

Hyperthyroidism in childhood: peculiarities of the different clinical pictures

Giuseppina Zirilli, Maria Rosa Velletri, Federica Porcaro, Giuseppina Di Giovine, Pina Maisano, Giuseppina La Monica

Department of Pediatric, Gynecological, Microbiological and Biomedical Sciences, University of Messina, Messina, Italy

Summary. *Background:* clinical and biochemical picture of hyperthyroidism in children may significantly change according to its etiologies. *Objectives:* to report the most recent views about epidemiology, pathophysiology, clinical and biochemical course, diagnostic procedures and management of hyperthyroid syndrome in childhood, according to its different etiologies. *Design:* Graves' disease and Hashimoto's thyroiditis are responsible for 84% and 12%, respectively, of all the cases of hyperthyroidism in childhood. Hyperfunctioning thyroid nodules (<3% of cases), TSH-secreting adenomas (~1%) and McCune-Albright syndrome (~1%) are distinctly less common. The main hormonal and immunological features of all these conditions were summarized in Table 1, whereas their anamnestic and clinical peculiarities and the diagnostic procedures which may be useful in the differential diagnosis were reported in Table 2. *Conclusions:* 1) hyperthyroid syndrome in childhood may present with very different clinical pictures, which are specifically related to the respective etiologies; 2) diagnostic procedures and therapeutic management are not the same in the various conditions. (www.actabiomedica.it)

Key words: Graves' disease, hashitoxicosis, hyperfunctioning thyroid nodules, TSH-secreting adenomas, McCune-Albright syndrome

List of abbreviations

AITD: autoimmune thyroid disease; DS: Down syndrome; GD: Graves' disease; HT: Hashimoto's thyroiditis; HTN: Hyperfunctioning thyroid nodules; Htx: hashitoxicosis; MMI: methimazole; MRI: Magnetic resonance imaging; MAS: McCune-Albright syndrome; RAIU: radioactive iodide uptake; TRABs: thyrotropin receptor autoantibodies; TS: Turner syndrome; US: ultrasonography.

Background

Hyperthyroidism is a thyroid dysfunction disorder which is characterized, in childhood, by impaired concentration and school performance, headache, hyperactivity, fatigue, palpitations and tachycardia, systolic hypertension, heat intolerance, increased fre-

quency of bowel movements and consequent diarrhea, weight loss and tremors. All these clinical manifestations are due to the peripheral effects of the high FT4 serum levels, which reflect a hormone overproduction by thyroid gland.

Hyperthyroidism is relatively rare in children (yearly incidence of 8 per 1,000,000 children less than 15 years old and 1 per 1,000,000 children less than 4 years old). Although Graves' disease (GD) is by far the most common cause of children's hyperthyroidism, nevertheless other pathologies may be less frequently involved in its etiology and clinical and biochemical picture of hyperthyroid syndrome may significantly change according to the different etiologies (Table 1).

The aim of this review is to report the most recent views about epidemiology, pathophysiology, clini-

Table 1. Hormonal and immunological findings in children with hyperthyroidism according to the different etiologies, whose relative prevalences (%) are also reported

Disorder	FT4 [°]	TSH ^{°°}	TPOAbs [•]	TRABs ^{••}	Relative prevalence*
Graves' disease	High	Low	Positive	Positive	84
Hashitoxicosis	High	Low	Positive	Negative	12
Hyperfunctioning thyroid nodules	High - normal	Low	Negative	Negative	<3
TSH-secreting adenomas	High	High - normal	Negative	Negative	~1
TSH receptor activating mutations	High	Low	Negative	Negative	~1

[°] Free thyroxine serum levels, ^{°°} Thyrotropin serum levels, [•] Thyroid peroxidase autoantibody serum levels, ^{••} Thyrotropin receptor autoantibody serum levels, * as cause of hyperthyroidism in children

cal and biochemical course, diagnostic procedures and management of hyperthyroid syndrome in childhood, according to its different etiologies.

Graves' disease

It is the commonest cause of hyperthyroidism, which is responsible for 84% of pediatric cases (1). It is a rare disease, at least in childhood, accounting for 1 to 5% of all patients with GD. It may occur at any age during childhood, but its frequency increases with age, peaking during adolescence (1). Its prevalence rate in young people between 10 and 19 years is 1.07% (2), that is distinctly lower than that reported for Hashimoto's thyroiditis (HT), i.e. 1.3% (3).

GD is predominant in girls and in the individuals with autoimmune thyroid disease (AITD) familial antecedents. Its development is conditioned by both genetic and environmental factors (4,5). Another important risk factor is the predisposition to autoimmunity, as also confirmed by its frequent association with other autoimmune diseases, such as juvenile idiopathic arthritis, pernicious anemia, systemic lupus erythematosus, Addison's disease, celiac disease and vitiligo (6). The existence of a strong association with type 1 diabetes has been questioned (7), whereas the existence of HT antecedents in the past history of children with GD has been demonstrated as relatively common (3.7% of cases) (8). These findings suggest that, in the pediatric general population, there exists a continuum between HT and GD within the spectrum of AITDs (8).

Another important risk factor for GD development is the association with both Turner syndrome (TS) (9-14) and Down syndrome (DS) (15-17), i.e.

two chromosomopathies which are known to be associated with an increased risk of AITDs (18-21).

From a clinical point of view GD is characterized by the common and aspecific manifestations of thyrotoxicosis. Other more specific signs are thyromegaly, which is almost constant, and exophthalmos, that is detectable in only 20% of cases, at least in our experience (16), whilst it is generally considered as a typical clinical sign of GD in adulthood. Ocular signs are generally less severe in children than in adults (22) and can be attributed to the inflammation and muscle swelling rather than to infiltrative disease of the orbital structures (5). As expected, these signs (lid retraction and eye proptosis) may spontaneously improve in most children after euthyroidism restoration (22). Also pretibial myxedema is more infrequent in children than in adults (22). Absolutely typical of pediatric GD is the acceleration of linear growth and bone maturation associated with prolonged hyperthyroidism (23).

A differential diagnosis between GD and the other causes of thyrotoxicosis is mandatory, considering that management approach may be extremely different according to the different etiologies. In clinical practice, the combination of goiter, ocular signs, thyrotoxicosis symptoms, positive thyrotropin receptor autoantibodies (TRABs), in the absence of a nodule at ultrasonography (US), is virtually diagnostic of GD (5). The radioactive iodide uptake (RAIU) is very infrequently indicated for differential diagnosis and may be taken into consideration only in the children in whom a discrete nodule(s) is palpable or evident at US (5).

Although there is currently no evidence-based strategy for the management of GD in childhood (24), nevertheless methimazole (MMI) is generally considered as the first-line therapy, whereas propylthiouracil

should be avoided, due to the high risk of iatrogenic hepatitis (24,25). In the patients displaying good compliance with MMI and no major side effects, this treatment should be significantly prolonged over time, in order to potentiate its effects in terms of remission rates (26). However, if no remission is obtained within 1-2 years of MMI treatment, surgery or I131 should be considered for a radical therapy, with the choice according to patient's age (25).

Long-term outcome and sensitivity to pharmacological treatment are significantly conditioned by age, thyroid size, severity of biochemical picture and TRAB serum levels at GD presentation (24,25). The association with other autoimmune diseases (7) or TS (14) or DS (16) does not seem to be able to significantly affect both sensitivity to pharmacological treatment and evolution over time of GD in childhood.

Hashimoto's thyroiditis

HT is the commonest form of thyroiditis in childhood (27) and the most frequent cause of pediatric thyroid diseases in iodine-replete areas of the world.

In 6.5-13.8% of children HT may present with a picture of either subclinical or overt hyperthyroidism (28-31), a condition that is also known as hashitoxicosis (Htx). Htx is the second commonest cause of hyperthyroidism in children (Table 1), preceded by GD (32). It is believed to result from unregulated release of stored hormones during inflammatory-mediated destruction of thyroid gland at HT presentation. Its presenting clinical and biochemical manifestations may be similar to those observed in GD and, therefore, differential diagnosis between Htx and GD may not be initially easy, at least if based on only clinical and biochemical features (33,34). However, the assessment of TRAB serum levels (that are generally undetectable in Htx) may be very useful for an early differential diagnosis.

Htx next evolution may widely vary in the different cases but is always characterized by a definitive resolution over time (33,34). In only few cases MMI treatment may be necessary for a short time, whilst non-pharmacological therapies are never needed (34).

In the cases presenting with HT-related subclini-

cal hyperthyroidism (suppressed TSH levels with FT4 serum concentrations within normal limits), a spontaneous normalization of TSH levels spontaneously occurs during the first 24 months from diagnosis, as well as in age-matched children with Htx (35). Therefore, HT-related subclinical hyperthyroidism and Htx might be seen as different biochemical stages along the same continuum (35).

Hyperfunctioning thyroid nodules (HTN)

This is a condition whose prevalence increases with age achieving its peak after the age of 50 and is significantly higher in women.

HTNs represent less than 3% of all causes of hyperthyroidism in pediatric age (36). In fact, thyroid nodules in children are generally non-functioning and the proportion of HTNs in the different pediatric series of solitary thyroid nodules has been reported to be very low (36).

The biochemical picture which is most frequently detected in the children with HTNs is subclinical hyperthyroidism, that is not compatible with clinically appreciable alterations of thyroid status. These findings are not surprising considering that the reason for thyrotoxicosis caused by HTNs is a slow multiplication of autonomous follicles, as also substantiated by the positive relationship between nodular size and severity of hyperthyroidism, which is known to exist.

Despite the relative rarity of HTNs as cause of hyperthyroidism in pediatric age, this diagnosis should be taken into consideration in all the children with a mild picture of thyrotoxicosis and no thyroid autoimmunity signs, provided that a discrete nodule is palpable or evident at US (5). In these cases it is indicated to perform a gland RAIU, which may evidence either a hyperfunctioning nodule surrounded by non-fixing thyroid tissue or an increased uptake at the nodular site and the remaining thyroid tissue visible on the scan.

Spontaneous resolution of HTNs is unlikely and the possibility of a subsequent toxic evolution needs to be carefully considered. Moreover, the risk of malignancy, although remote, cannot be completely excluded. Therefore, a surgical treatment is indicated not only in the cases with toxic HTNs, but also in those

Table 2. Anamnestic, clinical and diagnostic procedure features in children with hyperthyroidism according to the different etiologies

Disorder	Familial history of thyroid disorders	Personal antecedents of autoimmune diseases	Goiter	Thyroid US*	Thyroid RAIU**	CNS MRI°
Graves' disease	+	+	+	hypoechoogenic pattern	not indicated	not indicated
Hashitoxicosis	+	+	±	hypoechoogenic pattern	not indicated	not indicated
Hyperfunctioning thyroid nodules	±	-	±	nodular image	hot nodule	not indicated
TSH-secreting adenomas	-	-	-	not indicated	not indicated	pituitary adenoma
TSH receptor activating mutations	-	-	±	hypo/isoechoic nodules	not indicated	not indicated

*US = ultrasonography, **RAIU = radioactive iodide uptake, ° CNS MRI = central nervous system magnetic resonance imaging

with HTNs, progressive enlargement of nodules and subclinical hyperthyroidism. In fact, several cases of primary carcinoma occurring in HTNs have been reported in the most recent pediatric literature (37-40).

Central hyperthyroidism

A picture of hyperthyroidism may sporadically occur as consequence of an increased TSH overproduction by unregulated pituitary TSH-secreting cells (pituitary adenoma). In children the commonest hormonally active pituitary adenoma is prolactinoma, followed in order of frequency by the non-functioning (non-secreting) adenoma, ACTH-secreting adenoma and GH-secreting adenoma (41). TSH-secreting pituitary adenomas are very rare especially in childhood (42) and biochemical analysis shows in these cases an elevated FT4 serum level with a non-suppressed or high TSH (Table 1). Magnetic resonance imaging (MRI) is the gold standard neuroradiological investigation for diagnosis of pituitary adenomas (Table 2) and for differential diagnosis between microadenomas and macroadenomas (43). Surgery is the only available therapy for TSH-secreting adenomas, whereas pharmacological therapies may be effective in the management of prolactinomas and GH-secreting pituitary adenomas (43).

McCune-Albright syndrome (MAS)

In children with MAS thyroid alterations are known to occur in 31% of cases (44). In only 11.1%, however, a picture of hyperthyroidism may be observed (44). Therefore, MAS is a very uncommon cause of hyperthyroidism in childhood, although thyropathy is the second most frequent endocrinopathy in children with MAS, preceded by precocious puberty (45-47).

The pathogenesis of MAS-related hyperthyroidism is the constitutive activation of G α protein in thyroid tissue that leads to cAMP overproduction stimulating growth of thyrocytes and FT4 hypersecretion (44). A pathogenetic role of autoimmunity or pituitary activation can be excluded (44).

The typical picture that is observed in the children with MAS-related hyperthyroidism is a micronodular goiter evolving, over time, into a nodular goiter with a bigger hypo/isoechoic nodule, inhomogeneous gland structure and diffuse hypervascularization (44). Pharmacological treatment, with lower MMI doses than those needed in GD, gives a satisfactory, albeit not definitive, remission of hyperthyroidism (44).

On overall, anamnestic, clinical and diagnostic procedure features in children with hyperthyroidism according to the different etiologies are summarized in Table 2.

To conclude: 1) hyperthyroid syndrome in childhood may present with very different clinical pictures, which are specifically related to the respective etiologies; 2) diagnostic procedures and therapeutic management are not the same in the various conditions.

References

- De Luca F, Alessi L, Bruno E, et al. Graves' disease in childhood: new epidemiological, pathophysiological and therapeutic insights. *Minerva Pediatr* 2014 Dec 12. [Epub ahead of print]
- Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. *Autoimmun Rev* 2003; 2: 119-25.
- Tozzoli R, Perini R. Malattie autoimmuni nei primi anni di vita: dai sintomi alla diagnosi di laboratorio. *Riv Ital Med Lab – It J Lab Med* 2007; 3: 45-50.
- Hemminki K, Li X, Sundquist J, Sundquist K. The epidemiology of Graves' disease: evidence of a genetic and an environmental contribution. *J Autoimmun* 2010; 34: J307-13.
- Cappa M, Bizzarri C, Crea F. Autoimmune thyroid diseases in children. *J Thyroid Res* 2011; 675703. doi: 10.4061/2011/675703.
- Boelaert K, Newby PR, Simmonds MJ, et al. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med* 2010; 123: 183.e1-9.
- Lombardo F, Messina MF, Salzano G, et al. Prevalence, presentation and clinical evolution of Graves' disease in children and adolescents with type 1 diabetes mellitus. *Horm Res Paediatr* 2011; 76: 221-5.
- Wasniewska M, Corrias A, Arrigo T, et al. Frequency of Hashimoto's thyroiditis antecedents in the history of children and adolescents with graves' disease. *Horm Res Paediatr* 2010; 73: 473-6.
- Livadas S, Xekouki P, Fouka F, et al. Prevalence of thyroid dysfunction in Turner's syndrome: a long-term follow-up study and brief literature review. *Thyroid* 2005; 15: 1061-6.
- Fukuda I, Hizuka N, Kurimoto M, et al. Autoimmune thyroid diseases in 65 Japanese women with Turner syndrome. *Endocr J* 2009; 56: 983-6.
- Wasniewska M, Corrias A, Messina MF, et al. Graves' disease prevalence in a young population with Turner syndrome. *J Endocrinol Invest* 2010; 33: 69-70.
- Gawlik A, Gawlik T, Januszek-Trzciakowska A, Patel H, Malecka-Tendera E. Incidence and dynamics of thyroid dysfunction and thyroid autoimmunity in girls with Turner's syndrome: a long-term follow-up study. *Horm Res Paediatr* 2011; 76: 314-20.
- Bakalov VK, Gutin L, Cheng CM, et al. Autoimmune disorders in women with turner syndrome and women with karyotypically normal primary ovarian insufficiency. *J Autoimmun* 2012; 38: 315-21.
- Valenzise M, Aversa T, Corrias A, et al. Epidemiology, presentation and long-term evolution of Graves' disease in children, adolescents and young adults with Turner syndrome. *Horm Res Paediatr* 2014; 81: 245-50.
- Goday-Arno A, Cerda-Esteve M, Flores-Le-Roux JA, Chillaron-Jordan JJ, Corretger JM, Cano-Pérez JF. Hyperthyroidism in a population with Down syndrome (DS). *Clin Endocrinol* 2009; 71: 110-4.
- De Luca F, Corrias A, Salerno M, et al. Peculiarities of Graves' disease in children and adolescents with Down's syndrome. *Eur J Endocrinol* 2010; 162: 591-5.
- Salzano G, Lombardo F, Arrigo T, et al. Association of five autoimmune diseases in a young woman with Down's syndrome. *J Endocrinol Invest* 2010; 33: 202-3.
- Elsheikh M, Dunger DB, Conway GS, Wass JA. Turner's syndrome in adulthood. *Endocr Rev* 2002; 23: 120-40.
- Roizen NJ, Patterson D. Down's syndrome. *Lancet* 2003; 361: 1281-9.
- Aversa T, Lombardo F, Corrias A, Salerno M, De Luca F, Wasniewska M. In young patients with Turner or Down syndrome, Graves' disease presentation is often preceded by Hashimoto's thyroiditis. *Thyroid* 2014; 24: 744-7.
- Aversa T, Salerno M, Radetti G, et al. Peculiarities of presentation and evolution over time of Hashimoto's thyroiditis in children and adolescents with Down's syndrome. *Hormones* 2015 in press, accepted for publication on February, 19, 2015.
- Grüters A. Ocular manifestations in children and adolescents with thyrotoxicosis. *Exp Clin Endocrinol Diabetes* 1999; 107 Suppl 5: S172-4.
- Wong GW, Lai J, Cheng PS. Growth in childhood thyrotoxicosis. *Eur J Pediatr* 1999; 158: 776-9.
- Léger J, Carel JC. Hyperthyroidism in childhood: causes, when and how to treat. *J Clin Res Pediatr Endocrinol* 2013; 5 Suppl 1: 50-6.
- Rivkees SA. Pediatric Graves' disease: controversies in management. *Horm Res Paediatr* 2010; 74: 305-11.
- Léger J, Gelwane G, Kaguelidou F, Benmerad M, Alberti C; French Childhood Graves' Disease Study Group. Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study. *J Clin Endocrinol Metab* 2012; 97: 110-9.
- Wasniewska M, Vigone MC, Cappa M, Aversa T, Rubino M, De Luca F; Study Group for Thyroid diseases of Italian Society for Pediatric Endocrinology. Acute suppurative thyroiditis in childhood: relative frequency among thyroid inflammatory diseases. *J Endocrinol Invest* 2007; 30: 346-7.
- Demirbilek H, Kandemir N, Gonc EN, Ozon A, Alikasifoglu A. Assessment of thyroid function during the long course of Hashimoto's thyroiditis in children and adolescents. *Clin Endocrinol* 2009; 71: 451-4.
- Özen S, Berk Ö, Şimşek DG, Darcan S. Clinical course of Hashimoto's thyroiditis and effects of levothyroxine therapy on the clinical course of the disease in children and adolescents. *J Clin Res Pediatr Endocrinol* 2011; 3: 192-7.

30. Wasniewska M, Corrias A, Salerno M, et al. Thyroid function patterns at Hashimoto's thyroiditis presentation in childhood and adolescence are mainly conditioned by patients' age. *Horm Res Paediatr* 2012; 78: 232-6.
31. De Luca F, Santucci S, Corica D, Pitrolo E, Romeo M, Aversa T. Hashimoto's thyroiditis in childhood: presentation modes and evolution over time. *Ital J Pediatr* 2013; 39: 8.
32. Williamson S, Greene SA. Incidence of thyrotoxicosis in childhood: a national population based study in the UK and Ireland. *Clin Endocrinol* 2010; 72: 358-63.
33. Nabhan ZM, Kreher NC, Eugster EA. Hashitoxicosis in children: clinical features and natural history. *J Pediatr* 2005; 146: 533-6.
34. Wasniewska M, Corrias A, Salerno M, et al. Outcomes of children with hashitoxicosis. *Horm Res Paediatr* 2012; 77: 36-40.
35. Aversa T, Valenzise M, Corrias A, et al. Subclinical hyperthyroidism when presenting as initial manifestation of juvenile Hashimoto's thyroiditis: first report on its natural history. *J Endocrinol Invest* 2014; 37: 303-8.
36. Niedziela M. Thyroid nodules. *Best Pract Res Clin Endocrinol Metab* 2014; 28: 245-77.
37. Tfayli HM, Teot LA, Indyk JA, Witchel SF. Papillary thyroid carcinoma in an autonomous hyperfunctioning thyroid nodule: case report and review of the literature. *Thyroid* 2010; 20: 1029-32.
38. A Damle N, Gupta S, Kumar P, Mathur S, Bal C. Papillary carcinoma masquerading as clinically toxic adenoma in very young children. *J Pediatr Endocrinol Metab* 2011; 24: 1051-4.
39. Ruggieri RM, Campenni A, Giovinazzo S, et al. Follicular variant of papillary thyroid carcinoma presenting as toxic nodule in an adolescent: coexistent polymorphism of the TSHR and Gs α genes. *Thyroid* 2013; 23: 239-42.
40. Gabalec F, Svilias I, Plasilova I, Hovorkova E, Ryska A, Horacek J. Follicular variant of papillary carcinoma presenting as a hyperfunctioning thyroid nodule. *J Pediatr Hematol Oncol* 2014; 36: e94-6.
41. Jackman S, Diamond F. Pituitary adenomas in childhood and adolescence. *Pediatr Endocrinol Rev* 2013; 10: 450-9.
42. Fliers E, Boelen A, van Trotsenburg AS. Central regulation of the hypothalamo-pituitary-thyroid (HPT) axis: focus on clinical aspects. *Handb Clin Neurol* 2014; 124: 127-38.
43. Cannavò S, Venturino M, Curtò L, et al. Clinical presentation and outcome of pituitary adenomas in teenagers. *Clin Endocrinol* 2003; 58: 519-27.
44. Tessaris D, Corrias A, Matarazzo P, et al. Thyroid abnormalities in children and adolescents with McCune-Albright syndrome. *Horm Res Paediatr* 2012; 78: 151-7.
45. Feuillan PP, Shawker T, Rose SR, Jones J, Jeevanram RK, Nisula BC. Thyroid abnormalities in the McCune-Albright syndrome: ultrasonography and hormonal studies. *J Clin Endocrinol Metab* 1990; 71: 1596-601.
46. Mastorakos G, Mitsiades NS, Doufas AG, Koutras DA. Hyperthyroidism in McCune-Albright syndrome with a review of thyroid abnormalities sixty years after the first report. *Thyroid* 1997; 7: 433-9.
47. Congedo V, Celi FS. Thyroid disease in patients with McCune-Albright syndrome. *Pediatr Endocrinol Rev* 2007; 4 Suppl 4: 429-33.

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Correspondance:

Giuseppina Zirilli, MD

Dipartimento di Scienze Pediatriche,

Ginecologiche, Microbiologiche e Biomediche,

Policlinico Universitario di Messina,

Via Consolare Valeria, 98125 Messina, Italy

Tel. +39 090 692407

Fax +39 090 2212143

E-mail: zirillig@gmail.com