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RESEARCH

Graves' disease in children with Down syndrome

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Abstract

While subclinical or overt hypothyroidism are common in Down syndrome (DS); Graves' disease (GD) is rare (ranges 0.6–3%). We aimed to evaluate the clinical features, course, and treatment of GD in children with DS and compare them with those without DS. Among 161 children with GD, 13 (8 female, 5 male) had DS (8%). Data were collected retrospectively from patients' medical records. The mean age at diagnosis was 10.6 ± 4.5 years, with a female-to-male ratio 1.6:1. The main symptoms were weight loss ($n = 6$), increased irritability ($n = 3$), and increased sweating ($n = 3$). None had orbitopathy. Seven of 11 patients with a thyroid ultrasound at diagnosis had a goitre. On admission, all had thyroid-stimulating hormone (TSH) <0.01 mU/L (normal range (NR): 0.51–4.30), free triiodothyronine, free thyroxine (mean ± SD.), and thyrotrophin receptor antibodies (median, range) were 22.2 ± 10.2 pmol/L (NR: 3.5–8.1), 50.2 ± 18.7 pmol/L (NR 12.6–20.9), and 17.0 (2.89–159.0) U/L (NR <1), respectively. Patients were treated either with methimazole ($n = 10$) or carbimazole ($n = 3$), a dose of 0.54 ± 0.36 mg/kg/day. The treatment was 'block and replace' in ten patients and 'dose titration' in three patients, with a mean duration of 43.4 ± 11.0 months. Of 13 patients, four are still receiving primary treatment, three are in remission, one patient had two medically treated recurrences, three underwent surgery without complications, and two patients were lost to follow-up. Our data show that the clinical course of GD in patients with DS was similar to those without DS and suggest that a prolonged medical therapy should be the preferred option.

Keywords: anti-thyroid drug medication; autoimmune thyroiditis; Down syndrome; Graves' disease; hyperthyroidism

Introduction

Graves' disease (GD) is the primary aetiology of hyperthyroidism in children and adolescents, with a prevalence of about 1 in 10,000 (1). Down syndrome (DS) is one of the most common chromosomal disorders, occurring in nearly 1 of 700 births in the USA (2). Patients with DS are at an increased risk of thyroid dysfunction, with overt or subclinical hypothyroidism being the most common, with an estimated frequency of 400 to 1950 in 10,000 (3). Although the incidence of GD in the paediatric population has been reported to be higher in DS than in the general population, it is still rare, with incidences between 60 and 300 in 10,000 (4, 5). The incidence of GD in DS seems to increase with age. Among a large population of 320 children with DS aged between 5 days and 10 years, Tüysüz *et al.* found no case of hyperthyroidism (6), whereas Calcaterra *et al.* identified four patients with GD at a mean age of 13.4 years in a cohort of 91 children and adolescents with DS (7).

The clinical course and outcome of GD in children with DS have been investigated in a limited number of case series with case numbers ranging from one to

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four cases (8, 9, 10, 11). Generally, GD in DS children is symptomatic, easy to diagnose, and often associated with other autoimmune diseases (12, 13). The most extensive series of 28 children and adolescents was published from Italy by De Luca *et al.* (5). They evaluated the clinical characteristics of 28 patients with DS and GD and reported that these patients presented at an earlier age had no gender predominance and less severe course than patients with GD without DS. These authors have also demonstrated that GD in DS is often associated with other autoimmune diseases and a higher frequency of prior Hashimoto thyroiditis (HT). Six of their 28 patients with GD and DS had antecedents of HT (5).

The disease activity was well controlled with low-dose anti-thyroid drug (ATD) treatment in the majority of the patients. In contrast, Goday-Arno *et al.* stated that none of their 12 patients responded to the treatment with carbimazole (CBZ) after a mean period of 40 months, and all required a definitive treatment (4). It still needs to be determined when a definitive treatment for these patients should be introduced. A recent study found that TSH levels might normalise notably from the second year of treatment in patients with DS and GD (14).

Our study aimed to evaluate clinical features, course, and response to the treatment with ATDs in patients with DS and to compare the results with those of GD patients without DS.

Patients and methods

Study design and subjects

We reviewed longitudinal data of 161 children and adolescents diagnosed with GD over a 17-year-period between January 2004 and December 2021 inclusive in three tertiary care centres in Germany. Data were collected retrospectively from patients' medical records. Demographics, clinical characteristics, responses to treatment, and outcomes were analysed. GD is defined as (i) elevated free thyroxine (fT4) (normal range (NR): 10–25 pmol/L), (ii) completely suppressed thyroid-stimulating hormone (TSH) (NR: 0.5–4.5 mU/L), and (iii) elevated thyrotrophin receptor antibodies (TRABs >1.0 IU/L). We excluded patients with neonatal hyperthyroidism as well as patients with negative TRABs as seen in Hashimoto's disease with hyperthyroidism.

The results as well as the outcomes in patient numbers such as primary treatment, recurrence, remission, and definitive treatment were compared with GD patients without DS.

Study variables and statistical analyses

Auxological parameters, including height, weight, and body mass index (BMI, calculated by weight in kilogram divided by height in m^2), were noted on admission, every 3 months in the first year and annually thereafter. Standard deviation scores (SDSs) were calculated according to German references (15). For patients with DS, we used disease-specific growth curves (16). Pubertal status was assessed according to Tanner staging (17, 18).

At the onset of GD, clinical symptoms, accompanying diseases, presence of ophthalmopathy, and, if available, thyroid ultrasound results were recorded. The presence of goitre was defined as a total thyroid volume (mL) on admission above 2 S.D. For normative data on thyroid volume, we used the German KIGGS data (19) for children aged 6 years and older. For younger children, we used the data of Suzuki *et al.* (20). Laboratory parameters were measured locally at each centre using competitive assays.

There was no standard treatment protocol during the time of the study. However, treatment was implemented in accordance with international consensus statements. The treatment with ATDs was continued at least 2 years and thereafter an attempt was made to discontinue therapy in selected patients with negative TRABs. As this study was carried out in three centres, the choice of treatment regimen regarding dose titration (DT) vs 'block and replace' varied between doctors in each centre.

The remission of the disease was defined as the absence of symptoms of hyperthyroidism along with normalisation of laboratory measurements (fT3, fT4, and TSH concomitantly negative TSHRab) at least 6 months after cessation of ATDs. Recurrence was considered when TSHRab became positive after remission, in combination with elevated fT4 and suppressed TSH levels.

Orbitopathy was defined as the presence of symptoms including eye-lid retraction, lid oedema, proptosis, and frank exophthalmos.

Continuous variables were described as medians and ranges or means ± S.D. χ^2 test was used for categorical variables. Statistical significance was assumed if $P < 0.05$, and all analyses were performed using IBM SPSS Statistical Software (version 29.0.0, SPSS Inc., Chicago, IL, USA).

The process of retrospective analysis was evaluated and approved by the local institutional review boards or ethics committees (IRB Bonn University, Ref. no. 256/19).

Results

Among 161 children and adolescents with GD (129 females, 32 males), we identified 13 children (8 f) with genetically proven DS (8%). All patients were treated with ATDs either with methimazole (MMI) or CBZ.

Detailed clinical and laboratory information of the patients with DS is provided in Table 1.

The clinical characteristics of children with GD and DS in comparison with GD children without DS are shown in Tables 2 and 3.

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Table 1 Individual data of children and adolescents with GD and Down syndrome.

Patient		At diagnosis			Follow-up		Outcome		
No	**Sex**	**Age** (years)	**ATD therapy**	**ATD dose** (mg/kg)	**ATD duration** (months)	**ATD stop**	**Remission/follow-up after stop** (months)	**Relapse**	**Therapy** (mg/kg)
1	m	4.1	M, DT	0.39	36	No	ATD ongoing	–	M, 0.15
2	m	5.1	M, BR	0.34	32	No	ATD ongoing	–	M, 0.14
3	f	15.9	C, BR	0.34	51	Yes	Yes/40	No	LT4
4	f	14.8	M, BR	0.50	45	No	Lost	Lost	Lost
5	f	9.7	M, BR	0.50	6	No	ATD ongoing	–	M, 0.50
6	f	16.4	C, BR	0.41	31	No	No	Yes	C, 0.14
7	m	4.8	M, BR	1.60	32	Yes	Yes/68	No	No
8	m	15.4	M, DT	0.54	61	No	No	–	Surgery, LT4
9	f	10.6	M, BR	0.54	48	No	No	–	Surgery, LT4
10	f	7.3	M, BR	0.46	38	Yes	Yes/43	No	No
11	f	15.0	M, DT	0.51	10	No	ATD ongoing	–	M, 0.50
12	f	9.9	C, BR	0.29	54	No	Lost	Lost	Lost
13	m	8.9	M, BR	0.50	31	No	No	–	Surgery, LT4

ATD, antithyroid drug; BR, block and replace; C, carbimazole; D, dose titration; f, female; m, male; LT4, levothyroxine; M, methimazole.

GD was diagnosed at a mean age of 10.6 ± 4.5 years in children with DS. The patients were slightly younger and more frequently prepubertal than patients without DS. The female-to-male ratio was 1.6:1 and in patients without DS 4.5:1. The most common presenting symptoms were weight loss ($n = 6$), increased irritability ($n = 3$), and increased sweating ($n = 3$). Seven of 11 DS patients with a thyroid ultrasound at diagnosis had a goitre. Graves's orbitopathy was not detected among our patients with DS, but it was found in 18.7% of patients without DS. At diagnosis, the laboratory data of DS patients were almost similar to those of patients without DS.

Table 2 Baseline features of children with Graves' disease (GD) and Down syndrome (DS) in comparison with GD children without DS (No-DS); data from Myrelid *et al.* (16) were used to calculate height- and BMI-SDS values for DS.

	DS	No DS
Number of patients	$n = 13$	$n = 148$
Sex (F/M)	8/5	121/27
Ratio F/M	1.6:1	4.48:1
Age at diagnosis (years)		
Mean ± S.D.	10.6 ± 4.5	11.9 ± 3.5
Median (range)	9.9 (4.1–16.4)	12.4 (1.4–17.8)
Tanner stage (B/G)		
B1/G1	$n = 8$	$n = 48$
B2/G2	$n = 0$	$n = 14$
B3/G3	$n = 0$	$n = 14$
B4-5/G4-5	$n = 5$	$n = 54$
Height-SDS median (range)	−0.03 (−1.42–2.73)	0.49 (−3.10–3.43)
BMI-SDS median (range)	−0.45 (−6.91–1.79)	−0.19 (−4.10–2.96)

DS patients were treated either with MMI ($n = 10$) or CBZ ($n = 3$) with a mean initial dose of 0.54 ± 0.36 mg/kg/day; two patients received additional beta blocker therapy. The method of treatment was 'block and replace (BR)' in ten patients and DT in three patients (Table 1).

At the time of data analysis, four DS patients were still receiving primary treatment, three were in remission, one patient had two medically treated recurrences, three underwent near-total thyroidectomy without complications, and two were lost to follow-up. Details of outcome in these 11 patients were discussed in the following paragraphs.

All four patients on ongoing ATD treatment (2 males, 2 females) never stopped ATD (2 DT, 2 BR) and are currently treated with MMI (Table 1). Three DS patients (1 males, 2 females) had achieved remission after 38 (32–51) months (median-range) after CBZ ($n = 2$) and MMI ($n = 1$) (Table 1). ATD treatment regimen was BR in all patients, and their current ages are 23.9 years, 14.7 years, and 14.1 years with a remission for 40 months, 68 months, and 43 months, respectively.

In our cohort, we had one female patient (patient 6, Table 1) with a relapse due to poor adherence during primary ATD treatment. She is now 21.8 years old and still treated with CBZ alone (7.5 mg/day). Two patients were lost to follow-up (patients 4 and 12, Table 1). Both patients were female and received ATD (BR). At last visit, patient 4 was 18.5 years old and was receiving MMI for 54 months with a poor compliance. Patient 12 was 14.4 years old at last visit and on CBZ for 45 months. Due to elevated TRABs, an operation was recommended but the patient was not brought to further appointments.

Three patients (1 females, 2 males) underwent a definitive treatment with near-total thyroidectomy after a median duration of 4 years of ATD treatment without remission and increasing thyroid volume (Table 1). The decision of

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Table 3 Clinical characteristics of children with GD and Down syndrome (DS) in comparison with GD children without DS (No-DS), data shown as median (range).

	DS ***n*** = 13	No DS ***n*** = 148
Clinical symptoms at diagnosis (*n*, %)		
Weight loss	6 (46%)	48 (32.4%)
Irritability, behaviour changes	3 (23%)	68 (45.5%)
Increased sweating	3 (23%)	34 (22.9%)
Goitre	7/11 (63.6%)	92/125 (73.6%)
Orbitopathy	0/13	24/128 (18.7%)
Associated diseases (*n*)		
Type 1 diabetes	1	7
Heart defect	2	0
Coeliac disease	1	2
Laboratory data at diagnosis		
TSH (mU/L)	0.01 (0.01–0.02)	0.01 (0.01–0.13)
fT3 (pmol/L)	18.6 (11.0–41.1)	22.1 (4.7–65.0
fT4 (pmol/L)	45.6 (24.4–96.6)	42.8 (14.0–250)
TRABs (U/L)	17.0 (2.8–159)	9.34 (1.6–138)
TPO (U/mL)	125 (18–2898)	265 (5–12056)
Therapy at diagnosis (*n*, %)		
Thiamazole	10 (77%)	107 (72.3%)
Carbimazole	3 (23%)	39 (26.3%)
β-Blocker	2 (15.3%)	44 (29.7%)
Primary therapy (*n*, %)		
Thiamazole dose (mg/kg)	0.50 (0.34–1.60)	0.45 (0.04–1.32)
Carbimazole dose (mg/kg)	0.31 (0.29–0.34)	0.52 (0.03–0.78)
Block and replace	10 (77%)	93 (62.8%)
Dose titration	3 (23%)	55 (37.1%)

definitive treatment was made in accordance with the patient and families. No complication of surgery including keloid scarring, recurrent laryngeal palsy, and persistent hypocalcemia was observed. Due to hypothyroidism after surgery, all patients were treated with L-T4 (median dose: 1.54 µg/kg/day). The patients had higher levels of fT3, fT4, and TRABs at diagnosis in median (range 31.4 (21.741.1) pmol/L, 60.1 (57.3–96.6) pmol/L, and 25.4 U/L (18.3–45.0), respectively) than patients who achieved a remission (16.1 pmol/L (14.0–18.2), 36.4 pmol/L (34.9–38.6), and 16.0 (14.2–17.8) U/L, respectively). The number was too small to perform any statistical analysis.

Discussion

Patients with DS have a susceptibility towards several autoimmune diseases, such as HT, GD, type 1 diabetes mellitus, celiac disease, alopecia, vitiligo, and idiopathic arthritis (13, 21). The frequency of autoimmune thyroid disorders increases with age, affecting mainly females during adolescence (22). In patients with DS, the progress of HT to GD is more common than in the general population (23, 24). The prevalence of GD has been reported at a higher rate in children with DS than in the general population (25), but overall, it is rare (4). Therefore, it is not remarkable that almost all data on GD in children with DS has been published as case series with case numbers ranging from 1 to 4 cases (8, 9, 10, 11).

In the present study, we analysed data of 13 DS patients with this rare condition and compared them to the data of 148 GD children without DS. Our study provides longitudinal data with a relatively long follow-up period. Our data confirm previous results showing that DS children with GD were younger at diagnosis with no significant gender difference (4, 5). The female-to-male ratio of GD children without DS was similar to the literature.

In their series of 12 patients with DS and GD, Goday-Arno *et al.* reported that all patients had a diffuse goitre, and three had ophthalmopathy (4). Our study found a goitre frequency of 7/11 and no case of ophthalmopathy. Data on the frequency of ophthalmopathy are inconsistent in the literature. One study reported a lower frequency of ophthalmopathy than in patients without DS; however, ophthalmopathy occurred at a younger age (4), whereas another study found that patients with DS had similar frequencies of both ophthalmopathy and other clinical manifestations compared to patients without DS (5). Two other paediatric studies reported opthalmopathy in 3 of 12 patients (13) as well as in 5 of 36 patients (14). These variable results for eye problems in DS presumably reflect the confounding effect of the low patient numbers.

There is still a controversial debate in the literature regarding the ATD treatment of these patients. Goday-Arno *et al.* (4) stated that none of their 12 patients responded to the treatment with carbimazole after a mean period of 40 months and all required a definitive treatment, whereas De Luca *et al.* (5) reported a better clinical response to medical treatment of children with GD and DS than of patients without DS. In their DS group, no patients needed surgery or radioiodine ablation.

In a recent study, clinical management of hyperthyroidism was investigated in children with and without DS (14). It was shown that remission was observed in 5 of 11 patients with DS and in 6 of 25 patients without DS, whereas recurrence was no different between the two groups. Younger age is associated with relapse after discontinuation of medical treatment (14). The younger age at presentation might explain the relapse rate in children with DS. Accordingly, our results suggest a generally good clinical response to medical treatment, while definitive treatment was necessary in 3 of 13 patients.

Dos Santos *et al.* (14) also stated that ATDs for longer periods should be considered since nearly all of their patients received medical treatment for more than 2 years. Our DS patients received medical treatment with a mean duration of 43.4 ± 11.0 months and the majority responded well. We also did not observe any serious side effects of ATDs. Nonetheless, due to the scarce recurrence in our study, we could not perform any further analysis regarding predictors for a relapse.

It remains debatable when a definitive treatment for GD patients should be introduced. A recent consensus paper in GD in general suggests that the family should be informed regarding the estimated success rates of medical treatment, and definitive treatment options should be discussed in case of failure or intolerance of medical treatment (26). The current options for definitive treatment include radioactive iodine therapy or surgical thyroidectomy. It has been suggested that the surgical treatment of hyperthyroidism in patients with DS should be reserved for those with serious side effects of medical treatment and those demanding a prompt resolution to thyrotoxicosis (4). Comorbidities and anaesthesia considerations may influence the individual therapeutic decision. Some authors imply that thyroid surgery might be not the optimal treatment modality due to possible difficulties in anaesthesia in DS patients associated with their craniofacial abnormalities and short necks (3, 27). There is a considerable variation of definitive treatment among different countries. In Germany, thyroid surgery is the preferable definitive treatment in the paediatric age group.

The main limitation of our study is the small number in the DS group due to the rarity of this condition. Moreover, four of our patients were still receiving primary ATD treatment and only three patients were in remission state. For that reason, no multivariate analysis to demonstrate the predictors of remission in these patients could be performed. However, our findings will contribute to the scarce literature on this topic.

The present study has several strengths. First, we included only patients with positive TRABs and excluded children with other causes of hyperthyroidism, such as Hashimoto's disease with hyperthyroidism, neonatal hyperthyroidism, or hyperthyroidism due to rare conditions like McCune Albright syndrome or non-immune hyperthyroidism. Our study provides information regarding clinical features and long-term management of patients with GD. Secondly, we include a large control group of GD patients without DS from the same local background, allowing us to compare the characteristics of GD between the two groups. Of note, our findings suggest that the presenting biochemical features and responses to treatment did not significantly differ between patients with and without DS. Thirdly, our data on treatment show that surgical management of GD in patients with DS might be an option.

In conclusion, the results of our cohort suggest that patients with DS and GD present at an earlier age have similar clinical features as GD patients and respond to medical treatment. We suggest documenting all patients with DS and GD in a registry to extend the knowledge of this rare disease.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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Author contributions

ANC, VS, HGD, KF, and MM collected the patients' data. ANC and HGD analysed the data and wrote the first draft of manuscript. JW and BG contributed to the interpretation of the results. All authors revised and approved the final version of the manuscript.

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