on average five biochemical tests; thyroid as well as orbital imaging is done in 84% of cases. Antithyroid drugs remain the treatment of choice for 94% of respondents, and even so in case of recurrences (66%). For GO, 70% recommend a wait-and-see policy; intervention, preferably with steroids, is advocated by two-thirds of respondents in cases of worsening or still-active eye disease despite euthyroidism.

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Introduction

Graves' disease is frequently associated with clinical manifestations of thyroid eye disease, also called Graves' ophthalmopathy (GO). Graves' disease is the most common cause of thyrotoxicosis, accounting for about 95% of juvenile thyrotoxicosis (1). The paediatric age group of 0–15 years comprises only 5–6% of the total number of thyrotoxic patients (2). It follows that Graves' hyperthyroidism during childhood and

adolescence is relatively rare, occurring mostly in patients with a family history of autoimmune thyroid disease or in the context of associated autoimmune disorders like type 1 diabetes mellitus and Addison's disease (2, 3). The annual incidence of thyrotoxicosis in Denmark is 0.1 per 100 000 in children of 0–4 years with no sex difference; in the age group 5–9 years the incidences are 0.1 and 0.96 per 100 000 for boys and girls, respectively, and between 10 and 14 years they are 0.48 and 3.01 per 100 000 for boys and

girls, respectively (1). Juvenile GO may be even more rare. The most accurate data on the incidence of GO are derived from a population-based cohort study in Olmsted County, MN, USA (4). Incidence rates (cases per 100 000 population per year) in the age groups 5–9, 10–14 and 15–19 years were for females 3.5, 1.8 and 3.3, respectively, and for males 0, 1.7 and 0, respectively. Only 6 out of the 120 incident cases of GO observed in this cohort study were below the age of 20 years. The low incidence explains why there are few studies on childhood GO.

The available studies suggest that childhood GO is less severe than adulthood GO (5). This is evident from a comparison of the relative frequency of the various eye changes between children and adults with GO. Taken the 42 childhood GO cases from four studies published so far (6–9) and contrasting them with 152 new consecutively referred adult GO patients (10), it is clear that soft-tissue involvement and proptosis are the predominant eye changes in childhood GO whereas the more severe manifestations of restricted eye muscle motility and optic dysfunction almost never occur in children. The question then arises why childhood GO is less severe. The female preponderance is similar between children and adults with Graves' hyperthyroidism (87 and 83% respectively), but the prevalence of smoking is much lower in children than in adults (4 and 47% respectively) (9, 10). Smoking is a risk factor for GO, and the odds increase significantly with increasing severity of GO (11). One study observes that the manifestations of GO begin to resemble more closely the adult findings when adolescence approaches (6); conceivably this could be explained by increasing smoking prevalence with age. Because the condition not infrequently starts at puberty, the patients may be seen by either paediatric or adult endocrinologists. In 1994 a European questionnaire study was published on diagnosis and treatment of thyrotoxicosis in childhood (12), and in 1998 a European questionnaire study was published on diagnosis and treatment of GO in adults (13). The issue of childhood GO was not addressed in these two papers.

In view of the above, we embarked on a questionnaire study among members of the European Society for Paediatric Endocrinology (ESPE) and the European Thyroid Association (ETA) with the following specific aims. First, we wanted to know the proportion of GO cases among patients with Graves' hyperthyroidism in the age group of 18 years and younger. Second, we were curious whether childhood GO could be related to smoking prevalence. Third, we wanted to record the diagnostic and therapeutic approaches to a standard case (and some variants) of a 13-year-old girl with Graves' hyperthyroidism and moderately severe active GO. The study design allowed evaluating any differences in approaches between paediatricians and endocrinologists.

Patients and methods

Questionnaires were sent between November 2004 and January 2005 to approximately 300 members of ESPE and ETA who had an electronic address. The questionnaire contained three general questions and a standard case of a 13-year-old girl with Graves' hyperthyroidism and moderately severe active GO (Table 1).

Physicians were asked to outline their diagnostic and therapeutic approaches to the standard case according to a list of given biochemical thyroid-function tests, imaging techniques, specific eye investigations and various therapeutic options. Five variants of the standard case were presented, and physicians were asked whether case variants would change their therapeutic approach chosen for the standard case.

Results

119 questionnaires were returned but 52 respondents indicated they had no experience with the treatment of Graves' disease in childhood. The analysis was thus restricted to 67 returned and completed questionnaires, originating from 23 ESPE members (called paediatricians).

Table 1 The childhood GO questionnaire.

(A) General questions	
1	How many cases of childhood GO (patients up to 10 years old in prepubertal stage) have been seen in your institution in the last 10 years and how many among adolescents (11–18 years old)?
2	How many cases of Graves' hyperthyroidism (up to 18 years old) have been seen in your institution in the last 10 years?
3	Is there an official figure on the percentage of smokers among teenagers in your country?
(B) Standard case	
A 13-year-old Caucasian girl developed over the last 6 months lack of ability to concentrate in school, failure in school, weight loss and nervousness. Pulse rate of 120/min, diffuse goiter around 30 g, and signs of moderately severe and active thyroid ophthalmopathy. Specifically, she had moderately severe eyelid swelling, some chemosis and redness of the eyes, but not caruncle swelling, no pain behind the eyes and no redness of the eyelids. Exophthalmometer reading was 21 mm for both eyes. She also had impairment of elevation for both eyes with inconstant diplopia. She is not a smoker.	
1	What is your diagnostic approach?
2	What is your therapeutic approach?
(C) Case variants	
Is your therapeutic approach to the standard case changed in case of:	
1	slight worsening of GO after 4 months;
2	age of 7 years;
3	age of 15 years, recurrent hyperthyroidism after a course of antithyroid drugs, still active GO;
4	age of 15 years, euthyroid, active GO;
5	driving problems, because of mild diplopia?

cians) and 44 ETA members (called endocrinologists). It should be noted that the ETA membership list does not discriminate between basic scientists and clinicians, so in reality the response rate was much higher. Respondents came from 25 countries, predominantly from Europe but also included one from Brazil, three from the USA and two from Japan (Table 2). Leaving out the results from these six respondents from outside Europe did not make any real difference in the overall results.

A total of 1963 patients with juvenile Graves' hyperthyroidism had been encountered by respondents over the last 10 years; on average 4.6 cases per year by each paediatrician and 2.3 cases per year by each internist. One-third of the patients with Graves' hyperthyroidism had GO. Among the patients with GO, one-third were ≤ 10 years old (77% of them being seen by paediatricians) and two-thirds were in the age group of 11–18 years (56% of them being seen by paediatricians; Table 3).

The answers of respondents with regard to smoking prevalence among teenagers in their country were incomplete and mostly based educated guesswork. Therefore we grouped countries of respondents according to smoking prevalence among teenagers as given by official data from the World Health Organization (WHO; Table 4). A higher prevalence of smoking was associated with a higher frequency of GO among juvenile patients with Graves' hyperthyroidism ($P < 0.0001$ by χ^2 test). Whereas in countries with a smoking prevalence among teenagers of $\geq 25\%$ the distribution of GO cases was 36.6% (236 cases), in countries with a smoking prevalence of $< 20\%$ the distribution was 25.9% (117 cases; Table 4).

The diagnostic approaches to the standard case are listed in Table 5. On average, five biochemical thyroid function tests were requested by respondents, paediatrici-

cians asking one test more than internists (5.6 compared with 4.6, $P < 0.005$). Thyroid-stimulating hormone (TSH), free thyroxine (FT₄) and TSH.R-Ab were almost universally ordered, and thyroperoxidase antibodies (TPO-Ab) and FT₃ by about 60%. Thyroid imaging was requested by 56 of 67 respondents (84%), with ultrasound by 46 and with scan by 10. Orbital imaging was asked by 59 of 67 respondents (88%), with magnetic resonance imaging or computed tomography by 42, with ultrasound by 14 and with octreoscan by 3.

The preferred treatment of Graves' hyperthyroidism of the standard case was clearly antithyroid drugs, chosen by 94% of respondents. A wait-and-see policy was recommended for the co-existing GO of the standard case by 70%, and corticosteroids by 28% (Table 6). The therapeutic approach did not differ between paediatricians and internists. With regard to the therapeutic approach of case variants (Table 7), a younger age of 7 years did not affect management very much. Antithyroid drugs were still the treatment of choice (66%) for recurrent hyperthyroidism, whereas ¹³¹I therapy was now chosen by 25% and thyroidectomy by 9%. Worsening of GO after 4 months or still-active GO when euthyroid was viewed by 68 and 63% of respondents respectively as an indication to start specific eye treatment, mainly with steroids. In case of driving problems, 36.5% recommended eye muscle surgery and 21% prisms. One respondent remarked that diplopia in his experience is never seen in childhood GO.

Discussion

The results of our questionnaire study demonstrate three interesting epidemiological features of childhood GO.

Table 2 Responses to the questionnaire on childhood GO.

(A) Number of returned questionnaires

	Paediatricians	Adult endocrinologists	Total
Returned and completed	23	44	67
Returned, no experience	8	44	52
Total	31	88	119

(B) Number of respondents per country

Italy, 17; UK, 16; Greece, 11; Denmark, 9; Belgium & Germany, each 8;
The Netherlands, Romania & France, each 6; Sweden, 5; Poland & Switzerland, each 4;
Turkey & USA, each 3; Japan & Spain, each 2;
Austria, Brazil, Bulgaria, Canada, Czech Republic, Portugal, Hungary, Russia, & Serbia, each 1

(C) Number of returned questionnaires when six non-European respondents were excluded from the study

	Paediatricians	Adult endocrinologists	Total
Returned and completed	20	41	61
Returned, no experience	8	44	52
Total	28	85	113

Table 3 Number of patients with childhood GO seen in the last 10 years.

	Paediatricians	Adult endocrinologists*	Total
No. of respondents	23	38	61
No. with Graves' hyperthyroidism	1073 (100%)	890 (100%)	1963 (100%)
No. with GO	411 (38.3%)	230 (25.8%)	641 (32.6%)
No. of respondents	21	36	57
No. with GO	364 (100%)	217 (100%)	581 (100%)
No. with GO age $\leq$ 10 years	143 (39.3%)	42 (19.4%)	185 (31.8%)
No. with GO age 11–18 years	221 (60.7%)	175 (80.6%)	396 (68.2%)

* 6 out of 44 returned and completed questionnaires from adult endocrinologists did not answer this question.

Table 4 Occurrence of childhood GO in Graves' hyperthyroidism as a function of smoking prevalence among teenagers.

Smoking prevalence*	No. with Graves' hyperthyroidism	No. with GO
1 $\geq$ 25%	644 (100%)	236 (36.6%)
2 20–25%	818 (100%)	223 (27.3%)
3 < 20%	452 (100%)	117 (25.9%)

* Data per country based on the WHO regional office for Europe, tobacco control database, 2003 (<http://data.euro.who.int/tobacco>). Numbered groups induced the following countries: (1) Turkey, Bulgaria, Germany, Czech Republic, Spain, Hungary and France; (2) Switzerland, UK, The Netherlands, Romania, Belgium, Canada, Russia, Portugal and Poland; (3) Denmark, Italy, Serbia, Sweden, USA, Brazil and Greece.

First, GO occurs in about one-third of patients with juvenile Graves' hyperthyroidism. Second, GO is less common below the age of $\leq$ 10 years than in the age group of 11–18 years. Third, the occurrence of GO is related to the smoking prevalence among teenagers. One may question the accuracy of the obtained study

results in view of the retrospective nature of the questionnaire: respondents had to memorize the cases of juvenile Graves' disease seen in the last 10 years. This certainly constitutes a major limitation of the present study, which is liable to recall bias. In view of the rarity of juvenile Graves' disease (respondents did see on average only 3.2 cases per year), however, we think recall bias is not a major issue in our study: physicians in general remember exceptional cases better than ordinary cases. Moreover, the large number of almost 2000 collected cases of juvenile Graves' disease will in all likelihood effectively neutralize distortion inherent to small case series reported by many of the respondents. We also noted internal consistency in the given answers to the questionnaire: paediatricians, although fewer in number than endocrinologists, did see the majority of childhood GO cases, which is according to expectation.

The 33% incidence of GO among patients with juvenile Graves' hyperthyroidism is rather similar to the corresponding figure for adult patients with Graves' hyperthyroidism. A previous review found GO to be

Table 5 Diagnostic approaches to a standard case of childhood Graves' hyperthyroidism with GO.

	No. of respondents ordering specific tests		
	Paediatricians (n = 23)	Adult endocrinologists (n = 44)	All (n = 67)
TSH	23	44	67 (100%)
FT ₄	23	40	63 (94%)
TSH.R-Ab	21	38	59 (88%)
TPO-Ab	16	26	42 (63%)
FT ₃	18	22	40 (60%)
Tg-Ab	14	15	29 (43%)
TT ₃	8	8	16 (24%)
Tg	2	3	5 (8%)
TT ₄	1	4	5 (8%)
Urinary iodine	3	1	4 (6%)
No. of tests per respondent	5.6	4.6	4.9
Thyroid ultrasound	18	28	46 (69%)
Orthopsy visual fields	16	27	43 (64%)
Visual acuity			
Orbital MRI or CT	12	30	42 (63%)
Orbital ultrasound	7	7	14 (21%)
Thyroid scan	4	6	10 (15%)
Orbital octreoscan	1	2	3 (5%)
No. of tests per respondent	2.5	2.3	2.4

Tg-Ab, thyroglobulin antibodies; TT₃, total triiodothyronine; Tg, thyroglobulin; TT₄, total thyroxine; CT, computed tomography; MRI, magnetic resonance imaging.

Table 6 Therapeutic approach to a standard case of childhood Graves' hyperthyroidism with GO.

	No. of respondents preferring specific treatment		
	Paediatricians (n = 23)	Adult endocrinologists (n = 44)	All (n = 67)
Graves' hyperthyroidism			
Antithyroid drugs	22	41	63 (94%)
Thyroidectomy	1	2	3 (4.5%)
¹³¹ I therapy	0	1	1 (1.5%)
GO			
Wait and see	14	33	47 (70.1%)
Corticosteroids	8	11	19 (28.4%)
Retrobulbar irradiation	0	0	0
Somatostatin analogues	1	0	1 (1.5%)

present in 42 out of 182 (23%) patients with childhood Graves' hyperthyroidism (summarized from four series) and in 118 out of 1050 (18%) adult patients with Graves' hyperthyroidism (taken from four large series) (5). A confounding factor in this respect might be how the presence of GO is established: most endocrinologists would require eye changes of NO SPECS class 2 (soft tissue involvement) or higher classes, whereas some paediatricians diagnose GO already in the presence of only upper-lid retraction or stare with or without lid lag (NO SPECS class 1) (14). One study reported on 40 children with Graves' hyperthyroidism seen in a single institute between 1980 and 1998; the average number of 2.2 cases per year in this study is rather close to the mean number of 3.2 annual cases reported by respondents (frequently on behalf of their institution) in our study.

Among the 40 children, seven were prepubertal, 21 pubertal and 12 postpubertal, with no significant difference in the incidence of GO among the three groups (14). This is again in rather good agreement with our own study results. It is thus reasonable to conclude that GO occurs in about the same proportion of patients with childhood Graves' hyperthyroidism as in adult Graves' hyperthyroidism, and that the lower incidence of GO in the prepubertal stage (age ≤ 10 years) as compared with the (post)pubertal stage (age 11–18 years) is fully explained by the lower incidence of Graves' hyperthyroidism in the youngest age group.

One of the other limitations of our questionnaire study is that we didn't ask respondents to specify the frequency of the various eye changes in their GO patients. We refrained from doing so because recall bias would heavily affect the obtained data. Nevertheless, there appears to be consensus in the literature that severe GO is uncommon in childhood (3, 15). The question thus arises – assuming about equal incidence of GO among children and adults with Graves' hyperthyroidism – of why children have relatively mild GO and adults more severe GO (5). In this respect our study provides a very interesting clue: the difference might be caused by exposure to tobacco smoke. Circumstantial evidence for this statement can be derived from two findings in our study. First, a higher prevalence of smoking among teenagers was related to a higher proportion of GO among patients with childhood Graves' hyperthyroidism. Second, among patients with GO in countries with a smoking prevalence of $< 25\%$ among teenagers, about 20% were ≤ 10 years old and 80% were 11–18 years; in contrast, in countries with a smoking prevalence of $\geq 25\%$ the distribution among the two age groups was roughly

Table 7 Therapeutic approach to variants of a standard case of childhood Graves' hyperthyroidism with GO.

Variation	No. of responders	Response	
1 GO a bit worse after 4 months. Will you initiate treatment?	59	Yes	40 (68%)
		Probably	3 (5%)
		No	16 (27%)
2 The patient is 7 years old. Is your therapeutic approach the same?	47	Yes	38 (81%)
		No	9 (19%)
3 The patient is 15 years. Recurrence of hyperthyroidism 2 years after ATD. GO still active. What kind of treatment for hyperthyroidism do you recommend?	44	ATD	29 (66%)
		RAI	11 (25%)
		Surgery	4 (9%)
4 The patient is 15 years old, euthyroid, with active GO. What type of treatment do you recommend?	52	Nothing	13 (25%)
		Steroids	30 (57%)
		SM-analogues	3 (6%)
		ATD	3 (6%)
		Eye drops	3 (6%)
5 The patient has driving problems because of mild diplopia. What would you recommend?	52	Surgery	19 (36.5%)
		Prisms	11 (21%)
		Nothing	7 (13.5%)
		Refer	6 (11.5%)
		SM-A analogues	4 (8%)
		Irradiation	3 (5.5%)
		Steroids	2 (4%)

ATD, antithyroid drugs; RAI, radioactive iodine; SM, somatostatin; SM-A, somatostatin analogues.

50% and 50%. As it is unlikely that children below the age of 10 are all smokers, the overrepresentation of GO in children below 10 years living in an environment in which 25% or more of their peers smoke might be due to passive smoking.

With regard to the diagnostic approach to the standard case of Graves' hyperthyroidism, the results are almost identical to those obtained in the questionnaire study on this topic 11 years ago (12): virtually all respondents order TSH and FT₄, and at least two-thirds measure also TSH-R-Ab and TPO-Ab. Thyroid imaging is done in 84% of cases; in the 1994 study a thyroid scintiscan was performed in 40% and thyroid ultrasound in 56%. Antithyroid drugs remain the treatment of choice (chosen by 94% in the present study and by 99% in the 1994 study), even in case of recurrent hyperthyroidism (66% in the present study, 86% in the 1994 study). It is obvious that there remains a big discrepancy in the therapeutic approach of juvenile thyrotoxicosis between the USA and Europe. ¹³¹I therapy has been recommended for a long time in the USA also for children (15, 16), but European physicians are reluctant to apply ¹³¹I therapy at young age because of concern for long-term adverse events induced by ionizing irradiation.

With regard to the management of childhood GO, 84% of respondents requested some kind of orbital imaging (computed tomography, magnetic resonance imaging or ultrasound), 64% ordered specific ophthalmological investigations and 70% recommended a wait-and-see policy for the eye changes. Active intervention (predominantly with steroids) was considered appropriate in case of worsening of eye changes or no improvement of eye changes when the patient had become euthyroid. There was little enthusiasm for alternative treatment options like somatostatin analogues or retrobulbar irradiation. There was no difference in approach between paediatricians and endocrinologists. The chosen approach is akin to that in adult patients with GO.

Childhood GO really has a very low incidence. From our data it can be calculated that an individual endocrinologist or endocrine center will see about one case per annum. To obtain more reliable epidemiological data or to perform randomized clinical trials for delineating optimal treatment of childhood GO requires collaboration in multicenter studies across a number of countries.

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