NEURO-PSYCHIATRIC ONSET OF GRAVES’ DISEASE IN CHILDREN. CASE REPORT AND LITERATURE REVIEW

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NEURO-PSYCHIATRIC ONSET OF GRAVES’ DISEASE IN CHILDREN. CASE REPORT AND LITERATURE REVIEW (Abstract): Children with thyrotoxicosis are usually hyperactive with behavioral problems, difficulty in concentration and attention. Neuropsychiatric disturbances in children with Graves’ disease (GD) can be mistaken for “true” psychiatric or neurologic disorder delaying the diagnosis and the correct therapeutic approach. We present the case of an 8 years old with important height and weight gain in the last two years. The patient had a medical history of ADHD. Despite the psychotherapy the behavior has not improved. Physical examination revealed increased weight and height, exophthalmia and lid retraction, diffuse goiter, important tremor, hyper talkativeness, warm and moist palms and tachycardia. The diagnosis of GD was confirmed by the values of thyroid hormones and the presence in high titers of thyroid stimulating hormone receptor antibodies (TRAb). After several months of treatment with ATDs only, we have switched “on block and replace” therapy. During the 3 years surveillance, the height and weight velocity rates remained increased with an advanced bone age. Once euthyroidism achieved and maintained, also the neuropsychiatric abnormalities, including irritability, anxiety, sleep disturbances and mood changes improved. The school performances improve to, and the inability to concentrate disappeared after several months. At the moment the patient is still on a minimal dose of ATD with normal hormonal levels. Neuropsychiatric manifestations can be the first sign of thyrotoxicosis in children and adolescents. A close collaboration with parents is required in order to have the desired results: euthyroidism and disappearance of neuropsychiatric dysfunctions. Keywords: THYROTOXICOSIS, CHILDREN, MOOD DISORDERS, HYPERACTIVITY.

Thyroid dysfunction may cause, or be associated with, a wide range of psychiatric and or neurological disorders in children and adolescents. Graves’ disease (GD) is the most common cause of thyrotoxicosis in pediatric population with a prevalence of 1 in 10,000 children (1). GD account for 10-15% of childhood thyroid diseases and its incidence rises from 0.1/100,000 in young children to 3/100,000 in adolescents (2). GD is more common in girls than in boys (3). The classic clinical picture includes diffuse goiter, exophthalmia, increase appetite, weight loss, palpitations, excessive physical activity, nervousness, thermo phobia, tremor, accelerated linear growth (1). Children with thyrotoxicosis are usually hyperactive with behavioral problems such as: difficulty in concentration and attention, disturbances which may lead to decreased cognitive performance (4).
Neuro-psychiatric disturbances in pediatric GD are rare and can be mistaken for “true” psychiatric or neurologic disorder delaying the diagnosis and so, the correct therapeutic approach. Hyperthyroidism can present as a hypomania or maniac-like state, anxiety, depression, mixed mood disorders, emotional lability and irritability (5). It is believed that hyperthyroidism affect the activities of neurotransmitters (serotonin and dopamine) in the central nervous system and possibly account for the neuropsychiatric abnormalities. Thyroid hormones are responsible for the modulation of the beta-adrenergic response to catecholamines in the central nervous system and so, may contribute to psychotic behaviors in thyrotoxic patients (6). GD is associated with, or may cause, a spectrum of central and/or peripheral neurological dysfunction and a considerable variation in clinical phenotype is described (7). There is a connection between the effects of thyroid hormones and several frequent psychiatric disorders. Minor changes in thyroid hormone concentrations, may have important effects on cerebral function. This may manifest as alterations in mood, behavior and cognition (8).

The diagnostic of GD may be very challenging in children due to clinical manifestations which may mimic a neuropsychiatric disorder. It takes sometimes a long period of time until the positive diagnosis of GD is done. This will interfere with growth and development of the child and also may lead to serious cardio-vascular complications. Here we report a girl with GD who was initially diagnosed with attention deficit hyperactivity disorder (ADHD) due to important cognitive deterioration, difficulties with attention and hyperactivity.

**CASE REPORT**

We present the case of an 8 years old girl admitted in our department for important height and weight gain in the last two years. The patient had 18 months history of increasing irritability, insomnia, mood swings, and impaired concentration. Her mother said that she become unfriendly with colleagues at school and the anxiety, nervousness, restlessness, diminished concentration and hyperkinesia lead to her poor school performance. Due to difficulties with concentration and attention and hyperactivity she was diagnosed with ADHD and underwent psychological counseling. Despite the psychotherapy the behavior has not improved. Moreover, she has developed an uncontrolled appetite which leads to a rapid increase in weight.

Physical examination revealed increased weight and height (both at +2 SD), exophthalmia and lid retraction (fig. 1). At palpation thyroid was soft, diffuse enlarged, smooth, and non-tender (fig.1). The patient presented hyperkinesia, important tremor, hyper talkativeness, warm and moist palms, tachycardia (110 beats/minute) and normal blood pressure.

The thyroid ultrasound examination revealed a 40 mL thyroid volume (normal value according WHO (9) for age and sex is 6.9 mL), intense hypoechoic structure and an increased vascularization in Doppler mode (fig. 2).

![Fig. 1. Lid retraction and diffuse goiter at clinical examination.](image-url)
Fig. 2. Thyroid with increased volume, important hypoechoogenic structure and increased vascularization on neck ultrasound.

All these data were specific for autoimmune thyroid disorder. The hormonal profile was in accordance with the clinical picture of hyperthyroidism (thyrotoxicosis): TSH (thyroid stimulating hormone) = 0.022 μIU/mL (normal values 0.35-5.6), fT4 (free thyroxin) = 1.44 ng/dL (normal values 0.89-1.76), fT3 (free triiodothyronine) =10.5 pg/mL (normal values 2.4-8.6). The presence in high titers of antithyroid antibodies: anti-peroxidase (TPOAb) > 1,000 IU/mL (normal values 0-35) and anti-thyroglobulin (TGAAb) > 3,000 IU/mL (normal values 0-40) was also recorded. Considering the presence of thyrotoxicosis with ophthalmopathy, suggestive for GD, we have measured the level of thyroid stimulating hormone receptor antibodies (TRAb) which showed very high values 37.4 UI/L (positive> 1.5).

The treatment was started with anti-thyroid drug (ATD) Thiamazole 15 mg/day with caution for side effects such as: agranulocytosis, thrombocytopenia, hepatitis, skin rash, and urticaria. Also, a β blocker (propranolol) was added in order to manage the tachycardia and also to improve the metabolism of T4 in T3 at cellular level.

After two months the patient was retested for thyroid function and the physical examination was performed. The girl's mother said that it was very difficult for her to persuade her daughter to take the medication. Indeed, the hormonal picture was slightly improved (TSH still low, fT4 normal and fT3 8.9 vs. 10.5 pg/mL (before ATD). The tremor was present, blood pressure was normal and heart rate= 90 beats/minute. The patient was seen every 3 months for a period of 3 years. This strict follow-up was necessary due to unpredictable evolution with ATD treatment (tab. I).

It was very difficult to set a dosage able to achieve euthyroidism. Even slight increase or decrease in daily dosage of Thiamazole (according with fT4 and fT3) were succeeded by important variations of TSH, fT4 and fT3 values. After several months of treatment with ATD only, we have switched “on block and replace” therapy (high dose of ATD with levothyroxine in order to achieve euthyroidism). During the 3 years surveillance, the height and weight velocity rates remained increased with an advanced bone age. Once euthyroidism achieved and maintained, also the neuropsychiatric abnormalities, including irritability, anxiety, sleep disturbances and mood changes improved. The school performances improve to, and the inability to concentrate (major complain at the first visit) disappeared after several months. Regarding the ophthalmopathy, the evolution was positive with no aggravation of exophthalmia. At the moment the patient is still on a minimal dose of ATD with normal hormonal levels.
TABLE I

<table>
<thead>
<tr>
<th>DATE</th>
<th>TSH (0.35-5.6 µIU/mL)</th>
<th>fT4 (0.89-1.76 ng/dL)</th>
<th>fT3 (2.4-8.6 pg/mL)</th>
<th>TPOAb 0-35 IU/mL</th>
<th>TGAb 0-40 IU/mL</th>
<th>TRAb &gt;1.5</th>
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<td>0.022</td>
<td>1.44</td>
<td>10.5</td>
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<td>&gt;3,000</td>
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<tr>
<td>10. 2015</td>
<td>0.026</td>
<td>1.50</td>
<td>8.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
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<td>0.004</td>
<td>1.22</td>
<td>-</td>
<td>&gt;1,000</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
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<tr>
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<td>10.5</td>
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<td>7.38</td>
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DISCUSSION

Our case illustrates the diagnostic difficulties in pediatric GD. The intensity of psychological disturbances overlapped the classical manifestation of thyrotoxicosis. The delay in diagnosis and treatment of GD in this 8 years old girl lead to interference in growth and development including increased height velocity rate. Moreover, due to behavioral problems, the compliance on medical treatment was very challenging. The improvement of the biological picture has been very difficult to achieve. Long-term suppressed TSH along with fluctuations of fT4 and fT3 (which is more important as treatment efficacy marker in pediatric GD) were present throughout several months. The presence of anti-thyroid antibodies (TPOAb and TGAb) with stimulatory or inhibitory effect, in high titers can explain the irregular pattern of fT4 and fT3.

The literature indicates that remission rates in children are less than 25% following many years of ATD treatment. Puberty, TRAb levels and thyroid volume influence remission rates (1). Another particularity of this case was the weight of this girl that has been increased over the entire follow-up period. Commonly the children with GD present poor weight gain (4) due to hypermetabolism and hyperactivity. In our case the patient was overweight all the time despite the prolonged, uncontrolled thyrotoxicosis.

Pediatric Graves' disease is an autoimmune disorder due to thyroid stimulation by thyroid receptor antibodies (TRAb) (1). The pathophysiology of GD is not fully understood but it speculates the role of selenium (Se) in the lymphocytic chronic thyroiditis. Se supplementation has a stimulatory effect on glutathione peroxidases and thioreductases and inhibits the Human Leukocyte Antigen – DR isotype (HLA-DR) molecule (10, 11).

Beside the medical treatment with ATD in pediatric GD, the surgical option remains for cases which do not respond to ATD or develop serious adverse events (leucopenia, agranulocytosis). Total thyroidectomy is recommended in order to avoid the recurrence on the remaining thyroid tissue but the
post-operative complications such as hypoparathyroidism or recurrent laryngeal nerve injury should be considered (12, 13). The radioactive iodine use in pediatric GD represents an alternative to ATD and surgery (1).

Thyroid hormones have direct and important effect on brain function (8). Thyrotoxicosis in children is associated with neurological manifestations such as tremor, seen in the hands, face, and legs. Tremor is more commonly seen in pubertal/post pubertal than in prepubertal children (7) and is thought to be secondary to stimulation of the beta-adrenergic system and it is seen both at rest and with intention (7).

Other rare neurological manifestations in pediatric GD are: intermittent encephalopathy (14), acute confusional state (followed by thyroid storm) (15), choreiform movements (7). Seizures also can occur and vary from generalized tonic-clonic to complex partial, or more focal findings (7).

Hyperthyroid state can associate with cerebral ischemic events, and in most cases, patients recover from their neurologic symptoms after achieving euthyroidism. One possible explanation might be a hemodynamic compromise, induced by an increase in the cerebral metabolism and oxygen expenditure (16). Thyroid hormones may increase vascular sensitivity to the sympathetic nervous system and induce changes in the arterial walls. Vasculitis induced by antithyroid drugs may cause changes in the intracranial arteries. Cerebrovascular hemodynamic changes induced by thyrotoxicosis were considered to be responsible for the cerebral ischemic events. In addition, thyrotoxicosis-induced hypercoagulability may influence ischemic events (17, 18, 19). ADHD and autism spectrum disorder can mimic the onset of GD in children, so is very important always to test the thyroid function in children or adolescents with hyperactivity or comportment disorders (20, 21). Psychiatric disorders, loss of consciousness and movement disorders may all be manifestations of pediatric GD (8).

CONCLUSIONS

Neuropsychiatric manifestations can be the first sign of thyrotoxicosis in children and adolescents. This may delay the diagnostic and proper treatment of thyrotoxicosis leading to important complications in pediatric GD. It is very important to assess the thyroid function in children with mild behavioral, mood disorders or neurological/neuromuscular disturbances. A close collaboration with parents is required in order to have the desired results: euthyroidism and disappearance of neuro-psychiatric dysfunctions.

REFERENCES

Neuro-psychiatric onset of Graves’ disease in children. Case report and literature review


