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CASE REPORT

Clinical features of pediatric Graves' orbitopathy

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Abstract Pediatric Graves' orbitopathy is rare, thus its clinical picture is less well defined in comparison with the adult population. Therefore it is our aim to describe the clinical spectrum at our tertiary referral center. We identified 11 patients under the age of 18 years (3♂, 8♀; range 3–16 years, mean age 14.5 years) with Graves' disease and signs of orbitopathy. Seven of them where reevaluated (mean follow-up 25 months, range 3–66 months). Eyelid retraction and proptosis were the predominant signs in 10/11 of our patients. In six patients, Hertel readings ranged from 22 mm or above. Mild ocular motility impairment was seen in four children. Active orbitopathy or severe impairment of visual acuity/ocular motility, corneal or optic nerve involvement was not observed in our study. Our series confirms that pediatric Graves' orbitopathy lacks significant inflammatory features; however, proptosis is common and may be marked. All seven patients who were reevaluated did not show any clinically significant change of ocular signs during the observation period. In particular, there was no improvement of proptosis despite restoration of euthyroidism.

Keywords Children · Graves' disease · Graves' orbitopathy · Orbitopathy · Pediatric

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Graves' orbitopathy (GO) is an autoimmune inflammatory orbital disease strongly linked to autoimmune hyperthyroidism [syn. Graves' disease (GD)]; it may rarely be seen in patients suffering from Hashimoto's thyroiditis, or even in euthyroid patients [1, 2]. Autoimmune hyperthyroidism is the most common cause of juvenile thyrotoxicosis in children and adolescents [3, 4]. Its incidence in Europe has been reported to be 0.8 per 100,000 children per year, the female-to-male ratio being about 3:1 up to 5:1 [2, 5]. Family history of thyroid disorders is found in 19–48% of cases [2, 6–8]. The diagnosis of GD is based on clinical signs of thyrotoxicosis, hyperthyroidism on laboratory thyroid function testing, and the presence of thyroid-stimulation autoantibodies [2, 9, 10]. Treatment options for GD are antithyroid medication (carbimazole, methimazole, propylthiouracil), surgery (near-total, subtotal/total thyroidectomy), and radioiodine [5, 11, 12]. In Europe, the first choice of treatment would be medical. Second-line therapy consists of surgery [4, 5, 11].

As GD and thus GO is less common in children than in adults, its clinical picture is less well defined

in comparison with the adult population. Incidence rates of GO in children are between 1.7 and 3.5 cases per 100,000 population per year [3] and 0.79–6.5 per 100,000 children [1]. Most studies conclude that ocular signs of GD in this age group are milder than in adults [4, 6, 7, 9, 13, 14]. Occurrence of GO-related eye symptoms has been reported to be similar to adulthood, being found in one- to two-thirds of all children suffering from GD [1–3, 5, 7, 10, 12]. GO is less common in children under the age of 11 years (31.8%) compared with adolescents (11–18 years: 68.2%) [3].

Pediatric GO is generally considered to be mild, and consequently therapy mostly consists of a wait-and-see policy [3]. It remains unclear why a more severe course of this disease is usually not encountered at this age. A possible explanation is that severe GO is more often seen in smokers—active smoking being unusual in childhood. In the rare event of active or more severe orbitopathy, systemic administration of corticosteroids [1], orbital fat decompression and eyelid surgery [6] have been performed in selected cases.

Methods

The records of patients with the diagnosis of childhood GD seen in the Department of Pediatric Endocrinology of the Children's Hospital and the Department of Ophthalmology of the Johannes-Gutenberg-University in Mainz, presenting with clinical signs of GO, were reviewed retrospectively.

Diagnosis of GD was based on clinical, sonographic, and laboratory findings. All patients had thyroid stimulating hormone receptor (TSHR) stimulating antibodies. The following ophthalmological findings were recorded: best-corrected Snellen acuity, slit-lamp investigation (Haag Streit BQ 900; Haag Streit, Könitz, Switzerland), intraocular pressure obtained by Goldmann applanation tonometry in primary position in mmHg (Goldmann applanation tonometers; Haag Streit), proptosis measured by Hertel's exophthalmometry (Oculus, Wetzlar, Germany) in mm, monocular ductions documented in degrees, eyelid signs (lid aperture, upper and lower lid retraction; normal upper eyelid position was considered to be 1–1.5 mm below the superior limbus, normal lower eyelid position was considered to be at the level of the inferior limbus [9]) as well as direct and indirect funduscopy.

Table 1 Normal exophthalmometric values (in mm) in children according to [17]

Age (years)	50th percentile	3rd; 97th percentile
3–5	9.5	6; 14
6–7	11	7; 14
8–10	12	8; 15

Normal exophthalmometry in European (Caucasian) adults is reported to be less than 20 mm, with an inter-eye difference of less than 2 mm [2, 9, 15]. However, normal values depend on type of exophthalmometer, age, and gender [16]. Normal values for children under the age of 11 years are reported by Nucci (Table 1) [17]. Reliable normal values for older children are not available due to extreme variability recorded during puberty [17]. Therefore, we assumed a pathological protrusion of the globe in children below 11 years, if values were above the 97th percentile as given in Table 1. In patients aged 11 years and older, values >19 mm were considered pathological.

General information recorded in the charts included age, sex, age at onset of GO and GD, treatment of thyroid dysfunction, and smoking history. All investigations were performed according to the Declaration of Helsinki.

Results

Between August 2002 and October 2008, 11 patients with GO were investigated. Clinical data are presented in Table 2. Mean age at diagnosis was 14.5 years (range 3–16 years). Ten patients showed pathological exophthalmometry readings, as defined in the "Methods" section. Upper lid retraction (6/10 patients) was not very marked. In contrast, lower lid retraction was more frequent, more pronounced, and persisted during follow-up. Four patients exhibited a limitation of ductions, however this only affected the extremes of gaze and did not result in a subjective complaint of double vision. The remainder of ophthalmological examination (slit lamp, intraocular pressure, funduscopy) was unremarkable. None of our patients showed a relevant impairment of visual

Table 2 Clinical data

Case no.	Age (years)[a]/ sex (f/m)[b]	First visit/ follow-up (months)	Thyroid status	Lid retraction (mm)		Lid aperture (mm)	Exophthalmometry (mm)	Ocular motility	CAS[d]	BCVA[e]
				Upper	Lower					
1	10/f		Euthyroid	0/0	1/1	13/13	22/22	Normal	1/7	1.0/1.0
		12	Euthyroid	0/0	1/1	n.d.	23/23	Limited[c]	1/7	1.0/1.0
2	3/f		Hyperthyroid	0/0	1/1	9/9	18/18	Normal	0/7	1.0/1.0
		60	Euthyroid	1/1	1/1	11/14	19/20	Limited[c]	0/7	0.8/0.8
3	7/f		Euthyroid	0/0	1/1	n.d.	n.d.	Normal	0/7	1.0/1.0
		3	Euthyroid	1/1	1/1	9/9	18/18	Normal	0/7	1.0/1.0
4	10/f		Hyperthyroid	1/1	1.5/1.5	16/16	19/18	Normal	0/7	1.0/1.0
		66	Euthyroid	0/0	1.5/1	12/11	19/21	Normal	0/7	1.0/1.0
5	16/f		Hyperthyroid	0/0	1/1	12/12	24/25	Normal	1/7	1.0/1.0
		28	Euthyroid	0/0	2.5/2.5	12/12	24.5/25	Normal	1/7	1.0/1.0
6	16/m		Hyperthyroid	0/0	1/1	12/13	23/23	Normal	2/7	1.0/0.8
		25	Euthyroid	0.5/0.5	1/1	11/12	20/22	Normal	1/7	1.0/1.0
7	10/f	0	Euthyroid	n.d.	n.d.	10/9	24/24	Normal	1/7	0.8/0.8
8	15/m	0	Euthyroid	0/0	1/1	14/14	23/23	Limited[c]	1/7	1.0/1.0
9	15/m	0	Hyperthyroid	1/1	1/1	n.d.	19/17	Normal	0/7	1.0/1.0
10	16/m		Euthyroid	0/0	3/3	15/15	25/26	Limited[c]	2/7	1.0/1.0
		8	Euthyroid	0/0	3/3	15/15	25/26	Limited[c]	1/7	1.0/1.0
11	14/f	0	Hyperthyroid	1/0	0/2	14/12	19.5/19	Normal	0/7	1.0/1.0

[a] Age at initial presentation; [b] f = female, m = male; n.d. = not done; [c] limited to the extremes of gaze; [d] CAS = Clinical Activity Score; [e] BCVA = best-corrected visual acuity

acuity. Despite quite marked proptosis, none of our patients showed any significant inflammatory signs and symptoms as reflected by low Clinical Activity Scores (CAS, see Table 2) [18].

There was no history of active smoking in any of our patients. Passive smoking was reported in patients 7 and 10. Follow-up data were available in seven children (mean follow-up 25 months, range 3–66 months).

Discussion

The clinical manifestation of GO in all 11 patients consisted of eyelid retraction and proptosis. Lower lid retraction was detected in all patients exhibiting proptosis, and thus most probably reflects protrusion rather than mere lid involvement. The frequency of these findings is very similar to that reported in other studies, finding lid retraction in 84.5% and proptosis in 74% [9]. Despite the quite marked proptosis—six children had Hertel readings of 22 mm or more—we did not see corneal involvement. Signs of active orbitopathy as defined by Clinical Activity Score [18] (chemosis, lid swelling and redness, etc.) were lacking. None of the children developed severe GO, and administration of antithyroid drugs was sufficient to control hyperthyroidism. None of our patients received any specific treatment for eye disease. During the observation period four patients showed mild extraocular muscle dysfunction. The low frequency of extraocular muscle involvement is well known [2, 9, 14]. Thus, our small series confirms other studies describing rather mild clinical characteristics of GO in childhood [7, 9, 14].

Remarkably, restoration of euthyroidism did not result in pronounced improvement of ocular signs, especially proptosis. This feature of pediatric GO is well known, but not well understood [7, 9, 14, 16]. Liu et al. and Uretsky and co-workers found

persisting proptosis in children during follow-up as long as 6 years [7, 13]. To a certain extent this finding might be explained by the problem of exophthalmometry during adolescence; as measurements tend to increase with age [17, 19] and especially in puberty, this could in part account for the higher values detected in this age group. Nevertheless, the lack of clinical improvement parallel to normalization of thyroid function seems to contrast with GO in adult patients: Perros and co-workers reported that, during an observation period of 1 year, 64.4% of adult GO patients showed improvement of their orbitopathy, restoration of euthyroidism being the only therapeutic intervention [20]. In this latter regard, our study population is quite similar to Perros' data, as in our patients only treatment with antithyroid drugs was needed to achieve euthyroidism. On the other hand, clinically satisfactory improvement of proptosis is often missing even in the adult population, necessitating decompression surgery.

Though our study is small and suffers from bias due to its retrospective nature, we are confident that this lack of GO improvement detected in our patients is not only due to the study design. Obviously, the natural course of childhood GO differs significantly from that seen in adulthood.

In summary, our case series confirms previous data, characterizing pediatric GO to show remarkably little inflammatory activity and to lack severe, sight-threatening complications. While this difference may in part be attributed to differing smoking habits—explaining the more pronounced inflammatory component and eye muscle involvement in adult GO patients [21]—the low tendency to improve as euthyroidism is restored still remains to be explained.

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