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Unusual Presentation and Rare Comorbidity of Graves-Basedow's Disease in Children

Agota Muzsnai

Abstract

Graves'-Basedow's disease (GD) is a well-defined hyperthyroid disorder caused by circulating antibodies that results the overproduction of thyroid hormones. All but a few children present with some degree of thyroid gland enlargement and most have two or more signs of excessive thyroid activity, such as tremor, irritability/nervousness, tachycardia etc. Fully developed clinical picture is easy to recognize while often the onset is insidious. Thyroid hormones affect many body systems, so signs and symptoms of Graves' Disease can be wide ranging. A survey on PubMed literature was conducted to gather all published pediatric Graves-Basedow's cases with unusual presentation at the time of diagnosis. We found all together 70 manuscripts with relevant information from 1978 to 2020 but mainly adult cases. One third of them were found to meet the criteria we focused on and were included in this paper, though in some situation the unusual findings do not consist part of hyperthyroidism, the rare manifestation is only a coexistence, or the serious disease even precedes the GD. Dermatopathy, hepatic dysfunction, impaired fluid balance, concomitant disorders in thyrotoxicosis, tricky laboratory findings, a phenomenon of metamorphic thyroid autoimmunity, peculiarities of thyroid dysfunction in children with Down syndrome, apparent associations, and reconstitution GD are highlighted in this chapter. Awareness about the relation of these remote findings to GD, or frequent coexistence with GD is important for early diagnosis. Finally, a reasonable suspicion for Graves' Disease may ultimately help to prevent unnecessary investigations and treatment.

Keywords: hyperthyroidism, thyrotoxicosis, thyroid autoimmunity, antibodies, rare disorder, Hashimoto thyroiditis, Turner syndrome, Down syndrome, reconstitution GD, children

1. Introduction

In pediatric age group the Grave's-Basedow disease (GD) is by far the most common cause of hyperthyroidism, accounting for greater than 95% of cases. The underlying process is an autoimmune reaction with cell proliferation and excess function (overproduction of thyroid hormone) caused by anti-thyrotropin receptor antibody (TRAb). When using term thyrotoxicosis, it depicts the clinical and biochemical manifestations of excess thyroid hormones. The annual incidence of thyrotoxicosis was less than 1 per 100,000 children <15 years of age in the last

century and rised slowly above 1.5 per 100,000 by 2012 with the pubertal dominance up to 80%. In spite of the GD is a rare disorder in children, physicians should consider Graves' Disease in any child with clinical manifestations of hyperthyroidism, regardless of the age.

All but a few GD children present with some degree of thyroid gland enlargement and most have two or more signs of excessive thyroid activity. The clinical manifestations of hyperthyroidism during fetal life are tachycardia, cardiac arrhythmia, intrauterine growth retardation and may be associated with nonimmune fetal hydrops, craniosynostosis. Features of this condition in the neonate include irritability, tachycardia, hypertension, cardiac failure and arrhythmias, diarrhea, poor weight gain, vomiting, jaundice, hepatosplenomegaly, ophthalmopathy, craniosynostosis and thyroid enlargement. In childhood hyperkinesis, tachycardia, tremor, frequent stools, nervousness are the signs of hyperthyroidism but in young children these are less characteristic, often unrecognized. In school-age hyperthyroidism neuropsychiatric symptoms such as hyperactivity and poor school performance are common features. Adolescents usually present with classic signs including weight loss despite of good appetite, diarrhea, nervousness, and heat intolerance. Fully developed clinical picture is easy to recognize while often the onset is insidious. Thyroid hormones affect many body systems, so signs and symptoms of Graves' Disease can be wide ranging.

This chapter is aimed to draw attention to less common or less distinctive signs and symptoms which can be in relation to GD at the time of diagnosis. A survey was conducted on PubMed literature to gather all published pediatric Graves-Basedow's cases with unusual presentation at the time of diagnosis. We found all together 70 publications with relevant information from 1978 to 2020 but mainly adult cases. Half of them (36) were found to meet the criteria we focused on and were included in this paper, though in some situation the unusual findings do not consist part of hyperthyroidism, the rare manifestation is only a coexistence, or the serious disease even precedes the GD. Awareness about the relation of these rare manifestations or disorders to GD is essential to avoid wrong diagnosis, unnecessary investigations, or fatal outcome due to delay of diagnosis.

2. Unusual signs and symptoms

2.1 Dermopathy and acropachy

Thyroid dermopathy (TD), also called pretibial myxedema and thyroid acropachy (TA) together with Graves' orbitopathy (GO) are extrathyroidal manifestations of GD. Graves' ophthalmopathy in children not as common as in adults and less severe than in later age. Dermatological symptoms are rare and in general develop sequentially: Dermopathy is usually present if the patient is also affected with GO. The very rare acropachy occurs only in patients who also have dermopathy [1]. Or in other words, acropachy is an indicator of severity of ophthalmopathy and dermopathy. All have an autoimmune origin, the immune reaction is targeted to TSH receptor and, likely, the IGF-I receptor. Typical presentation of dermopathy is nonpitting edema or plaque-like lesions on the pretibial region, while thyroid acropachy presents as digital clubbing, swelling of digits and toes, and periosteal reaction of extremity bones. Awareness about the relation of TA to GD is important as clubbing usually is not a patient complaint and is noted only by clinical observers. Recently Kraus CN and al. reported a case of acropachy in a child as well as reviewed the literature of pediatric thyroid dermopathy [2].

2.2 Cholestasis

Hepatic dysfunction is commonly observed in patients with thyroid disease, it can be categorized mainly into group with either hepatocellular damage (transaminases elevations), or intrahepatic cholestasis (bilirubin elevation). In newborn, the hypothyroidism is the most typical thyroid disorder associated with cholestasis. Jaundice due to intrahepatic cholestasis may be a salient symptom in GD patients, and very occasionally, it is the presenting manifestation of thyrotoxicosis. The mechanism of liver injury in pure hyperthyroid states is not well understood, and no correlation was documented between abnormal liver biochemical tests and thyroid hormone levels. A contributing factor appears to be relative hypoxia in the perivenular regions, due to an increase in hepatic oxygen demand without an appropriate increase in hepatic blood flow [3], the other might be the thyroid hormones themselves with a direct toxic effect on hepatic tissue in hypermetabolic state [4]. If other possible causes of cholestasis are excluded, recovery occurs parallelly with restoration of euthyroidism. In the absence of another evidence of liver disease, and when jaundice is purely due to the hyperthyroidism, thionamide drugs may be used with monitoring of serum bilirubin and liver function tests [5]. Newborns and adolescent patient were reported with jaundice/hyperbilirubinemia as manifestation of GD hyperthyroidism [6–8].

2.3 Polydipsia, nocturnal enuresis

Disturbance of water homeostasis can lead to polyuria-polydipsia syndrome, which is a diagnostic challenge. Polydipsia is a nonspecific symptom in various diseases, often accompanied by polyuria. Increased thirst and/or nocturnal enuresis can be the main complains, and a careful case history usually reveals the primary reason (disturbed input or output). Polydipsia has been described as a presenting symptom of hyperthyroidism in adults. A few years back a serendipitous identification of GD in identical twin girls with polydipsia was published [9]. Though etiology of nocturnal enuresis is not fully understood, evidence is growing that enuresis may have a central origin: bedwetting children have lower brainstem reflex control (impaired prepulse inhibition) than normal controls [10]. A case of a 9-year-old boy has been reported by the same team who suffered from hyperthyroidism and a new appearance of enuresis. Bedwetting ceased and prepulse inhibition – measured as a parameter of central control – increased during on course of anti-thyroid therapy [11]. In our praxis we experienced two GD cases where nighttime incontinence was the presenting feature of recurrent hyperthyroidism.

3. Rare concomitant disorders

3.1 Thyrotoxic periodic paralysis

Thyrotoxic periodic paralysis (TPP) is a rare disease of the muscles secondary to hyperthyroidism presenting sudden attacks of short-term muscle weakness, stiffness, or paralysis. The underlying mechanism is malfunctions in the ion channels in skeletal muscle cell membranes: An increased influx of potassium into skeletal muscle cells leads to profound hypokalemia and paralysis. Hypokalemia in thyrotoxic hypokalemic periodic paralysis (THPP) results from an intracellular shift of potassium and not total body depletion. The symptoms may be mild or severe, and they may last for minutes or days, involving the whole body or just one or both limbs. The severity of the disease does not correlate with the hormone levels,

and muscle paralysis simply resolves by achieving the euthyroid state. TPP most frequently seen in Asian men and also reported in Hispanic adolescent males [12, 13]. Fatal outcome of a 10-years-old girl with delayed diagnosis of hyperthyroidism should draw attention to the awareness about this rare but potentially lethal disorder [14].

3.2 Encephalopathy

Presenting feature of encephalopathy in GD and Hashimoto's thyroiditis would be similar (seizures, stroke-like episodes, cognitive decline, neuropsychiatric symptoms etc.) but characteristics of thyroid derangement is reversed. Thyroid function is not an issue in Hashimoto's encephalopathy which is renamed now as 'steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT)', while brain dysfunction is associated to hyperthyroid state in GD. Hecht T and coworkers reported on a 7-year-old girl with generalized seizures, somnolence, fever, and respiratory distress. The increase of sinus tachycardia with good hydration, sufficient analgesia, and hyperthermia led to the determination of thyroid hormones, and therefore finally to the diagnosis of a thyrotoxic crisis in Graves' Disease. Symptoms were disappeared by thyrostatic therapy [15]. They concluded that thyrotoxic crisis should be considered a differential diagnosis in case of resistant unexplained sinus tachycardia, seizures, and encephalopathy.

4. TSHR-blocking autoantibody (TBAb)

In Graves-Basedow's patients TRAb stimulates thyroid hormone synthesis by activating the TSH receptor (stimulating TRAb /TSAb/, TSHR agonist). TSHR antibodies that lack agonistic activity but are competitive inhibitors of TSH binding can cause hypothyroidism (blocking TRAb/TBAb/, TSHR antagonist). There is a wide variety of TSHR antibody assays employed in the past and nowadays. Depending on the underlying method, two types of assays are important for determination of circulating autoantibodies: Competition for ligand binding or measuring bio-response. A rare history of monozygotic 10-year-old twins was published who presented with hyper- and hypothyroidism, respectively [16]. Both girls had antibodies against thyrotropin receptors as measured by a radioreceptor assay. Analyzing further the sera in a functional bioassay, the TSH receptor antibodies of the hyperthyroid twin displayed stimulatory activity typical of Graves' Disease, while the antibodies of the hypothyroid twin acted as pure antagonists at the TSH receptor level. This is a proven pediatric case with hypothyroidism due to thyroid (or TSH)-blocking antibodies, where the pathogenesis was similar to GD. In the following 30 years an extensive work of research groups has led to significant improvements that has enabled bioassays to be employed routinely in clinical laboratories: 1, Two human monoclonal antibodies (MAbs) with TSHR agonist activity (M22 and K1-18), one human MAb with TSHR antagonist activity (K1-70) and one human MAb (5C9) with both TSHR antagonist and TSHR inverse agonist activity have been isolated [17]. 2, Currently available highly sensitive and specific assays to measure TRAbs use the human TSHR monoclonal antibody (Mab) M22 instead of the TSH [18]. Based on a research-use only service offered by RSR Limited, an adult case of woman with fluctuating hypo- and hyperthyroidism was published providing proof that a patient can produce a mixture of blocking and stimulating TSHR autoantibodies at the same time [19].

5. Metamorphic thyroid autoimmunity

Here we overview the phenomenon of metamorphic thyroid autoimmunity anticipating, that more investigational studies are needed to reveal the underlying mechanism, and larger epidemiological studies are needed to confirm that this finding is not unusual but is rather under-recognized in pediatric population. The term metamorphic thyroid autoimmunity was introduced by Ludgate M. and Emerson H. commenting cases with a conversion from Hashimoto thyroiditis (HT) to GD or vice versa [20–22]. A few years later Wasniewska M et al. aimed to ascertain HT in the history of GD children order to assess the relative frequency of this phenomenon [23]. Based on retrospective data of a cohort of 109 GB children and adolescents without coexistent chromosome abnormalities they calculated the frequency between 3 and 4%. Reporting results they confirmed the existence of a possible continuum between HT and GD within the spectrum of autoimmune thyroid diseases. In search of switching process from HT to GB in patient with either Turner syndrome (TS) or Down syndrome (DS) the same team found that antecedents of HT were significantly more common in chromosomopathy group ($9/35 = 25.7\%$) compared to age-matched GD patients ($4/109 = 3.7\%$) [24]. Guessing the clue of this immunological paradigm it should take into high consideration that attribute of HE is a cell-mediated destruction of thyroid tissue with hypo- or euthyroidism while GB is a TRAB-mediated gland activation presented in hyperthyroidism. In general, thyroid autoimmunity involves loss of tolerance to thyroid proteins in genetically susceptible individuals in association with environmental factors, no single mechanism explains the altered immune-reaction. Further immunological and genetic investigations can add explanatory information to this unusual pendulum swinging thyroid autoimmunity.

6. Peculiarities in Down syndrome

6.1 Asymptomatic vs. cumulative presentation

Thyroid derangement is the most frequently encountered endocrinopathy in Down syndrome (DS) affecting almost half of the patients (7 - 66%). Based on this fact the life-long monitoring of the thyroid function is recommended for all DS patients. Thyroid abnormalities encompass mainly any kind of hypothyroidism (congenital, primary, subclinical, or overt hypothyroidism), isolated hyperthyrotropinemia, Hashimoto thyroiditis or very rarely GD. Autoimmune thyroid disease is uncommon in young children with Down's syndrome but is common after 8 years of age [25]. A Spanish group [26] reported on three DS children with GD: Two of them were asymptomatic for thyroid hyperfunction (a 14-year-old girl and an 8-year-old boy), while the third child (a 12-year-old girl) presented goiter, nervousness, weight loss and tachycardia. In addition to the typical features of hyperthyroidism, the patient showed right-side heart failure and elevated transaminases, which disappeared with antithyroid treatment. Though annual biochemical screening for early detection of thyroid hypofunction is reasonable, regular auxological and clinical assessment in syndromic patients is also important.

6.2 Metamorphic thyroid autoimmunity

HT and GB are two different disease entities in the spectrum of thyroid autoimmunity presenting dominantly with hypothyroidism (HT) or with hyperthyroidism

(GB). A metamorphosis of both clinical and biochemical phenotype from HT to GD or vice versa has been discussed for more than 10 years [22] based on sporadic cases. A tapered Italian team conducted several retrospective studies to shed light on this phenomenon in pediatric population. In 2015 they published a research paper reconstructing the conversion process from HT to GD and the subsequent evolution of GD in a series of 12 children (7 girls/5 boys) with DS [27]. All patients fulfilled the criteria for diagnosis of HT and GD taking laboratory measurements and ultrasonography scan. Time interval between HT diagnosis and GB presentation ranged from 0.7 to 6.5 years, and Graves' Disease showed a milder clinical and biochemical course in this cohort. Summing up they conclude that „1, DS children might be incline to manifest over time a phenotypic metamorphosis from HT to GH and to subsequently fluctuate from hyperthyroidism to hypothyroidism; 2) in DS GD may have a mild biochemical and clinical course” [27].

6.3 Unusual scenario

A DS case with an unusual thyroid constellation were published by Nebesio TD and Eugster EA. „A 10-year-old girl with Down syndrome was diagnosed with congenital hypothyroidism in the newborn period due to left thyroid hemiagenesis. Unexpectedly, her hypothyroidism resolved at the age of 3 years. After being off thyroid hormone replacement for 7 years and having normal thyroid function, she developed Graves' Disease with typical signs and symptoms of hyperthyroidism including diarrhea, inattention, and hyperactivity” [28]. This case highlights also the unpredictable course of thyroid disease which may occur in children with Down syndrome.

7. Coincidence in polyendocrinopathy APS3

The autoimmune polyglandular syndromes (APS1-4) encompass a wide clinical spectrum of disease with different (monogenic/complex) genetic etiologies and heterogeneous presentation. APS2 is defined by presence of primary adrenocortical insufficiency with either autoimmune thyroid disease or type 1 diabetes mellitus in the same patient. The clinical diagnosis of APS3 requires the presence of an autoimmune thyroid disease and an additional autoimmune illness other than Addison's disease; a frequent combination is pernicious anemia, vitiligo, alopecia, myasthenia gravis and Sjögren sy. Thyroid disease purports a variety of thyroid disorders. Hypothyroidism is more common than Graves' Disease, and GD tends to manifest at a younger age. Recently Klenczar K and coworkers reported on a 11-year-old female patient, who presented coincidence of T1DM with other autoimmune diseases, such as Graves-Basedow's disease, myasthenia gravis, vitiligo, and IgA deficiency [29]. The clinical picture of this case fulfilled the criteria of autoimmune polyglandular syndrome type 3.

8. Unexpected coexistence

Stickler syndrome is a rare genetically heterogeneous disorder of the connective tissue, caused by abnormal synthesis of type II, XI, or IX collagen. It is characterized by a distinctive facial appearance, eye abnormalities, hearing loss and joint problems. Ocular involvements are early onset cataract, myopia, abnormal vitreous humor, retinal detachment, and most of the patients exhibit short stature. Onesimo R et al. reported on a 5-year-old girl affected by Stickler syndrome who

was diagnosed with GD in preclinical state, during health supervision and evaluation by pediatric endocrinologist for short stature [30]. None of her family member suffered from autoimmune thyroid disorder and her medical history was negative for autoimmune disease. Association between Stickler's syndrome and GD in this case seems to be an incidental coexistence.

9. Reconstitution Graves' Disease

Reviewing the manuscripts on Graves' Disease and rare comorbidity, a new issue has been raised. Growing numbers of publication on the association between biological treatment for life-threatening and/or medication-refractory disorders, and the development of autoimmune hyperthyroidism in adults, call the attention to secondary GD [31, 32]. The use of different modality targeting the immune system as a curative therapy (e.g. hematopoietic stem cell transplantation /HSCT/, antithymocyte globulin/ATG/, antiretroviral therapy/ART/etc.), has had a profound impact on clinical outcomes. A subset of patients may experience immune restoration disease (IRD)/immune reconstitution inflammatory syndrome (IRIS) affecting the thyroid gland in two form, such as Hashimoto thyroiditis or Graves' hyperthyroidism. Although both are more common in children because of early thymic damage, it has received little attention in pediatric literature [33]. Sporadic cases were reported on challenging autoimmune processes: Defective T-cell function take place during the pathogenesis both of aplastic anemia (AA) and GD. Antithyroid drugs used for the management of GD may induce AA and GD may occur following treatment of severe aplastic anemia (SAA). The latter occurred in a 11-year-old girl who had been treated with allogenic HSCT at age of 8 years as having severe acquired AA [34]. A case of another child was published earlier with chronic relapsing severe aplastic anemia and GD [35]. Authors supposed a close relation in manifestation of hypertyroidism due to withdrawal of immunosuppressants. In adult patients the secondary GD may exhibit a fluctuating course, with alternating phases of hyper- and hypothyroidism, due to the coexistence of TRAb with stimulating and blocking function [36]. Clinicians need to remain vigilant when initiating immune reconstitution therapy, and a careful management and follow-up for thyroid function after these treatments are essential.

10. Discussion

In this chapter we presented a spectrum of unusual clinical findings, signs of Graves-Basedow's disease in childhood, but atypical laboratory results. Less common and less distinctive features detailed above are well documented in adults, which suggests that these are neither age-dependent nor characteristic to pediatric GD. Though the mechanism remains uncertain in majority of unusual manifestations, the recovery that occurs parallelly with restoration of euthyroidism, gives the evidence of their relation to GB hyperthyroidism. Metamorphic thyroid autoimmunity, a phenomenon of conversion from Hashimoto thyroiditis to Graves' Disease is also summarized without guessing the clue of this immunological paradigm. Existence of a continuum between HT and GD within the spectrum of thyroid autoimmunity is confirmed in pediatric population without coexistent chromosome abnormalities, also in children with Turner or Down syndrome. Beside this peculiar event sequence, GD in DS patient can be insidious by presenting delayed clinical symptoms even with multiple organ derangements. In some rare syndromic disorder regular clinical assessment and biochemical screening supports to reveal

the occurrence of Graves' hyperthyroidism. Finally, a very vulnerable population with malignancy, immune deficiency syndromes, hemoglobinopathies and other disorders attract attention with a possible secondary GB following immune reconstitution therapy. Awareness about the relation of these remote findings to GD, or frequent coexistence with GD is important for early diagnosis, and a reasonable suspicion for Graves' Disease may ultimately help to prevent unnecessary investigations and treatment.

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Author details

Agota Muzsnai

North-Buda Center, New St John's Hospital and Outpatient Clinic, Department of Pediatric Endocrinology, Budapest, Hungary

*Address all correspondence to: muzsnaia@freemail.hu

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