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Persistent Thyrotropin Receptor Antibodies Positivity Despite Prolonged Biochemical Euthyroidism in Graves' Disease Associated With Down Syndrome: A Case Report

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Abstract

Down syndrome (DS) is associated with a markedly increased prevalence of autoimmune diseases, reflecting immune dysregulation related to trisomy 21. Although Hashimoto's thyroiditis (HT) is the predominant thyroid disorder, Graves' disease (GD) remains relatively uncommon in this population. The optimal duration of antithyroid drug (ATD) therapy in patients with DS remains uncertain, particularly when thyrotropin receptor antibodies (TRAb) remain positive despite prolonged biochemical euthyroidism during treatment.

A 31-year-old man with DS presented with GD characterized by severe thyrotoxicosis (thyroid-stimulating hormone (TSH) <0.005 mIU/L; free thyroxine (FT4), 48 pmol/L) and markedly elevated TRAb, 69 IU/L). Carbimazole therapy achieved rapid clinical and biochemical control, allowing progressive dose reduction to a maintenance dose of 5 mg/day. After more than 40 months of continuous treatment, the patient remained clinically asymptomatic and biochemically euthyroid, while TRAb remained positive (4.3 IU/L). Definitive treatment options were considered but deferred after taking into account the patient's clinical and functional context, treatment tolerance, and family preference. Long-term low-dose carbimazole was, therefore, continued with regular clinical and biochemical follow-up.

This case illustrates persistent TRAb positivity despite prolonged biochemical euthyroidism during carbimazole therapy in GD associated with DS. Persistent conventional TRAb positivity may indicate ongoing TSH-receptor autoimmunity, but it does not by itself establish the functional activity of the antibodies or immunological remission. Because treatment withdrawal was not attempted, clinical remission after discontinuation of antithyroid therapy cannot be assessed. Treatment duration should, therefore, be individualized according to biochemical control, TRAb evolution, treatment tolerance, patient-specific functional considerations, and patient or caregiver preferences.

Categories: Internal Medicine, Endocrinology/Diabetes/Metabolism, Allergy/Immunology
Keywords: autoimmunity, carbimazole, down syndrome, graves´disease, thyrotropin receptor antibodies, trisomy 21

Introduction

Down syndrome (DS), resulting from trisomy 21, is the most common chromosomal disorder worldwide, affecting approximately 1 in 700-1,000 live births [1]. Beyond its characteristic neurodevelopmental and phenotypic features, DS is associated with a markedly increased susceptibility to autoimmune diseases, particularly autoimmune thyroid disorders, whose prevalence is estimated to be up to 25-fold higher than in the general population [2]. While Hashimoto's thyroiditis (HT) represents the predominant thyroid manifestation, Graves' disease (GD) remains relatively uncommon, with reported prevalence ranging from approximately 0.6% to 3% in individuals with DS [3].

The increased susceptibility to autoimmunity in DS is attributed to complex immune dysregulation involving altered lymphocyte homeostasis, enhanced type I interferon signaling, and increased autoantibody production [4]. GD results from a loss of immune tolerance to thyroid antigens, with thyroid-stimulating antibodies (TSAb) activating the thyroid-stimulating hormone (TSH) receptor on thyroid follicular cells and increasing thyroid hormone synthesis and secretion. These mechanisms may overlap with the immune alterations observed in DS and contribute to susceptibility to GD in this population [4].

Although current international guidelines recommend antithyroid drug (ATD) therapy for 12-18 months in most patients with GD, with long-term remission achieved in approximately 40-50% of cases [5], the optimal treatment duration in patients with DS remains uncertain. Published evidence suggests prolonged thyrotropin receptor antibodies (TRAb) positivity, lower remission rates, and a potential need for extended

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medical therapy or definitive treatment in this population. However, available data remain limited to small retrospective series and isolated case reports.

We report the case of a 31-year-old man with DS who remained on low-dose carbimazole because of persistent TRAb positivity despite more than 40 months of biochemical euthyroidism during ATD therapy. This case illustrates the therapeutic dilemma of balancing prolonged ATD therapy against definitive treatment in patients with DS and discusses an individualized management strategy.

Case Presentation

A 31-year-old man, a nonsmoker, with a known diagnosis of DS (trisomy 21) was referred to our endocrinology department for the management of newly diagnosed GD. The patient had significant cognitive impairment and required family assistance with daily activities and medical care. There was no personal or family history of autoimmune thyroid disease or other autoimmune disorders.

He presented with a three-month history of progressive weight loss (5 kg), palpitations, tremor, heat intolerance, and fatigue. Physical examination revealed tachycardia (112 beats/min) and a moderately enlarged, diffuse, non-tender goiter without clinical signs of thyroid eye disease. The remainder of the examination was unremarkable. No previous assessment for atlantoaxial instability was documented.

Laboratory investigations demonstrated overt thyrotoxicosis, with a suppressed TSH concentration (<0.005 mIU/L; reference range 0.4-4.0 mIU/L), elevated free thyroxine (FT4) concentration (48 pmol/L; reference range 12-22 pmol/L), and markedly positive TRAb (69 IU/L; reference value <1.7 IU/L) (Table *1*). Thyroid ultrasonography demonstrated diffuse thyroid enlargement with hypoechogenicity and marked hypervascularity, findings consistent with GD (Figure *1*). The diagnosis was established based on the characteristic clinical presentation, biochemical hyperthyroidism, positive TRAb, and ultrasonographic findings.

Parameter	At diagnosis	At 3 months	Month 40	Reference range
TSH (mIU/L)	< 0.005	1.8	2.1	0.4–4.0
FT4 (pmol/L)	48	15.3	14.2	12–22
TRAb (IU/L)	69	N/A	4.3	< 1.7
Carbimazole dose	30 mg/day	Tapering	5 mg/day	-

TABLE 1: Evolution of biochemical and immunological parameters during carbimazole therapy, at diagnosis and after 40 months

Sequential laboratory results showing biochemical and immunological parameters at diagnosis, after three months of carbimazole therapy, and at the most recent follow-up (month 40). TSH and FT4 normalized within three months of treatment initiation and remained stable thereafter. TRAb decreased markedly from the initial titre but remained above the upper limit of normal at month 40, consistent with persistent TSH-receptor autoimmunity despite sustained biochemical euthyroidism.

TSH: Thyroid-stimulating hormone; FT4: Free thyroxine; TRAb: Thyrotropin receptor antibodies

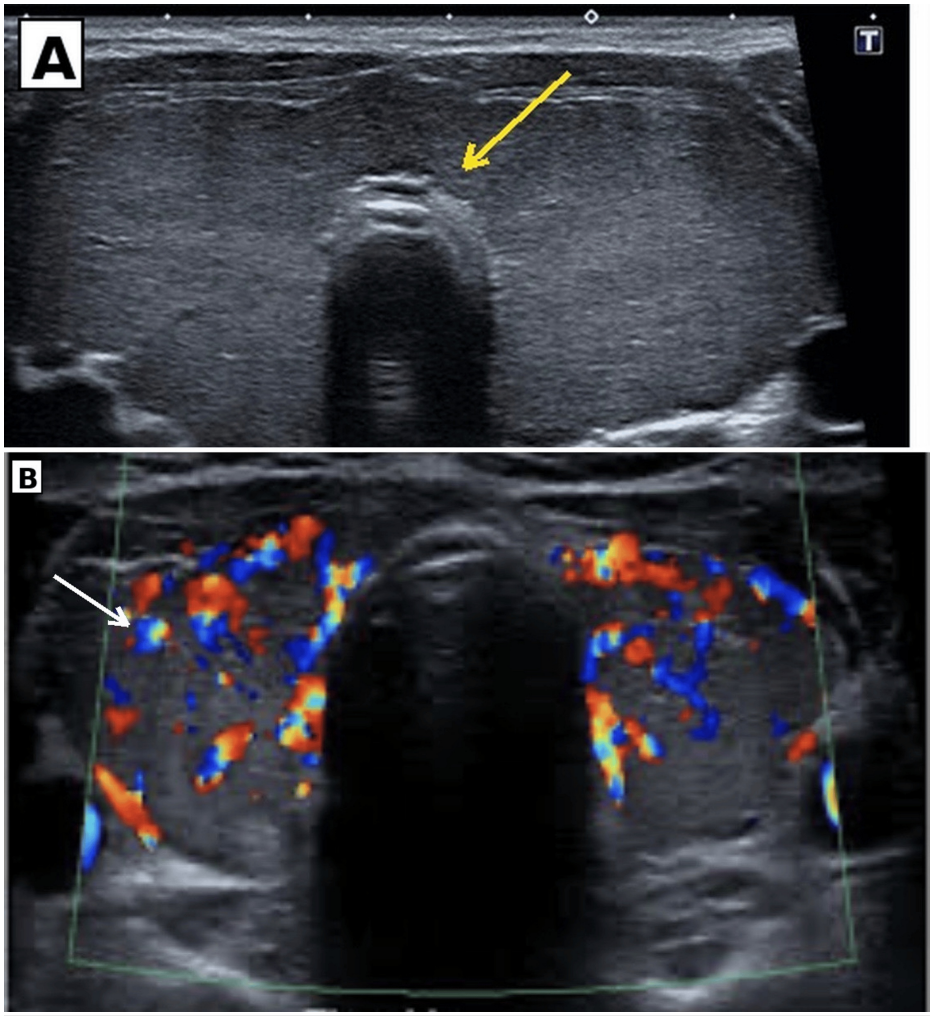


FIGURE 1: Thyroid ultrasonography demonstrated diffuse thyroid enlargement with hypoechogenicity and marked hypervascularity, findings consistent with GD

Panel A (B-mode, gray-scale): The yellow arrow indicates an area of diffuse parenchymal hypoechogenicity; Panel B (color Doppler): The white arrow indicates an area of marked hypervascularity

GD: Graves' disease

Treatment was initiated with carbimazole 30 mg/day using a dose-titration regimen, together with propranolol for symptomatic control. Clinical improvement was rapid, and biochemical euthyroidism was achieved within three months, allowing gradual reduction of carbimazole to a maintenance dose of 5 mg/day (Table *1*).

Throughout follow-up, the patient remained clinically asymptomatic and biochemically euthyroid. Carbimazole was well tolerated throughout the 40-month treatment period. Serial complete blood counts and liver function tests remained within normal limits, with no clinical or laboratory evidence of agranulocytosis or hepatotoxicity.

Despite prolonged biochemical euthyroidism during carbimazole therapy, repeat immunological assessment after 40 months demonstrated persistent TRAb positivity (4.3 IU/L), consistent with persistent TSH-receptor autoimmunity (Table *1*). In view of the persistent TRAb elevation, discontinuation of antithyroid therapy was considered to be associated with an increased risk of relapse.

Definitive treatment options were carefully discussed. Total thyroidectomy was not selected, in part because patients with DS have a higher prevalence of cervical spine abnormalities; therefore, cervical spine assessment should be considered before elective thyroid surgery. In addition, the patient's cognitive impairment required careful perioperative and anesthetic planning, reinforcing the need for an individualized therapeutic strategy. Radioiodine therapy was also considered but was judged less suitable

because adherence to post-treatment radiation safety precautions could have been challenging. Given the excellent tolerance of carbimazole, persistent TRAb positivity, sustained biochemical euthyroidism, and the family's preference to avoid definitive treatment, continuation of low-dose carbimazole was considered the most appropriate strategy (Figure *2*). The patient remains clinically stable on 5 mg/day of carbimazole with regular clinical, biochemical, and immunological follow-up.

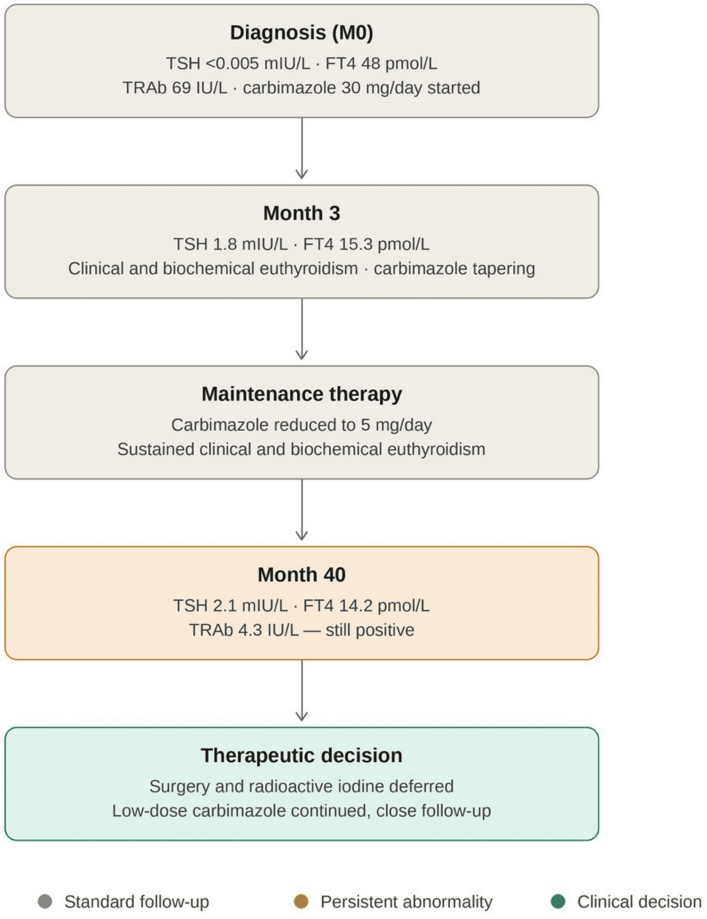


FIGURE 2: Clinical timeline showing biochemical and immunological evolution under carbimazole therapy, from diagnosis to month 40

Discussion

Immunological basis of GD in DS

The markedly increased prevalence of autoimmune disorders in individuals with DS is increasingly recognized as a consequence of complex immune dysregulation rather than simple genetic susceptibility. Overexpression of chromosome 21 genes, including the autoimmune regulator (AIRE) gene and interferon receptor genes (IFNAR1 and IFNAR2), contributes to defective central immune tolerance, chronic type I interferon activation, altered T-cell homeostasis, and enhanced B-cell activation, ultimately promoting autoantibody production [4,6,7]. While these mechanisms most commonly lead to HT, they may occasionally favor the production of stimulating TRAb, resulting in GD. Furthermore, autoimmune thyroid disease in DS appears to follow a more dynamic course than in the general population. Aversa et al. described the concept of "metamorphic thyroid autoimmunity", whereby patients may transition from HT to GD and subsequently evolve toward hypothyroidism, illustrating the unstable nature of immune regulation in this population [8].

Persistent autoimmunity and prolonged ATD Therapy

Current European Thyroid Association guidelines recommend ATD therapy for 12-18 months in most patients with GD, with treatment discontinuation generally guided by biochemical remission and TRAb status [5]. However, whether the conventional treatment paradigm can be directly extrapolated to

individuals with DS remains uncertain. Available evidence, although limited and largely derived from pediatric populations, suggests that prolonged ATD therapy may be required in a substantial proportion of patients with DS. Goday-Arno et al. reported that none of 12 patients with DS achieved remission after a mean of 40 months of carbimazole therapy, and all ultimately required radioactive iodine (RAI) treatment (Table *2*) [9]. More recently, Cebeci et al. described the largest multicenter cohort currently available, in which the mean duration of ATD therapy exceeded 43 months, while only 23% of patients achieved remission (Table *2*) [10]. Likewise, De Luca et al. and Aversa et al. observed that prolonged low-dose methimazole therapy was frequently necessary to maintain euthyroidism, with several patients remaining on treatment for many years (Table *2*) [8,11].

Author / Year	n	ATD Duration	Remission /Outcome	Outcome / Notes
Goday-Arno et al. 2009 [9]	12	Mean 40 months	0% (0/12)	All required RAI; hypothyroidism post-RAI in all
Aversa et al. 2015 [8]	12	2–7 years	4/12 stopped ATD (developed hypothyroidism)	8/12 still on ATD; metamorphic HT→GD pattern observed
De Luca et al. 2010 [11]	28	Variable (low-dose)	Majority controlled on low-dose ATD	Earlier onset; frequent comorbid autoimmunity
Cebeci et al. 2024 [10]	13	Mean 43.4 ± 11 months	3/13 (23%)	3 thyroidectomies (no complications); prolonged ATD therapy preferred
Present case 2026	1	40 months (ongoing)	Euthyroid; TRAb 4.3 IU/L (not discontinued)	ATD continued; definitive therapy deferred

TABLE 2: Summary of published series on GD in DS

Summary of published series describing GD in patients with DS, including ATD duration, remission rates, and clinical outcomes, compared with the present case. Across these small and heterogeneous series, ATD therapy was frequently continued beyond the conventional 12-18-month treatment period, although reported remission rates varied substantially between studies.

ATD: Antithyroid drug; RAI: Radioactive iodine; HT: Hashimoto's thyroiditis; GD: Graves' disease; DS: Down syndrome; TRAb: Thyrotropin receptor antibodies

Recent evidence has also renewed interest in prolonged low-dose ATD therapy beyond the conventional 12-18-month course. Azizi and Malboosbaf demonstrated that long-term methimazole therapy is associated with sustained biochemical control, a low incidence of adverse effects, and reduced relapse rates in carefully selected patients [12]. Although these data were not generated specifically in individuals with DS, they provide additional support for extending ATD therapy when persistent TRAb positivity suggests ongoing autoimmune activity and treatment is well tolerated. Our patient's clinical course closely parallels these observations. Despite more than 40 months of continuous carbimazole therapy and sustained biochemical euthyroidism, TRAb remained persistently positive, indicating persistent TSH-receptor autoimmunity despite hormonal control. Our observation highlights that biochemical euthyroidism during ATD therapy may persist despite detectable TRAb, underscoring the potential value of TRAb monitoring when considering treatment duration. Moreover, conventional TRAb immunoassays detect antibodies binding to the TSH receptor without distinguishing between TSAb and thyroid-blocking antibodies (TBAb). Consequently, persistent TRAb positivity does not fully characterize its functional profile. Because only conventional TRAb assays were available, it was not possible to determine whether persistent antibody positivity reflected predominantly stimulating (TSAb) or blocking (TBAb) antibodies. Functional characterization of these antibodies could have provided a more refined assessment of the underlying autoimmune status and may have further informed therapeutic decision-making.

Therapeutic decision-making

The optimal definitive treatment for GD in individuals with DS remains uncertain and should be individualized. Total thyroidectomy offers definitive disease control but requires careful preoperative assessment because cervical spine instability and congenital cardiac anomalies are more prevalent in DS than in the general population [13]. Radioiodine therapy represents an effective alternative; however, in patients with significant cognitive or functional impairment, adherence to post-treatment radiation safety precautions may require additional caregiver support.

In our patient, prolonged low-dose carbimazole therapy was favored for several reasons. First, treatment had been remarkably well tolerated over more than three years, with no hematological or hepatic adverse effects. Second, the patient remained clinically asymptomatic and biochemically euthyroid throughout follow-up. Third, persistent TRAb positivity was considered to indicate an increased risk of relapse if treatment were

discontinued. Finally, after multidisciplinary discussion, the patient's family expressed a clear preference to avoid definitive treatment. Taken together, these considerations favored continuation of medical therapy rather than immediate thyroidectomy or radioiodine treatment. This strategy is consistent with current European Thyroid Association recommendations supporting prolonged ATD therapy in selected patients with persistent TRAb positivity and good treatment tolerance [5].

Clinical implications

Although based on a single observation, our case is consistent with an emerging concept supported by the available literature: GD associated with DS may be characterized by prolonged autoimmune activity and lower remission rates after conventional ATD therapy. These observations suggest that treatment decisions based solely on conventional treatment durations may require careful individualization in patients with DS. Therapeutic decisions should instead integrate TRAb kinetics, long-term treatment tolerance, patient-specific factors, cognitive and functional status, and caregiver preferences within a multidisciplinary framework.

Limitations

The limitations inherent to a single case report should be acknowledged. Our observations cannot establish causality or determine the optimal duration of ATD therapy in patients with DS. Formal cervical spine imaging was not performed because surgery was not ultimately pursued, and no genetic or immunological analyses beyond routine TRAb assessment were available. Nevertheless, the detailed longitudinal follow-up, prolonged treatment duration, and comparison with the available literature provide useful clinical context and support individualized management in this uncommon setting.

Conclusions

GD associated with DS may present a therapeutic challenge when TRAb remain positive despite prolonged biochemical euthyroidism during ATD therapy. Persistent TRAb positivity should be interpreted alongside thyroid function, treatment tolerance, and patient or caregiver preferences, as conventional assays do not distinguish between stimulating and blocking antibodies. Regular clinical and biochemical follow-up, including periodic assessment of TRAb and monitoring for ATD-related adverse effects, is appropriate. Importantly, biochemical euthyroidism during carbimazole therapy should not be equated with remission after treatment withdrawal. In our patient, treatment was continued because of persistent TRAb positivity and good treatment tolerance; therefore, remission after treatment discontinuation could not be assessed.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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