CASE REPORTS

CONTEMPORARY DIAGNOSTIC AND THERAPEUTIC ABILITIES IN CHILDHOOD THYROID-ASSOCIATED OPHTHALMOPATHY WITH A CLINICAL CASE DESCRIPTION

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ABSTRACT

INTRODUCTION: Eye symptoms are comparatively frequent in the clinical evidence of Basedow’s disease in childhood. Severe forms of thyroid-associated ophthalmopathy are casuistic in pediatric patients. Early diagnose and evaluation of the severity of thyroid orbitopathy and relevant specialist treatment are key prognostic factors according to the contemporary consensuses.

AIM: The aim of the present study was to make a review of the contemporary diagnostic and therapeutic abilities in pediatric patients with Basedow’s disease and thyroid-associated ophthalmopathy. We present a clinical case of severe TAO in an 11-year-old girl with Basedow’s disease. The combined therapeutic scheme based on the EUGOGO (European Group on Graves’ orbitopathy) consensus of 2008 includes not only thyrostatics but also local ophthalmic agents and pulse corticosteroid therapy, followed by an alternating dose regimen. The favourable outcome of the treatment is determined to a great extend by the close collaboration between the pediatric endocrinologist and the ophthalmologist.

CONCLUSION: It is concluded that children with thyroid-associated ophthalmopathy should promptly be referred to a specialized centre for evaluation of the severity of orbitopathy and an adequate therapy. This is of crucial importance for the preservation of patient’s sight.

Key words: Basedow’s disease, childhood, thyroid-associated ophthalmopathy, therapeutic regimens

INTRODUCTION

Thyroid gland diseases are the second most frequent endocrinopathies in childhood after diabetes and the condition of hypothyroidism is the prevailing one. The serious effects on the intellectual development of the child when the diagnosis of congenital hypothyreosis is delayed make it very necessary to have specialized knowledge and examination.1,2

Far rarer in childhood are the disorders with hyper-function of the thyroid gland, in particular Basedow’s disease. Because of that and in view of the more untypical course of the disease in children, Basedow’s disease is usually not considered, all the more that the initial symptoms may be non-specific and are often related to the characteristics of puberty when the disease first appears usually.3

The incidence of Basedow’s disease in childhood varies within wide limits as reported by different studies. In the USA, for example, approximately 10% of the children born to mothers with Basedow’s disease had elevated levels of the thyroid hormones, but only 1-2% had clinical evidence of hyper-thyroidism. A Dutch study reported that the national annual incidence of thyreotoxicosis in 0-14 years children was 0.79 per 100 000. The maximum frequency was in the age group from 10 to 14 years.4 Marked differences in the incidence of the disease were found for the various countries and ethnic groups. A recent study in Hong Kong for example documented an incidence of 6.5 per 100 000 Chinese children.5

Except for the cases of neonatal hyperthyroid-

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Received 01 March 2010; Accepted for publication 31 March 2010
ism, which are extremely rare, thyreotoxicosis in late childhood is usually a manifestation of the autoimmune disorder Basedow’s disease. It is characterized by diffuse enlargement of the thyroid gland, hyperthyroidism and, not so rarely, by ophthalmopathy. The pathogenesis of the disease is associated with the production of antibodies against TSHR – the TSH receptor of the thyroid gland cells. The reasons for the ophthalmopathy are not clarified to the full, but it is supposed that there is a cross-reactivity of the circulating antibodies against the thyroid antigens with the antigens of the orbital and extra-orbital tissues (particularly the orbital preadipocyte fibroblasts and the retro-orbital muscle antigens). The varied clinical evidence of thyroid-associated ophthalmopathy (TAO) depends on the main tissue damage. The orbital cytokines produced by the antigen-stimulated T-Ly and by the fibroblasts play a key role in the pathogenesis of ophthalmopathy.6,7

The severity of TAO in childhood is smaller in comparison with adults. Severe forms of the disorder are mostly found in adolescent patients, and modern studies have definitely proved the key role of smoking, which becomes more frequent in that period of life. Even passive smoking alone is a risk factor. The incidence of TAO is greater in countries where smoking is more popular among the adolescent population. One European study reported TAO in 33% of the pediatric patients with Basedow’s disease.8

Over the last 5 years, 15 children with Basedow’s disease with clinical and laboratory evidence have been hospitalized at the Clinic of Pediatric and Genetic Diseases in Plovdiv. Eleven of our patients had eye symptoms of various severity ranging from mild exophthalmos to TAO. Two of the children had to undergo a high-dose continuous treatment of the ophthalmopathy. Our detailed literature survey, the good results we obtained and the comparatively poor experience of pediatric endocrinologists in the treatment of this rare complication were the cause to present one of these cases.

In the present article we demonstrate a case of an 11-year-old girl with Basedow’s disease and severe form of TAO. The timely diagnose and the adequate treatment received by the patient in accordance with the modern consensuses was of crucial importance for the favourable outcome for the patient.

CASE DESCRIPTION

G.K. HPC №№ 4762/08, 3832/09, 4563/09. At the time of her first hospitalization at the Clinic of Pediatric and Genetic Diseases in Plovdiv the girl was 11 years old. She had a normal past history but had a family history of thyroid pathology - the mother had clinically proven Basedow’s disease with moderate thyroid-associated ophthalmopathy. About one year before admission to the clinic the child had increasing vitiligo. Several months later the following symptoms appeared: excessive tearing, progressive exophthalmos, increased sweating, weight loss of 5 kg, headache, emotional instability, easy fatigability. After 6 months the family asked for physician’s help – ophthalmologist, who referred the child to the Pediatric Department of Endocrinology at the Pediatric clinic in Plovdiv with the diagnose of Basedow’s disease. The outpatient ophthalmic status showed moderate exophthalmos after Hertel – base 100 mm, OD – 17 mm, OS – 16 mm at preserved eye motility in all directions, mild retraction of the upper eyelid and a hint of periorbital edema. Eye bottoms did not show pathological changes. Child’s medical status at admission showed: marked emotional instability up to non-adaptive behaviour, localized periorbital vitiligo, thyrotoxic facies, fine shaking tremor of the upper limbs, tachycardia to 134/min at sleep, blood pressure 125/50 mm, I-B grade of symmetrically enlarged thyroid gland with soft-elastic consistency and smooth surface. The biochemical and hormonal tests confirmed the clinical diagnose. Characteristic for Basedow’s disease was the echographic image of the thyroid gland – it was diffusely enlarged and with a well-established blood supply. Treatment with an oral thyrostatic was started – metizol at a high initial dose, as well as with a beta blocker – propranolol. The follow up of the child showed that treatment had a good therapeutic effect, which allowed gradual reduction of the thyrostatic dose. Table 1 presents the results of the laboratory tests in dynamics.

In July 2009 there was relapse of the thyrotoxic symptoms – weight loss, tachycardia, sweating, easy fatigability, muscle weakness, significant increase of the exophthalmos to total eyelid retraction and excessive tearing. The family asked for help only two months after the onset of the new complains and once again the ophthalmologist referred the child for immediate hospitalization to the Pediatric clinic. Apart from the common hyperthyroid clinical evidence it was the ophthalmic status of the patient that aroused alarm: bilateral ophthalmopathy to inability to close the eyelids, positive signs of Graefe and Möbius, conjunctival hyperemia and punctate epithelial erosions in the lower half
of the cornea. Enlargement of the thyroid gland was also detected – both by palpation and by ultrasound study. The biochemical tests showed moderate elevation of the liver enzymes’ levels, marked elevation of the thyroid hormones and the TSH plasma levels were 0.00.

The severity of the clinical evidence of thyrotoxicosis and the severe form of TAO with corneal involvement imposed high-dose thyrostatic and beta-blocker treatment as well as immediate start of pulse therapy with methylprednisolone – 0.250 g MPS i.v., twice a day, for 3 consecutive days. Calcium and potassium treatment was also added as well as local ophthalmic therapy with systane and corneregel. After the end of pulse therapy we started alternating treatment with dehydrocortisone in doses of 30 mg every other day. One month later the child’s clinical status was manifestly improved, her weight had not changed, the heart frequency was normal and the blood pressure was 90/60 mm. Additional enlargement of the thyroid gland was detected, more solid consistency and marked non-homogeneity at echography. The results of the laboratory tests showed improvement. However, the exophthalmometry did not show significant dynamics and there was increased intraocular pressure so it was imperative to add cusimolol.

The control ophthalmic examination in December 2009 showed: exophthalmometry - basis 100 mm, OD 24 mm, OS 22 mm; preserved motility in all directions; epithelial erosions of the lower half of the right cornea. The thyrostatic treatment was temporary reduced but the new laboratory results imposed restoration of the high doses. The dose of dehydrocortisone remained unchanged - 30 mg every other day. After another consultation with an ophthalmologist in January 2010 the child was hospitalized for a second course of pulse therapy with methylprednisolone (300 mg i.v daily, for three consecutive days). In spite of the improved hormonal indicators the high-dose thyrostatic treatment was continued and L-thyroxin was additionally included in a dose of 25 μg daily. The further follow-up of the patient will indicate whether it will be necessary to apply other methods of treatment – medicinal and/or surgical.

DISCUSSION

Because of the comparatively low incidence of Basedow’s disease in children the correct diagnose of the disease is often late for several months. The usual alarming symptom to ask for help is poor concentration which results in certain problems with the school rates and patients usually are referred to different specialists – psychologists, neurologists and psychiatrics. Only after the appearance of more specific symptoms – enlarged thyroid gland, constant tachycardia, palpitations, fatigability, reduced tolerance to physical activity, increased intestinal peristalsis and nycturia, the diagnose becomes available.9

Basedow’s disease is often associated with eye symptoms as well – thyroid-associated ophthalmop...
pathy, orbitopathy (TAO, Graves orbitopathy), but usually the eye disturbances are milder than in adult patients. Mild eyelid retraction should be distinguished from the real exophthalmos. The quantitative assessment of the degree of eye-ball protrusion is performed by an ophthalmologist. The protrusion may be demonstrated parallel to edema of the eyelid and redness of the conjunctiva. Sometimes TAO may precede the manifestation of hyper-thyroidism by years – a fact that makes diagnose and in-time treatment difficult. Very rarely childhood TAO is of a severe form and necessitates the participation of a specialist-ophthalmologist in the treatment. It turns into a leading pathologic syndrome in Basedow’s disease because of the risks of severe damage of the optic nerve.\(^5\)\(^,\)\(^10\) In our study nearly all of the patients with Basedow’s disease had eye symptoms as well, but severe ophthalmopathy was found in only 2 of them – that means less than 1/5 of the hospitalized children.

Ophthalmopathy can be considered as\(^11\):

**Non-infiltrative ophthalmopathy, with functional alterations**, caused by the increased sympathetic tonus in hyperthyroidism:
- Bright and staring gaze
- Graefe’s sign
- Widened palpebral fissure
- It may be corrected by hyperthyroidism treatment

**Infiltrative ophthalmopathy**

1. Swelling of the intra-orbital tissues:
   - eyelids, loose connective tissue, conjunctivae, lacrimal glands - pain, irritation, stinging tearing, photophobia
2. Bulbar protrusion
   - > 20 mm (normal 18 – 20 mm)
   - constant lagophthalmos
   - corneal ulcerations
3. Infiltration of the oculomotor muscles (OMM)
   - paresis or paralysis of OMM
   - pain and diplopia – spontaneous or during motion
   - strabismus
4. Involvement of the optic nerve and the retina
   - retina – venous congestion and hemorrhages
   - edema of the papilla
   - defects in the parameters
   - reduced visual acuity to blindness
5. Increased intraocular pressure
6. Complications
   - fixed strabismus
   - panophthalmitis
   - optic nerve atrophy

**Examinations to confirm the diagnose TAO and to determine the degree of its severity.\(^1\),\(^5\)**
- TSH, FT\(_4\)
- MAT
- TRAB
- Hertel exophthalmometry
- Eye bottoms
- Visual acuity, intraocular pressure (IOP), perimeters, double vision
- Computed tomography of the orbits – transversal and frontal slices
- Echography of the orbits

In 2008 EUGOGO (European Group on Graves’ orbitopathy) suggested a consensus on defining the severity and activity of ophthalmopathy and the adequate therapeutic approach.

**Classification of TAO (EUGOGO, 2008).\(^1\),\(^12\),\(^13\)**

**Severe sight-threatening form** – with involvement of the optic nerve (DON-Dysthyroid Optic Neuropathy) and/or the cornea (ulcerations). This category warrants immediate treatment with pulse-Methylprednisolone – MPS, usually followed by treatment with oral corticosteroids (CS). If there is no significant improvement of DON after 1-2 weeks, the pulse dose should be repeated, and, if necessary, surgical decompression of the orbit should be carried out.

**Moderate form** – it is characterized by one or several of the following manifestations – eyelid retraction ≥ 2 mm, involvement of the periorbital soft tissues – edema, conjunctival injection, chemosis, proptosis ≥ 22 mm after Hertel for the Caucasian race; inconstant – in some directions or constant – in all directions diplopia. Initiation of CS therapy is determined by the activity of the process which is assessed by a point system - the so called CAS (clinical activity score). CAS is defined by 7 indicators:
- Spontaneous retro-bulbar pain
- Pain on attempted up- or down gaze
- Redness of the eyelids
- Redness of the conjunctiva
- Swelling of the eyelids
- Inflammation of the caruncle and/or plica
- Conjunctival edema

CAS more or equal to 3/7 speaks of activity of the process and demands medical treatment. Oculomotor disturbances are not indicative of TAO activity and do not determine including of CS in the therapy scheme.

MPS with or without alternating CS scheme is applied only in the active forms of moderate TAO.
Telegammatherapy is not indicated in childhood. In non-active forms or cases of stabilized active moderate forms as a result of the CS treatment some rehabilitative surgical interventions may become necessary – corrections of the diplopia, of the palpebral fissure width, blepharoplasty or decompressive orbitotomy after a six-month period of inactivity.

Mild form – with one or more of the following manifestations – irritation, tearing, photophobia, mild eyelid retraction (< 2 mm), mild manifestations on behalf of the periorbital soft tissues, proptosis < 22 mm after Hertel, transient diplopia – only at tiredness or at waking-up. In such cases only the general standards are applied and some rehabilitative surgical interventions may become necessary (Fig. 1).

The clinical case presented by us was classified as a severe form of TAO and that defined our choice of treatment.

Basedow’s disease rarely undergoes spontaneous remission, which means that treatment is usually indispensable. Three methods are promoted nowadays including thyrostatics for oral administration, radioiodotherapy and surgical treatment. When TAO is diagnosed and its grade of severity is defined correctly specific treatment for the ophthalmopathy is applied parallel with the already chosen thyrostatic treatment. There are various schemes of pulse-therapy and supporting CS treatment:

**Pulse-therapy** - with methylprednisolone (MPS) is applied in different schemes according to the different studies:
- MPS – 250-1000 mg/24 hours for 3 to 5 successive days depending on the severity of the condition
- MPS – 7.5-15 mg/kg/24 hours twice a day, every other day, in 2-week intervals, for a period of 2-3 months
- MPS - 500 mg i.v., once a week for a period of 6 weeks, followed by 250 mg i.v. once a week for another 6 weeks.

The total cumulative dose of MPS should not exceed 8 g in the course of treatment. The effectiveness of pulse therapy is 60-80 % and the risk of side effects is smaller compared to the risk of initial schemes of oral CS whose effectiveness does not exceed 50%. As there exist a risk of exacerbation of the process if the high dose and continuous CS treatment is suspended it is recommended recently to apply moderate pulse doses – 250-500 mg MPS/24 hours.

**Oral corticosteroid treatment** – prednisolone or dehydrocortisone
- Initial dose of 1 mg/kg/24 hours during the first week followed by reduction of the daily dose to

![Figure 1. Therapeutic algorithm of the different forms of TAO severity](image-url)
10 mg/24 hours – for a total of 3 months.
• Initial dose of 40-60 mg/24 hours, gradual reduction of the dose in intervals of 7-14 days to a supporting dose of 15 mg once a day – for a total of 4 to 6 months or more depending on the effect.

**Method of combined treatment** – it is more effective compared to the conventional one and with a lower risk of corticosteroid dependence and side effects.
• Pulse therapy with MPS followed by alternating doses of prednisolone 20-30 mg taken only once every second day, for a period of 4 to 8 months. On the background of the alternating therapy pulse doses of MPS may be also applied – in intervals of 1 to 3 months depending on the effect.
• The most severe cases are subjected to a three-step therapeutic scheme – pulse MPS, conventional doses of prednisolone for a period of up to 6 weeks and doses of 15-20-30 mg/24 hours, followed by alternating therapy: 3 days pulse therapy with MPS, 6 weeks conventional dose of prednisolone, 3 months alternating therapy – prednisolone every 48 hours.

**Alternative treatment:**
• In severe forms with no effect of the medicinal treatment – total ablation of the thyroid gland
• Somatostatin analogues – only after somatostatin receptors are proved by octreotide scintigraphy
• Cytokine-antagonists, including pentoxiphilin
• Antioxidants – alupurinol and nikkotinamide, selenium agents
• NSAID (non-steroid anti-inflammatory drug) – COX2 – inhibitor
• Immunosuppressors – cyclosporine, methotrexate.

**CONCLUSIONS**
Basedow’s disease may occur in childhood albeit comparatively rarely. The severe form of its complication - thyroid-associated ophthalmopathy, is a casuistic rarity in children. The prompt referring of TAO patients to specialist centers of pediatric endocrinology is of crucial importance for the prognosis. Early diagnose of TAO and defining its grade of severity should be performed by an experienced team of an ophthalmologist and a pediatric endocrinologist. The complex and adequate treatment based on the contemporary consensuses is a determinant factor for the preservation of the sight of the affected children.

**REFERENCES**
СОВРЕМЕННЫЕ ДИАГНОСТИЧЕСКИЕ И ТЕРАПЕВТИЧЕСКИЕ ВОЗМОЖНОСТИ ПРИ ТИРЕОИДАССОЦИИРОВАННОЙ ОФТАЛЬМОЛОГИИ В ДЕТСКОМ ВОЗРАСТЕ. ОПИСАНИЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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РЕЗЮМЕ

ВВЕДЕНИЕ: Главные симптомы сравнительно часто наблюдаются в клинической картине Базедовой болезни в детском возрасте. Тяжелые формы тиреоидассоциированной офтальмологии (ТАО) являются проблемой в детском возрасте. Ранний диагноз и оценка тяжести орбитопатии и ее специализированное лечение современные консенсыс считают ключевым прогностическим фактором.

Цель - обзор современных диагностических и терапевтических возможностей для пациентов с Базедовой болезнью и ТАО в детском возрасте.

Авторы представляют случай тяжелой ТАО у 11-летнего мальчика с Базедовой болезнью. Комбинированная терапевтическая схема, основывающаяся на консенсусе EUGOGO 2008 г., включает кроме тиреостатиков и локальные офтальмологические средства и пульскуртикостероидную терапию, за которой следует альтернирующий дозовый режим. Узкая коллаборация между детским эндокринологом и офтальмологом в ходе лечения определяет в большой степени благоприятный исход.

ЗАКЛЮЧЕНИЕ: Напрашивается вывод, что детей с тиреоидассоциированной офтальмологией следует своевременно направить к специализированному центру в целях оценки тяжести орбитопатии и проведения адекватной терапии. Это имеет решающее значение для сохранения зрения пациента.