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Graves' disease in children in the two decades following implementation of an iodine prophylaxis programme

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Abstract

Grave's disease (GD) is a form of thyroid autoimmune disease characterised by hyperthyroidism. It is a rare clinical problem in paediatrics. Development of disease is the result of genetic susceptibility and some environmental factors. One of the best-documented environmental factors involved in thyroid autoimmunity is iodine excess. The aim of our study was to analyse the clinical course and response to pharmacological treatment in children diagnosed with Graves' disease in first two decades after mandatory salt iodination. Records of 94 children diagnosed with GD in the years 1998-2017 were analysed. Medical data of patients was compared between two decades following implementation of iodine prophylaxis: 1998-2007 (first-decade group – FDG) and 2008-2017 (second-decade group – SDG); 34 and 60 patients, respectively. Medical data of FDG was obtained from archival records and previous analysis performed in 2006. Data of 60 patients from SDG were obtained from currently available medical records. Results were statistically analysed using Microsoft Excel and Statistica 11 software. Results: In our study, after mandatory salt iodination, the tendency of an increase in newly diagnosed GD in children without family susceptibility was observed. The antibody profile indicates the significant contribution of the autoimmune process involving all thyroid antigens; therefore, the term "autoimmune hyperthyroidism" seems to be more appropriate than classical GD in this group of patients. The first-choice treatment with methimazole rarely causes adverse events during the therapy, and they have benign character.

Key words: *children, Graves' disease, clinical course, salt iodination.*

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Introduction

Grave's disease (GD) is a form of thyroid autoimmune disease characterised by hyperthyroidism. It is a rare clinical problem in paediatrics, and the incidence is estimated at 0.1-3 per 10,000 children [1]. On the other hand, it is the most common cause of thyrotoxicosis in developmental age [1]. GD in prepubertal children is less common, but its course is usually more severe and more often requires radical therapy [2]. Development of disease is the result of genetic susceptibility and some environmental factors. Genetic predisposition is usually multifactorial, but some monogenic diseases are also associated with increased risk of GD, such as 21 trisomy [3, 4], Turner syndrome [5], or DiGeorge syndrome [6]. One of the best documented environmental factors involved in thyroid autoimmunity is iodine excess [7]. Increased incidence of autoimmune thyroid diseases was observed in countries after the introduction of iodine prophylaxis [8-10]. Higher incidence was noted after iodine fortification of salt, and it concerns especially young subjects with a genetic predisposition [11].

In Poland, mandatory salt iodination was introduced in 1997. Table salt is obligatorily enriched in iodine 30 ±10 mg KJ/1 kg NaCl [12]. Studies performed 10 years after introducing iodination classified Poland's status as iodine-sufficient in the general population [13].

The aim of our study was to analyse the clinical course and the response to pharmacological treatment in children diagnosed in our centre with Graves' disease in the first two decades after mandatory salt iodination.

Material and methods

We analysed retrospectively the records of 94 children diagnosed with GD in the Department of Paediatrics and Endocrinology, Medical University of Warsaw, in the

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years 1998-2017. The diagnosis was established on the basis of clinical symptoms of hyperthyroidism and confirmed by hormonal tests and the presence of TSH receptor antibodies (TRAb). Clinical and biochemical features were analysed at diagnosis: age at onset, the most common symptoms and complaints, biochemical abnormalities in laboratory test, anti-thyroid antibodies, and thyroid ultrasound. The response to antithyroid drug therapy and its side effects were assessed. Medical data of patients were compared between two decades following implementation of an iodine prophylaxis programme in Poland in the periods 1998-2007 (first-decade group – FDG) and 2008-2017 (second-decade group – SDG); 34 and 60 patients, respectively. Medical data of FDG was obtained from archival records and previous analysis performed in 2006 [14]. Data of 60 patients from SDG were obtained from currently available medical records.

Table 1. Clinical and biochemical findings at diagnosis (SDG)

Age at diagnosis	Median	Range
Entire group	14.96 years	3.3-17.5
Girls	14.92 years	2.7-17.5
Boys	14.92 years	5.4-17.4
Complaints	***n***	**%**
Fine, wet skin	42	70
Tremor	32	53
Weight loss	29	48
Heat intolerance	30	50
Shorten attention span	22	37
Muscle weakness	21	35
Fatigability	21	35
Restlessness	21	35
Irritability	17	28
Sleep disturbances	18	30
Hair loss	10	17
Frequent stooling	6	10
Hyperhidrosis	5	8
Increased appetite	4	7
Signs		
Tachycardia	55	92
Palpable goitre	51	85
Bruit over thyroid	18	30
TAO	16	27
Laboratory findings		
Elevated liver enzymes	28	47
Leucopaenia	5	8
Decreased cholesterol level	12	20
Decreased triglyceride level	4	7
Other abnormalities		
Increased blood flow in USG	48	80
Cardiac arrhythmia	5	8
Comorbidities		
Allergic disease	10	17
Other autoimmune disease	5	8
Genetic disorder	2	3

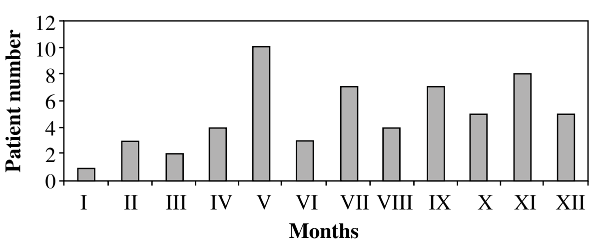

Fig. 1. Incidence rate in particular months of the year in children with Graves' disease

Free thyroxine (fT_4, normal range: 0.78-1.31 ng/dl) and triiodothyronine (fT_3, normal range: 2.33-4.35 pg/ml), thyroid stimulating hormone (TSH, normal range: 0.53-3.59 μIU/ml), anti-thyroid peroxidase antibodies (anti-TPOAb, normal range < 5.6 IU/ml), and anti-thyroglobulin antibodies (anti-TGAb, normal range < 4.1 IU/ml) were evaluated by chemiluminescence immunoassay (Architect i1000SR, Germany). The value of TSH receptor antibodies (TRAb) was measured by electrochemiluminescence immunoassay (Cobas e601, Roche); a positive value was considered as > 1.75 IU/l. Thyroid ultrasound was performed in each patient at the time of diagnosis.

Results were statistically analysed using Microsoft Excel software and reported as mean and standard deviation, median, maximal, and minimal values. Comparisons between groups was conducted using the Independent Samples T-test performed with Statistica 11 software. A p-value < 0.05 was considered statistically significant.

Results

Clinical features of Graves' disease at diagnosis

The symptoms at diagnosis were characteristic for hyperthyroidism and did not differ in FDG and SDG children. The most common clinical feature at diagnosis observed in children from SDG was tachycardia (Table 1), in four cases accompanied by cardiac arrhythmia, and in one case cardiac arrhythmia was not connected with tachycardia. The most frequent complaints were fine, wet skin and tremor. Polydipsia, dysphagia, vomiting, and pruritus were reported as first symptoms extremely rarely. Twenty-six per cent (10/39) of pubertal girls reported irregular menses (Table 1).

The frequency of newly diagnosed GD for each month in a year was analysed, and the tendency of increased newly diagnosed cases was observed from the end of spring to the end of autumn with a peak incidence in May (Fig. 1).

In SDG children the median TRAb value was 9.77 IU/l, range: from 2.46 to > 40 IU/l. Anti-TGAb and/or anti-anti-TPOAb concentrations at diagnosis were elevated in almost all tested patients (93%, Table 2); median values were

102.90 IU/ml (range 1.2-3488 IU/ml) and 226.55 IU/ml (range 0.2-6656 IU/ml), respectively.

Evaluation of treatment and side effects

The majority of SDG patients (n = 59) were treated with methimazole (MMI), only one patient received propylthiouracil (PTU) as initial therapy. Adverse drug reactions occurred in 13 patients (21.67%): hive (n = 3), pruritus (n = 1), leucopaenia (n = 4), elevated liver enzymes (n = 4), and purpuric skin lesions (n = 1). Thirty-two children (53%) developed hypothyroidism during the first course of ATD treatment and simultaneously received supplementation with L-thyroxin.

Remission was defined as being euthyroid for one year after cessation of therapy [2]. Relapse was defined as recurrence of hyperthyroidism at any time during the treatment or after withdrawal of thyrostatics.

In 56 children under observation longer than three months after starting ATD treatment, prolonged TSH suppression (> 3 months) was found in 18 (32%) patients. In 31 children observed ≥ 24 months, relapses after first-line treatment occurred in 10 patients (32%), and relapses after completion of antithyroid drug therapy occurred in six patients (19%). In children observed < 24 months (n = 29) relapses after first-line treatment were found in 14 patients (48%). Ten patients were referred for radioiodine therapy, and one patient was qualified for strumectomy.

Comparison of medical data of patients diagnosed with Graves' disease in two decades following implementation of iodine prophylaxis programme

In our centre there were 34 newly diagnosed patients in FDG and 60 patients in SDG. No statistically significant difference in the mean age and sex contribution at diagnosis between groups was found. Familial prevalence of GD was significantly more frequent in FDG than in SDG (29% vs. 7%; p = 0.004). The mean value of TRAb was higher in SDG, but no statistical significance was found (p > 0.05). Occurrence of thyroid autoimmune ophthalmopathy (TAO) in the second decade decreased (44% vs. 28.3%); however, the difference was not statistically significant (p > 0.05). Severe side effects of ATDs were observed significantly more often in FDG than in SDG (p < 0.05). All other clinical features of GD between FDG and SDG did not differ significantly (Table 3).

Table 2. Percentage of positive anti-thyroid antibodies in SDG children

Parameter	*n*	%
Positive TRAb	60	100
Positive anti-TGAb and/or anti-TPOAb	56	93

TRAb – TSH receptor antibodies; anti-TGAb – anti-thyroglobulin antibodies, anti-TPOAb – anti-thyroid peroxidase

Discussion

In our study, the two-fold higher number of patients in SDG suggests increasing incidence of GD in children in the last 10 years. However, the study was a single-centre

Table 3. Clinical characteristics of children with Graves' disease – two decades after mandatory salt iodination

Variable	FDG 1998-2007	SDG 2008-2017	*p*-value
***n* (%)**	34 (100)	60 (100)	–
Girls	28 (82.4)	52 (86.67)	NS
Boys	6 (17.7)	8 (13.33)	–
Mean age	11.7 ye (6.4-16.4)	13.7 ye (3.3-17.5)	NS
Positive family history of thyroid disease	13 (38)	18 (30)	NS
Positive family history of Graves' disease	10 (29)	4 (7)	0.004*
Other autoimmune disease	4 (11.7)	5 (8.3)	NS
Disorders with predisposition to autoimmune disease	Down syndrome: 3 (9)	Down syndrome: 1 (1.7)	
Allergic disease	8 (23.5)	12 (20)	NS
Mean TRAb value	8.87 IU/l (3.6-19 IU/l)	12.23 IU/l (2.46-40 IU/l)	NS
Presence of TAO	15 (44)	17 (28.3)	NS, 0.11
Side effects of ATDs	6 (17)	13 (21.67)	NS
Severe side effects of ATDs	3 (8.5)	0	0.02*

*n – number of patients, FDG – first decade group, SDG – second decade group, TRAb – TSH receptor antibodies, NS – no statistical significance, * statistically significant value, TAO – thyroid autoimmune ophthalmopathy, ATDs – anti-thyroid drugs* observation, hence it does not have epidemiological value. The next finding was significantly more frequent familial prevalence of GD in FDG than in SDG (29% vs. 7%; $p = 0.004$). The increased frequency of GD in children without familial (genetic) susceptibility suggests a significant influence of some environmental factors. Temporal relationship with the introduction of salt iodination justifies the conjecture that it had impact on GD development. Higher incidence of autoimmune thyroid disorder was detected in several countries after the start of mandatory salt iodination [8-11]. Polish authors [15] reported a significant increase of frequency of cytologically diagnosed autoimmune thyroiditis (AIT) in fine-needle aspiration biopsy in the years after initiation of iodine supplementation, and the difference was more pronounced in children than in adults (from 3% in 1992 up to 16% in 1999). Similar data were reported by authors from Greece [16] and from Argentina [17]. The impact of increased iodine supply on thyroid autoimmunity is confirmed in an animal model [18]. This phenomenon is elucidated by higher immunostimulatory properties of more iodinated thyroglobulin. In concert with this hypothesis Bulow *et al.* reported the increased prevalence of anti-TPOAb and anti-TGAb after 4-5 years of salt iodination [19]. The increased iodine supply is not the only environmental factor involved in autoimmunity. It is well known that some viral infections, vaccination, drugs, chemical pollution, and stress can be trigger factors in autoimmune thyroid disease development. We cannot definitely exclude the influence of the other factors; nevertheless, in our study children were not on special diets, were not treated for other chronic diseases, and were vaccinated according to a mandatory vaccination program.

The temporary association with introduction of mandatory salt iodination and the concordance with observations of other authors [15] support our conclusions that it could be responsible for changes in the autoantibodies profile in GD in our study group. In classical pathogenesis of GD anti-TPOAb and anti-TGAb appears secondary to TRAb, and their levels are lower than in Hashimoto thyroiditis (HT). The presence of anti-TPOAb and anti-TGAb is mainly associated with HT, but it can be present also in 70-90% of GD patients [20, 21]. In our study elevated values of TRAb were accompanied by anti-TPOAb and/or anti-TGAb in 97% patients at the time of diagnosis, and concentrations of these antibodies varied from slightly elevated to very high amounts. It might suggest that autoimmune processes in our patients with GD were primarily not only directed against TSH receptor but also involved other thyroid antigens at the onset of the disease. This may indicate that the pathogenesis of hyperthyroidism in these patients is similar to HT, and it could be named autoimmune hyperthyroidism rather than classical GD. What is more, recently some reports suggest a conversion of GD to HT [22, 23] and vice versa [24].

TAO occurs in one third of children with GD [25]. It occurs more frequent in female and post-pubertal patients [26, 27]. In our study a decreasing prevalence of TAO was observed in SDG, but the difference was not statistically significant ($p = 0.11$). However, this beneficial tendency might be connected with the decreasing popularity of smoking in Poland reported in recent years and decreased exposure to passive nicotinism in public areas [28]. Smoking has been proven as one of the strongest risk factors of TAO [29, 30].

In children, the recommended initial treatment of choice is antithyroid drug therapy with methimazole (MMI). Propylthiouracil (PTU) should not be prescribed in paediatric patients due to reports of PTU-induced ANCA-positive vasculitis and rapidly progressive PTU liver failure with a low chance of reversibility. In contrast, MMI is not associated with severe liver failure in children [31] or with high prevalence of MPO-ANCA [32]. Adverse events during MMI therapy are dose-dependent and affect up to 20% of children [33]. In our study, side effects of ATDs were reported by 17% to 21.7% of children in FDG and SDG, respectively. We observed significantly less frequent severe adverse drug events in SDG ($p < 0.05$). Probably this is connected with decreased use of PTU in recent years. In SDG only one patient was treated with PTU; in FDG more patients received PTU as initial treatment, and more severe effects were reported in that group. Many studies support the observation that pharmacological treatment of GD in children is not very effective [34]. It allows long-term remission only in 30% of patients [35, 36]. One of the most important relapse risk factors is lack of TSH normalisation during the first three months of treatment [37, 38]. In our study among SDG patients prolonged TSH suppression was found in 32% of children. The same percentage of children treated ≥ 24 months had relapses after first-line treatment. However, prolonged TSH suppression highlights a low chance of remission and can indicate candidate patients requiring definitive therapy in the future.

Our paper supports other authors' data regarding the seasonality of new diagnosis of GD with increased incidence from the end of spring to the end of autumn [37]. The hypotheses explaining this phenomenon include viral infections [37], allergic sensitisation [38], and decreased vitamin D concentration [39]. Seasonality is also observed in relapses of GD after completion of anti-thyroid drug therapy, with higher rates in spring and summer in comparison to autumn and winter [40].

Conclusions

We realise that our study has some limitations because of its retrospective character. We analysed medical records that were not originally designed for the study. Nevertheless, we can conclude that:

In our study, after mandatory salt iodination, a tendency of an increase in newly diagnosed GD in children without family susceptibility was observed.

The antibody profile in our group of GD children indicates the significant contribution of autoimmune processes involving all thyroid antigens; therefore, the term "autoimmune hyperthyroidism" seems to be more appropriate than classical GD in this group of patients.

The first-choice treatment with MMI rarely causes adverse events during the therapy, and they have benign character.

The authors declare no conflict of interest.

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