A RARE CASE OF INFANTILE GRAVE'S DISEASE

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ABSTRACT: The authors presents a rare case of a 12 years-old girl with Graves' disease with typical clinical features apearing after an emotional stress. After a first-line treatment with antithyroid drugs the thyrotoxic syndrome relapsed because the lack of compliance and side effects of this medication (carbimazole). Convenient preparation to achieve the euthyroid state allowed the young patient to support a near total thyroidectomy with immediate and long-term good result. Considerations about the pathways leading to Graves' disease, clinical and bioumoral diagnosis and especially the indications, advantages and failures of the three main methods of therapy i.e. antithyroid drugs, ablative radioiodine and surgery are discussed.

Keywords: graves'disease, children, surgery

INTRODUCTION

Hyperthyroidism is an autoimmune childhood rare condition. Yearly incidence is 8 per 1.000.000 children less than 15 years-old and 1 per 1.000.000 children less than 4 years-old, but Graves' disease is by far the most common etiology encountered in 95% of cases. Girls are more often affected, sex ratio being 3-6:1, except the neonatal form where the frequency is 50% for both sexes. (1,2) Main signs and symptoms include the "classical triad" i.e. exophthalmia, goiter and tachycardia, to whom added increased appetite, weight loss, sweating, hyperactivity, heat intolerance, palpitations, fatigue and diarrhea. (3-5) The diagnosis is made by T4, T3 and thyroid-stimulating hormone (TSH) measurements and also by imagistic studies such as ultrasonography and technetium 99m or^{123} I scan (these radioisotopes are trapped by hyperfunctioning teritories yielding an area of increased uptake) rarely used today. The treatment consists in administration of antithyroid drugs, destruction of the thyroid with radioactive iodine or reduction of the gland volume by subtotal thyroidectomy.(4,5) The remission rates vary from 30-40% with antithyroid medication but with a high percentage of recurrences. Radioiodine and surgery are also very effective, but with great risk of developping hypothyroidism requiring subsequent lifelong thyroid replacement. (4,5) We present the case of a 12 years old girl diagnosed with Graves' disease, in which unsuccesfull/bad tolerated medical treatment imposed the surgical intervention followed by complete recovery.

CASE REPORT

FC, a 12 years-old schoolgirl was guided by an endocrinologist to the IV[th] Surgical Clinic with a florid thyrotoxic syndrome exhibiting evident bilateral exophthalmia (20 mm), the sclera being visible among the limbal margin, lid lag, enlarged diffuse thyroid gland, sinusal tachycardia (100-110 beats/minute), tremors, excessive sweating and poor weight gain. Nervosity, mood changes, sleeping disorders and inability to concentrate at school were also present. Previously she received behavioural therapy for a supposition of ADHD syndrome. The

family history did not provide informations about thyroid disorders or any particular morbidity. Her complaints progressively appeared two years ago after a scholar failure with emotional lability, anorexia, eye changes and thyroid swelling. Clinical and laboratory tests confirmed the diagnosis of primary thyrotoxicosis (Graves' disease) and therapy with antithyroid drugs (carbimazole) controlled the disease for a few months. The lack of compliance and side effects i.e. skin rash and neutropenia compromised the hoped cure. Thereafter the patient's symptomatology and general condition rapidly worsened. Laboratory tests showed increased FT4 (45 pmol/l), FT3 (15 pmol/l) and supressed TSH levels (below 0.1 mU/l) and ultrasonography identified a huge, difuse, hypoechoic gland (Fig.1)

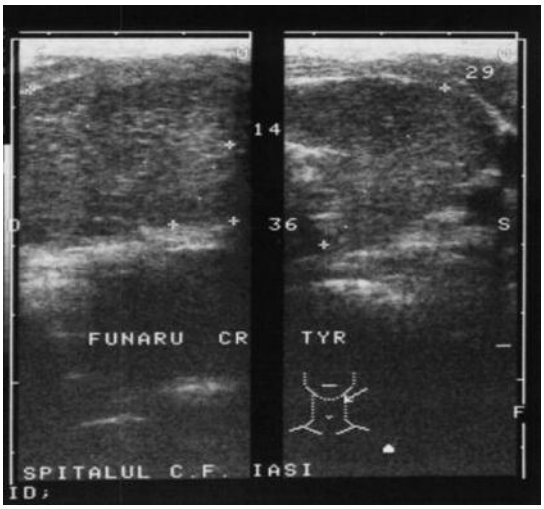

Fig. 1. Ultrasonography:difuse, hypoechoic thyroid gland (FC, 12 yrs)

Fig. 2. Operative piece – large goiter

Finally she attended the surgical clinic with impaired general condition which imposed an intensive and prolonged preoperative treatment with sedatives, beta-blockers agents and even Lugol's solution. A subtotal thyroidectomy was done, both lobes being resected except for a 1.5x0.5 cm patch of thyroid tissue close to the recurrent nerves. Surgery was particularly difficult because of the unusual large size of goiter (120 gm) and annoying bleeding. (Fig.3)

Postoperative course was troubled by a moderate thyroid crisis (fever, agitation, tachycardia) controlled whith medical therapy and the patient was discharged in the 5th postoperative day with complete recovery. Pathology revealed thyroid hypertrophy and hyperplasia with tall epithelium of follicular cells and absence of papillae, retention of pale colloid, round nuclei, lymphoid infiltration, vascular congestion and sclerosis. (Fig. 3)

The periodic checkings confirmed her clinical and biological healing. Eight years later, the patient got married giving birth to a perfectly normal babygirl.

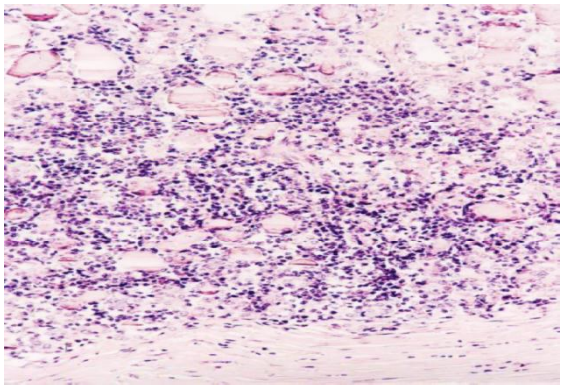

Fig.3. Follicular cells with tall epithelium and round nuclei, lymphoid infiltration, vascular congestion and sclerosis (HE x 200)

DISCUSSIONS

Rarely encountered in pediatrics, the neonatal, infantile and juvenile hyperthyroidism manifested usually as a Graves' disease with clinical moderate course, capricious evolution and spontaneous remission tendency or, on the contrary, towards severe complications. In literature there are about 100 observations of thyrotoxicosis of the newborn, two main varieties being differentiated as matter of occurrence and evolution. In the common form the disease is due to maternal antibodies transferred from the mother with recent or severe hyperthyroidism into the fetal compartment which stimulate the thyroid binding to the TSH receptors. These children presents at birth or immediately after, mild thyrotoxic symptoms whith complete remission until the age of 3 months. In the second less frequent form, the provenience from a mother with Graves' disease is not compulsory and the clinical phenomena may not be present immediately after birth; in these cases, it is a spontaneous appearance of the thyrotoxicosis in favourable genetic conditions (dominant transmission of autosomal type especially for the females). Initially, these two forms are impossible to differentiate, both presenting common complaints of variable intensity but in particular situations - especially from the second group - we also mention cases with severe evolution, manifestations of respiratory compression, dehydration, infections, icterus, thrombocythemia, thyroid crisis.(6) The diagnosis is sometimes difficult to establish, some guiding elements being the increased levels of thyroid hormones, the tendency of precocious ossification and especially the hereditary character of the endocrinopathy. (7,8) It must also be mentioned the well known associations between Graves' disease and human leukocyte antigens HLA-B8 and HLA-DR3 and other autoimmune diseases as *diabetes mellitus*, Addison's disease, *systemic lupus erythematosus*, rheumatoid arthritis, myasthenia gravis, vitiligo, immune thrombocytopenic purpura, and pernicious anemia. (6) Genetic factors are also involved; the inheritance is polygenic but monozygotic twins show 50% concordance for the disease suggesting that environmental factors play a role.The little patients with Graves' disease usually come from an endemic region and familial antecedents may find different thyroid diseases. The symptomatology is often atypical or incomplete, which may lead to delays or errors of diagnosis. The onset may be misdiagnosed, especially due to nonspecific symptoms like hyperactivity, nervousness, and emotional lability, often attributed to other causes like *attention deficit hyperactivity disorder*; alterations in mental status, deterioration of behavior and school performance can also be seen. The parents often address to psychiatrist or pediatric neurologist for these complaints and the diagnosis postponing particularly in patients with psychiatric disorders is a strong possibility.The weight loss, tremor, sweating, tachycardia, diarrhea, nocturnal enuresis and – in 1/3 cases – the diffuse, nontender, symmetric enlargement of thyroid gland are also encountered. The exophthalmia appears in approximately 50% of the cases; another eye findings include lid lag, lid retraction, stare, conjunctival injection, chemosis, periorbital edema, ophthalmoplegia and optic atrophy. Convulsions, proximal muscle weakness, fever, arrhythmia, systemic hypertension and congestive heart failure have been rarely reported. The pretibial myxedema is exceedingly rare in children. Accelerated growth and early epiphyseal closure may be seen. The diagnosis can be established in the majority of cases based on the anamnesis, careful and repeated clinical

observation and the hormonal measurements. Patients with Graves' disease have elevated levels of T4 and T3 and low or undetectable levels of TSH. Diagnostic radioiodine I 131 uptake is rarely performed. Either technetium 99m or^{123} I scan may be useful if the gland does not have a uniform consistency. Ultrasonography is a simple and noninvasive method that may show the size, volume, homogeneity, vascularity („inferno" thyroid) and anatomical reports with neighbouring structures. Differential diagnosis include Crohn disease, anorexia, depression, dysthymic disorders, pheocromocytoma. (8) While diagnosis of Graves' disease in childhood does not usually present peculiar problems, the treatment of this entity is still controversial including three methods i.e. administration of antithyroid drugs, ablation of the gland with radioiodine and surgery, each of them with successful outcomes but also with complications and failures. The therapy with antithyroid drugs (which inhibits thyroid hormone biosynthesis by decreasing the oxidation of iodide and iodination of tyrosine) use propylthiouracil (5-7 mg/kg/day), methimazole (0,5-0,7 mg/kg/day) or carbimazole (15mg/day with progressive decrease). Antithyroid medication is recommended as the first line treatment leading to a rapid and marked improvement of most simptoms. However definitive remission cannot be expected in more than 30-40% of children after a first course of therapy. There are reported more than 50% failures or relapses owing to lack of compliance or side effects imposing a definitive form of treatment. (9-11) Administration of radioactive iodine in children, preffered in US is viewed as a safe and effective method with high rate of successes but also with progressive risk of hypothyroidism (20-40% in the first year after therapy and 2-3%/year thereafter assuming a permanent monitorisation of the patient). Although the children with ablative doses of radioiodine have not revealed an aparent increased risk of thyroid carcinoma or leukemia, the possibility of these malignancies make this therapy less atractive for European physicians. (12-14) Surgical (near total or even total) thyroidectomy provides excellent and quick healings in more that 95 % of cases but complications as *hypoparathyroidism* and damage to the recurrent laryngeal nerve (1-3%), toxic recurrences or hypothyroidism (patients requiring lifelong T4 replacement) are mentioned. (15) For neonatal Graves disease beta-blockers, antithyroid medications or, in severe cases, iodides in the form of Lugol iodine solution or saturated solution of potassium iodide (SSKI) are used. The prognosis of the Graves' infantile disease depends on the process evolution, some symptoms especially the neuropsychic ones, can persist and aggravate, mainly in late diagnosed or insufficiently treated cases. The ocular complications have their own course. In addition, the growth disorders or puberty delay have a transient character, disappearing at the same time with the thyrotoxicosis.

CONCLUSIONS

Pediatric Graves' disease conserve many unknows both in its pathogeny and treatment so futher studies are necessary.

REFERENCES

1. Hayles AB: Problems of childhood Graves' disease. Mayo Clin Proc 1972, 47 :850-853
2. Kraiem Z, Newfield RS: Graves' disease in childhood. J Pediatr Endocrinol Metab 2001, 14: 229-242.
3. Bauer AJ: Approach of the pediatric patient with Graves' disease: when is the definitive treatment

warranted 4. J Clin Endocrinol Metab 2011, 96: 580-588

4. Krassas EG : Treatment of juvenile Graves'disease and its ophtalmic complication : the « European way ». Eur J Endocrinol 2004, 150 : 407
5. Dallas J, Foley T. Hyperthyroidism. In: Pediatric Endocrinology. *3rd ed*. 1996:401-415.
6. Polak M: Hyperthyroidism in early infancy, pathogenesis, clinical features and diagnosis with a focus of neonatal hyperthyroidism. Thyroid 1998, 8: 171-177
7. Diaconescu S: Hipertiroidismul la nou-nascuti, copii, adolescent. In MR Diaconescu : Hipertroidismul. Edit Junimea, Iasi: 114-116
8. Perrild H, Gruters-Kieslich A, Foldy-Rasmunssen U et al: Diagnosis and treatment of thyrotoxicosis in childhood. A European questionnaire study. Eur J Endocrinol 1994, 131: 467-473
9. Rivkees SA: Pediatric Graves' disease: controversies in management. Horm Res Paediatr 2010, 74: 305-311
10. Bergman P, Anldist AW, Cameron F: Review of the outcome of management of Graves' disease in children and adolescents. J Pediatr Child Health 2001, 37: 178-182
11. Kagelidou F,Carel JC, Leger J : Graves' disease in childhood : advances in management with antithyroid drugs therapy. Horm res 2009, 71 : 310-317
12. Rivkees SA, Cornelius EA: Influence of iodine-131 on the outcome of hyperthyroidism in children. Pediatrics 2003, 111: 745-749
13. Chao M, Jiawei X, Guoming W et al: Radioiodine therapy for pediatric hyperthyroid Graves' disease. Eur J Pediatr 2009, 168: 1165-1169
14. Read CH, Tansey MJ, Menda Y. A 36-year retrospective analysis of the efficacy and safety of radioactive iodine in treating young Graves' patients. *J Clin Endocrinol Metab* 2004, 89: 4229-4233
15. Sherman J Thompson GB, Lteif A et al: Surgical treatment of Graves' disease in childhood and adolescents, an institutional expeience. Surgery 2006, 140: 1056-1061