

Persistent remission of Graves' disease or evolution from Graves' disease to Hashimoto's thyroiditis in childhood – a report of 6 cases and clinical implications

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Abstract

BACKGROUND: The main clinical manifestations of autoimmune thyroid diseases are Graves' disease (GD) and Hashimoto's thyroiditis (HT). Graves' disease is the cause of most cases of hyperthyroidism in childhood. Indications for radical therapy (surgery or ¹³¹I treatment) in children are still a matter of discussion, as sustained (sometimes very long) remission of GD is possible, while the radical therapy almost always leads to hypothyroidism. Spontaneous evolution from GD with hyperthyroidism to HT with hypothyroidism may also be observed.

OBJECTIVE: The aim of the study was to analyze the clinical course of 6 cases of hyperthyroid girls with GD in whom a normalization of previously increased autoantibodies against thyrotropin (TSH) receptor (anti-TSHR) was observed together with a significant increase in autoantibodies against thyroid peroxidase (anti-TPO) and thyroglobulin (anti-Tg), with concomitant hypo- or euthyroidism but no recurrence of hyperthyroidism.

SUBJECTS: Patients' age at diagnosis ranged from 5.0 to 16.5 years. Two (2) patients had Turner syndrome, another one (1), diabetic, was on insulin therapy.

RESULTS: In all the girls, antithyroid drugs were administered and euthyroid state was achieved during the first 2.0–3.5 months of the treatment. Mild side effects were observed in only one case. The therapy was continued up to 1.5–4.0 years. Relapses during the therapy were observed in 2 cases. Up to now, no relapses have been observed for 0.5–7.5 years since the therapy withdrawal in 5 patients (1 patient was lost to follow-up), 2 patients are currently treated with levothyroxine due to hypothyroidism.

CONCLUSIONS: It seems that the prolonged pharmacotherapy with antithyroid drugs, followed by observation after remission of hyperthyroidism, may be an appropriate therapeutic option at least in some children with GD as they can be cured without radical therapy and the potential risks of such treatment.

Abbreviations:

AITD	- autoimmune thyroid diseases
anti-Tg	- anti-thyroglobulin antibodies
anti-TPO	- anti-thyroperoxidase antibodies
anti-TSHR	- anti-TSH receptor antibodies
FT ₃	- free triiodotyronine
FT ₄	- free thyroxine
GD	- Graves' disease
HRT	- hormonal replacement therapy
HT	- Hashimoto's thyroiditis
L-T ₄	- L-thyroxine
MMI	- methimazole
PTU	- propylthiouracil
rhGH	- recombinant human growth hormone
TBAb	- TSHR blocking antibodies
TRAb	- TSHR stimulating antibodies
Treg	- T regulatory cells
TS	- Turner syndrome
TSH	- thyroid-stimulating hormone, thyrotropin
TSHR	- thyroid-stimulating hormone receptor

INTRODUCTION

The main clinical manifestations of autoimmune thyroid diseases (AITD) are Graves' disease (GD) and Hashimoto's thyroiditis (HT). In the pathogenesis of GD, complex interactions between genetic and environmental factors are involved, leading to the production of autoantibodies against TSH receptor (anti-TSHR). Hashimoto's thyroiditis is associated with the presence of autoantibodies against thyroid peroxidase (anti-TPO) and/or thyroglobulin (anti-Tg). Thyroid stimulating anti-TSHR (TRAb) are pathognomonic of GD, however both anti-TPO and anti-Tg are also present in many patients with GD. In some of them, chronic autoimmune thyroiditis may develop, leading to hypothyroidism. Previously, GD and HT were considered as separate diseases, but – in recent years – they are understood to be the two ends of the spectrum of AITD. Factors determining the balance between these diseases in humans remain unknown, however the results of animal studies suggest the role of T regulatory cells (Treg) as a link between GD and HT (McLachlan *et al.* 2007).

Thyrotropin receptor antibodies which stimulate the thyroid cause Graves' hyperthyroidism, while TSHR antibodies which block TSH action (TBAb) are occasionally responsible for hypothyroidism. Sporadically, patients may switch from TRAb to TBAb (or *vice versa*) with concomitant thyroid function changes (McLachlan *et al.* 2013).

Graves' disease is the main cause of hyperthyroidism in childhood. It has recently been estimated that children represent only 1 to 5% of all cases of GD (Léger & Carel 2013). The incidence of GD in adolescents has been reported to range from 3 per 100 000 in Denmark (Lavard *et al.* 1994) to 14 per 100 000 in Hong Kong (Wong & Cheng 2001), with female predominance (Lavard *et al.* 1994; Wong & Cheng 2001). In the management of GD, the main therapeutic options are anti-thyroid drugs, radioiodine (¹³¹I) administration and

thyroidectomy. The treatment usually starts from pharmacotherapy with subsequent radioiodine or surgery in case of adverse events or recurrent hyperthyroidism.

Indications for such a definitive therapy (radical treatment) in children are still a matter of discussion. Only 20–30% likelihood of long-term remission (Hamburger 1985; Glaser & Styne 2008), the necessity of more prolonged pharmacotherapy in children than in adults, as well as the risk of adverse events related to the use of antithyroid drugs are the most important arguments for other methods of therapy (radioiodine, surgery). On the other hand, the phenomenon of sustained remission of GD, very high incidence of hypothyroidism after radioiodine or surgery requiring levothyroxine (L-T₄) substitution (and the potential complications of poorly controlled hypothyroidism in childhood, adolescence and adulthood), as well as the risk of hypoparathyroidism after thyroidectomy and the potential risk of malignancy after ¹³¹I administration in childhood should be taken into account. The authors of most recent review on hyperthyroidism in childhood, Léger and Carel (2013), clearly stressed the need of the improvement in GD management by identification of patients requiring only prolonged pharmacotherapy and those in whom early use of alternative methods of treatment may be beneficial.

Hashimoto's thyroiditis is the most common disease of thyroid gland in children in the areas of sufficient iodine supply. Recent report on a large group of children and adolescents with HT has shown more than 50% incidence of euthyroidism, more than 40% of hypothyroidism and 6% of hyperthyroidism (Hashitoxicosis) at the diagnosis of HT (Wasniewska *et al.* 2012). It is essential to distinguish between thyrotoxicosis caused by activation of TSHR by TRAb and transient phase of Hashitoxicosis during the initial phase of HT, related mainly to the release of stored thyroid hormones from the thyroid gland damaged by the inflammatory process (De Luca *et al.* 2013). The evolution from GD with hyperthyroidism to HT with hypothyroidism may be observed in some of the patients who were not subjected to radical therapy (Wood & Ingbar 1979; McLachlan *et al.* 2007).

The aim of present study was to report 6 cases of hyperthyroid girls with GD, in whom a normalization of previously increased TRAb levels during methimazole (MMI) or propylthiouracil (PTU) therapy was observed together with a significant increase in anti-TPO and anti-Tg antibodies concentrations, with concomitant hypo- or euthyroidism but no recurrence of hyperthyroidism during the follow-up after pharmacotherapy withdrawal.

CASE PRESENTATIONS

The detailed data of the patients and results of hormonal tests at diagnosis of GD are presented in Table 1. The data concerning the most recent assessment of

these patients after the antithyroid therapy withdrawal are collected in Table 2. For further details, see below the description of patients' clinical course.

Case no. 1

5-year-old girl, diagnosed in Outpatient Clinic of Endocrinology due to enlargement of thyroid gland, tachycardia, weight loss and diarrhoea. Patient's and family history were irrelevant. The diagnosis of GD was confirmed by decreased TSH and elevated free thyroxine (FT₄) and free triiodotyronine (FT₃) concentrations as well as increased TRAb level. In this girl, both anti-TPO and anti-Tg concentrations were also very high from the first months of the disease (see Table 1). Therapy with MMI was started from a daily dose of 15 mg (0.75 mg/kg). After 2 months of the treatment the patient presented with hypothyroidism and MMI dose was decreased to 5 mg/day and after the subsequent 12 months of treatment – to 2.5 mg/day. After 6 months

(18 months from the diagnosis), the recurrence of hyperthyroidism was observed. The dose of MMI was increased to 10 mg for 3 months and euthyroidism was achieved again, thus enabling to decrease MMI dose to 2.5 mg/day. The latter dose was administered for over 2 years. In the second year of treatment the patient presented with *vitiligo*. Puberty was normal, menstruations started at the age of 12 and have been regular. At present, the patient is 16 years old. For the 6 years of follow-up she has been euthyroid without any treatment, with slightly enlarged hypoechoic thyroid gland but with no focal lesions found in ultrascan (US) examination.

Case no. 2

6.5-year-old girl, diagnosed in the Department of Endocrinology and Metabolic Diseases due to the enlargement of thyroid gland and exophthalmia observed for a year, as well as tachycardia, weakness and weight loss observed for a few months. Patient's and family

Tab. 1. The detailed data of patients and the results of hormonal tests at diagnosis of GD.

Case	1	2	3	4	5	6
Age [years]	5.5	6.5	13.5	16.5	11.0	16.5
TSH [mU/l]	<0.005	<0.005	0.009	<0.005	<0.005	<0.01
FT ₄ [ng/dl]	1.88	>7.77	2.50	2.46	5.28	4.51
FT ₃ [pg/ml]	–	21.62	5.56	9.12	30.21	15.51
TRAb [IU/l]	3.80	10.30	7.05	3.82	8.97	2.97
anti-TPO [IU/ml]	>600.0	65.8	447.5	7.2	571.1	437.1
anti-Tg [IU/ml]	1614.0	4.8	775.8	410.6	42.6	2219.0
Time period to euthyroid state [months]	2.0	3.5	2.5	3.0	3.0	3.5
MMI therapy duration [years]	4.0	4.0	3.0	1.5	1.5	1.5
Adverse events	no	no	skin rash	no	no	no
N° of relapses	1	no	1	no	no	no

Reference ranges for laboratory tests:

TSH: 0.27–4.2 mU/l; FT₄: 0.93–1.7 ng/dl; FT₃: 2.56–5.01 pg/ml; TRAb: 0–1.75 IU/ml; anti-TPO: 0–34 IU/ml; anti-Tg: 0–115 IU/ml

Tab. 2. The most recent assessment of the patients after TRAb normalisation.

Case	1	2	3	4	5	6
Age [years]	16.0	18.0	18.5	18.0	14.5	18.5
Time period after MMI withdrawal [years]	6.5	7.5	2.0	no	2.0	0.5
L-T ₄ substitution	no	yes	no	no	yes	no
TSH [mU/l]	2.47	0.93	1.55	1.77	2.11	7.88
FT ₄ [ng/dl]	1.10	1.19	1.46	1.21	1.36	0.96
FT ₃ [pg/ml]	3.23	3.01	3.05	3.34	4.08	3.09
TRAb [IU/l]	0.62	negative	0.46	0.46	<0.3	1.70
anti-TPO [IU/ml]	>600	302.9	169.4	18.77	>600	248.8
anti-Tg [IU/ml]	1039	137.4	381.0	431.3	2143	1913
Current therapy	no	L-T ₄ , insulin	no	MMI 5 mg	L-T ₄	HRT

Reference ranges for laboratory tests:

TSH: 0.27–4.2 mU/l; FT₄: 0.93–1.7 ng/dl; FT₃: 2.56–5.01 pg/ml; TRAb: 0–1.75 IU/ml; anti-TPO: 0–34 IU/ml; anti-Tg: 0–115 IU/ml

history were irrelevant. The therapy with MMI was started from a dose of 10 mg (0.6 mg/kg) and continued in gradually decreased doses up to 2.5 mg/day for over 4 years. Ocular changes completely disappeared during a few months but *vitiligo* appeared. After MMI withdrawal, increased concentrations of anti-TPO and anti-Tg antibodies were observed, leading to subclinical hypothyroidism. In the age of 10 years the patient was also diagnosed with type 1 diabetes mellitus and started insulin therapy. Puberty was normal. At present, the patient is 18 years old, treated with insulin and L-T₄ at a daily dose of 25 µg due to subclinical hypothyroidism. US image of the thyroid is typical for HT.

Case no. 3

13.5-year-old patient referred to the Outpatient Clinic of Endocrinology by general practitioner due to goitre and exophthalmos, with no weight loss or other complaints. On admission, no evident signs or symptoms of hyperthyroidism were present. Thyroid hormones were slightly elevated, while TSH decreased but not suppressed, TRAb, anti-TPO and anti-Tg antibodies concentrations were increased. Patient's and family history were irrelevant. The therapy was started from 150 mg PTU (due to the temporary unavailability of MMI) and switched to MMI after 3 months but next returned to PTU due to skin rash as a side effect of MMI. The therapy with antithyroid drugs was withdrawn after 1 year. After 4 months from PTU discontinuation the patient was admitted to the Department of Endocrinology and Metabolic Diseases with enlarged and painful thyroid gland, without symptoms of generalized inflammatory process but with the relapse of hyperthyroidism and an increase in antithyroid autoantibodies. The therapy with PTU was restarted, leading to the recovery in a few months and continued for 2 years. Since the therapy withdrawal, the patient has remained euthyroid.

Case no. 4

16.5-year-old girl, initially admitted to the Department of Cardiology due to tachycardia with atrial fibrillation, was referred to consultant endocrinologist from our Department. Tachycardia, weakness and heat intolerance were observed for about 6 months, while weight loss was not reported. The thyroid gland was only slightly enlarged, eye examination was normal (CAS score – 0). Menstruations were regular. Patient's and family's history were irrelevant. Laboratory tests allowed to diagnose GD. The therapy with MMI at the initial dose of 40 mg (0.7 mg/kg) and with beta-blocker was started, leading to the relief of symptoms and to achievement of euthyroid state. After 1.5 years of treatment with MMI in a gradually decreased dose, up to 5 mg/day, the patient was lost to follow-up.

Case no.5

The girl with Turner syndrome (TS), karyotype 46,X,del(X)(p11.2), with short stature and mild pheno-

type features of TS, without any diagnosed congenital defects, treated with recombinant human growth hormone (rhGH) from the age of 9 years. At therapy onset she was prepubertal, euthyroid and she had no goitre. Spontaneous puberty started after 1 year of rhGH therapy. After 1.5 years of rhGH therapy she was admitted to the Department of Endocrinology and Metabolic Diseases due to weight loss, weakness, problems with concentration, irritability and poor heat tolerance. Physical examination showed the enlarged thyroid gland, tachycardia and increased growth rate over the past few months. The diagnosis of GD was confirmed by hormonal tests and increased TRAb concentrations. The patient was successfully treated with MMI at the initial daily dose of 20 mg (0.7 mg/kg), reduced gradually to 5 mg/day and continued during 1.5 years, however TRAb were undetectable after 6 months of treatment. Simultaneously, rhGH therapy was continued. At present, the patient is treated with low dose of L-T₄ due to subclinical hypothyroidism, with still negative TRAb and increased levels of anti-TPO and anti-Tg antibodies. Menstruations are spontaneous and regular.

Case no. 6

The patient with TS, karyotype 45,X, with short stature and mild typical phenotype features, without any diagnosed congenital defects, treated with rhGH from the age of 7.5 years. The therapy was withdrawn when she was 14 years old and attained the final height 157.0 cm. Due to the lack of pubertal features, invisible ovaries in ultrasonography and hypergonadotropic hypogonadism confirmed in hormonal tests, the patient started oestrogen substitution at the age of 13, followed by hormonal replacement therapy (HRT) introduced after 2 years and continued up to now. During routine control assessment at the age of 16.5 years, slightly increased FT₄ and FT₃ serum concentrations were measured, however the patient presented with only mild clinical features of thyrotoxicosis. She reported no symptoms suggesting hyperthyroidism, but the detailed review revealed slight weight loss and problems with learning. All the assessed antithyroid autoantibodies concentrations (TRAb, anti-TPO and anti-Tg) were elevated. The patient started MMI therapy at a daily dose of 40 mg (0.6 mg/kg), decreased to 5 mg/day after 3 months when hormonal tests have shown subclinical hypothyroidism and withdrawn after 1.5 years. The patient's observation is relatively short, however the course of disease is similar to that observed in the girls described earlier.

DISCUSSION

The hypothesis concerning progressive failure of thyroid function as a common finding in patients with GD, resulting from concomitant chronic thyroiditis, was put by Wood and Ingbar (1979), however the factors underlying this phenomenon were not fully understood. The authors reported positive antimicrosomal antibod-

ies in the majority of adult patients with the history of toxic goitre, treated with thionamide many years before the re-assessment (Wood & Ingbar 1979). Conversely, in 1980, Sugrue *et al.* reported no occurrence of hypothyroidism and about 60% relapse rate during long-term follow-up in the group of 162 patients, who were treated for at least 2 years with carbimazole due to hyperthyroidism. Next, in 1987, Tamai *et al.* (1987) reported the occurrence of hypothyroidism in up to 20% of patients with GD, caused either by autoimmune thyroiditis with thyroid destruction or by the appearance of autoantibodies blocking TSHR. In 2010, Umar *et al.* presented 4 cases of adult patients with HT following GD. In only one case, HT occurred after a few months of PTU therapy, while in the remaining cases – 7 to 25 years after the diagnosis of GD and after the withdrawal of antithyroid drugs.

In the context of the present report, particularly interesting seems to be the study by Sato *et al.* (1977). The authors stated that GD and chronic lymphocytic thyroiditis were closely related in the early stage of thyrotoxicosis in children, and that the degree of lymphocytic infiltration and degenerative changes in follicular epithelium influenced the clinical course of the disease. More severe features of chronic lymphocytic thyroiditis were associated with higher remission rate of GD (Sato *et al.* 1977). The predictive factors of remission in children with GD have been reported few years ago by Glaser and Styne (2008). At least 1 year remission after 2 years of PTU therapy was observed in 29% of patients. The only prognostic factors of remission were lower FT₄ and FT₃ concentrations at diagnosis, as well as euthyroidism after 3 months of pharmacotherapy, while patients' age, gender, the of goitre size and other clinical features of GD were not applicable as predictors of remission. However a tendency to a greater rate of remission was observed in older patients (over 14–15 years) (Glaser *et al.* 2008). Similarly, in 2000 Lazar *et al.* have reported more severe course of GD, low remission rate and long period to remission in prepubertal children, recommending earlier radical treatment in this age group.

The necessity of definitive therapy for the majority of children with GD has recently been stressed by Rivkees (2006). However, Glaser and Styne (2008) have suggested that prolonged pharmacotherapy could be effective in older children with early normalisation of thyroid hormone levels, while in others the alternative (radical) therapeutic options should be considered. A few years ago, Lee *et al.* (2007) suggested that the optimal treatment for paediatric GD should be surgery, while Rivkees and Dinauer (2007) definitely preferred radioiodine. According to the recommendations of American Thyroid Association (ATA), published in 2011 (Bahn *et al.* 2011), children with GD should be treated with MMI, radioiodine (except for those younger than 5 years) or thyroidectomy. As the remission after MMI therapy may be achieved in some chil-

dren, the administration of antithyroid drugs is usually the first-line method of treatment, however both radioiodine and surgery may be considered if clinical characteristics indicate low chance of remission and are necessary if remission is not achieved after pharmacotherapy (Bahn *et al.* 2011). It is considered that the potential risk of thyroid malignancy after radioiodine is low, especially if higher doses of ¹³¹I are used, however a long-term observation of patients treated with ¹³¹I in childhood or adolescence seems necessary (Lee *et al.* 2007; Rivkees & Dinauer 2007; Bahn *et al.* 2011; Léger & Carel 2013). In 2012, Cury *et al.* have published the data from the long-term follow-up of patients treated with radioiodine in childhood and adolescence, confirming the efficacy and safety of this method of therapy. On the other hand, the concerns about radioiodine therapy in children have widely been presented by Lee *et al.* (2007) who definitely preferred surgical treatment. In turn, thyroidectomy in children is associated with higher complication rates than in adults (especially hypoparathyroidism and vocal cord palsy) and must be performed by experienced surgeons (Rivkees & Dinauer 2007; Bahn *et al.* 2011; Léger & Carel 2013).

In adults, there is evidence that the remission of GD occurs usually during 12–18 months of pharmacotherapy, and the chance of later remission during prolonged therapy is very low (Abraham *et al.* 2005; Bahn *et al.* 2011). However, it was suggested more than 25 years ago that in children with GD prolonged therapy with antithyroid drugs increased the chance of remission, differently than in adults (Lippe *et al.* 1987). As it was reported by Smith and Brown (2007) that in children with GD, the levels of TRAb normalised after more than 2 years of treatment with antithyroid drugs, the recommendations concerning pharmacotherapy duration developed for adult patients should not be directly applied for children. It has been recommended by ATA that MMI as the first-line treatment for GD in children should be administered for 1–2 years and discontinued (or the dose reduced) to assess whether the patient is in remission (Bahn *et al.* 2011). Thus, longer MMI therapy duration may be more appropriate for children than for adults. Moreover, Léger *et al.* (2012) have reported an approximately 50% remission rate over 18 months after the therapy withdrawal in children with GD in whom 2-year therapy with carbimazole was administered, with up to 3 consecutive cycles of 2 years during 8–10 years in case of relapse of hyperthyroidism. Consequently, Léger and Carel (2013) have pointed at the need of prolonged use of antithyroid drugs for at least 2–4 years in children with GD in order to achieve the remission of the disease. According to current recommendations of ATA (Bahn *et al.* 2011), MMI is preferred in pharmacotherapy of hyperthyroidism due to the reported hepatotoxicity of PTU. The risk of agranulocytosis in children is believed to be very low, however the exact data are still lacking.

In our patients, the euthyroid state was achieved after a relatively short therapy duration (2.0–3.5 months). Initial TRAb concentrations ranged from 2.97 IU/l to 10.30 IU/l, normalised during MMI (or PTU) therapy and remained normal at subsequent follow-up assessments. The relatively low initial level of TRAb and the early normalisation of TRAb concentration during pharmacotherapy have been reported as important prognostic factors of the remission of GD in adults (Bahn *et al.* 2011; Léger & Carel, 2013; Léger *et al.* 2014). In children, the significance of TRAb normalisation as a marker of GD remission has been documented in a very recent study of Gastaldi *et al.* (2014).

Autoantibodies characteristic for HT (anti-TPO and/or anti-Tg) were high at diagnosis of GD in 5 out of 6 patients (in the last patient anti-TPO and anti-Tg increased after few months of MMI therapy) and remained increased at the most recent follow-up in all the patients. In 2 patients subclinical hypothyroidism was diagnosed, while the other 4 girls remained euthyroid despite high levels of anti-TPO and anti-Tg antibodies. It has previously been reported that in children HT preceded development of GD in just less than 4% of cases (Wasniewska *et al.* 2010). In our study, the increased levels of both anti-TPO and anti-Tg were found in the majority of patients at diagnosis of GD, indicating the possibility of pre-existing HT before the occurrence of GD. Unfortunately, the concentrations of antithyroid antibodies in all our patients were assessed for the first time only after the diagnosis of hyperthyroidism. The relatively higher incidence of HT preceding GD in children with Turner or Down syndromes with respect to the age-matched population of children without any of these syndromes, has been reported in the current study of Aversa *et al.* (2014).

It should be mentioned that the coincidence of other states, related to an increased risk of autoimmunity, was observed in 3 of 6 our patients (1 case of type 1 diabetes mellitus, 2 cases of Turner syndrome). It has been documented that GD is more frequent in children with other autoimmune conditions and with a family history of AITD (Léger & Carel 2013), however, it is seldom observed in girls with TS (Grossi *et al.* 2013). In the very recent study of Valensize *et al.* (2014), the incidence of GD in the patients with TS has been reported as 1.7%. Moreover, in the patients with TS, hyperthyroidism is generally related to HT (Grossi *et al.* 2013). In our patients with TS, increased TRAb concentrations were documented at the diagnosis of hyperthyroidism, confirming the diagnosis of GD.

There was no recurrence of hyperthyroidism after MMI withdrawal in 5 girls who completed pharmacotherapy of GD. Exophthalmos was observed at diagnosis in 2 girls, however it completely resolved as soon as euthyroid state was achieved, with no additional therapy.

It seems that the prolonged pharmacotherapy with antithyroid drugs, followed by observation after remission of hyperthyroidism, may be an appropri-

ate therapeutic option in many children with GD with normalisation of thyroid hormone levels and immunological remission of GD (normalisation of previously increased TRAb) as they can be cured without radical therapy and the potential risk of its complications. Some of the children may remain euthyroid and some may develop HT with hypothyroidism and high anti-TPO and anti-Tg concentrations but eventually they do not require definitive therapy for GD. However, this approach to the therapy of children with GD requires relatively longer antithyroid drug administration and is possible only in selected patients. It should be stressed that such observations were impossible in the patients who had been qualified to radical therapy after short-term pharmacotherapy.

Summing up, the obvious advantage of prolonged observation is avoiding the potential side effects following surgery and/or radioiodine administration. Nevertheless, further observation of the presented patients in adulthood and the prospective studies on larger groups of children with GD seem necessary in order to fully assess the relevance of the current report. In other words, it is noteworthy to establish whether and when the prolonged pharmacotherapy, followed by a long-term observation, may be recommended in children with GD in whom TRAb normalization was recorded.

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