

## Down syndrome and hyperthyroidism – two case reports

Zespół Downa i nadczynność tarczycy – opis dwu przypadków

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### Abstract

The 21 trisomy (Down syndrome, DS) is one of the most common chromosomal disorders in pediatric practice. Thyroid dysfunctions in these patients are very common. Hypothyroidism is diagnosed in nearly 50% of patients in this population and the number of patients increases with age. Hyperthyroidism is much less frequently diagnosed in children with DS. Hyperthyroidism treatment strategy is highly important for an undisturbed and balanced development of the children. We report two children with Down syndrome and hyperthyroidism. The processes of treatment were significantly different.

### Key words

Hyperthyroidism, Down syndrome

### Streszczenie

Trisomia 21 pary chromosomów (Zespół Downa, DS) jest jednym z częściej występujących zaburzeń chromosomalnych w praktyce pediatrycznej. Zaburzenia funkcji tarczycy często występują u tych pacjentów. Niedoczynność tarczycy jest rozpoznawana u blisko 50% pacjentów z ZD, a liczba ta wzrasta wraz z wiekiem. Nadczynność tarczycy jest rozpoznawana znacznie rzadziej u dzieci z ZD. Odpowiednia strategia leczenia nadczynności tarczycy jest bardzo istotna ze względu na możliwość zaburzenia rozwoju dzieci. Przedstawiamy dwa przypadki dzieci z zespołem Downa i nadczynnością tarczycy. Proces leczenia tych pacjentów był odmienny.

### Słowa kluczowe

nadczynność tarczycy, zespół Downa

## Introduction

The 21 trisomy (Down syndrome, DS) is one of the most common chromosomal disorders in pediatric practice. Thyroid dysfunctions in these patients are very common. Hypothyroidism is diagnosed in nearly 50% of DS patients and the number of patients increases with age [1,2]. The frequency of congenital hypothyroidism in children with Down Syndrome is 28 times higher than in general population. This is probably caused by hypoplasia of the thyroid gland (fibrosis of the gland) during fetal life [3]. Hyperthyroidism is much less frequently diagnosed, especially in children with DS.

A hyperthyroid state in children is mostly caused by Graves' disease. It can also be seen in acute and subacute thyroiditis, toxic nodules, toxic multinodular goiters, and thyroid hormone ingestion, however not commonly [4]. Being persistent in Graves' disease, thyrotoxicosis is transient in other conditions.

This condition can have a threatening impact on the process of growth and psychomental development in children and adolescents. The symptoms, including weight loss, heart arrhythmia, lack of concentration, and behavioral disturbances are distressing [5]. For these reasons, hyperthyroidism treatment strategy is highly important for an undisturbed and balanced development of the children.

We report two children with Down syndrome and hyperthyroidism. The processes of treatment were significantly different.

## Patient 1

An 8-year-old boy with Down syndrome was admitted to the Cardiology Department because he had 2 episodes of unconsciousness. On admission, he presented mental and

psychomotorical retardation; he spoke only some simple words. His weight was 39 kg, height -126 cm, and BMI – 24,6kg/m<sup>2</sup> (above 97<sup>th</sup> percentile), which indicates obesity. He has never been admitted to an endocrinological department before. Boy`s mother had a Hashimoto disease and hypothyroidism. Patient`s thyroid status on admission was: TSH 4,2 mIU/ml(0,4-3,8mIU/ml), fT4 – 1,0 ng/ml(0,86-1,8 ng/ml), fT3 – 4,65 pg/ml(2,4-6,5 pg/ml). His psychomotorical development was retarded. He didn`t speak and he had problems with walking. The therapy with L-thyroxin was started. During two years of the therapy, improvement in psychomotor development, and boy`s speech were noticed. The thyroid function was monitored every two months. After the next 6 months, the boy was admitted to an endocrinological department because he lost 10kg of weight within 3 months. The level of free tyroxine and triiodotironin were above normal range (fT3 6,9 (2,4-6,5 pg/ml); fT4 2,83 (0,86-1,8 ng/ml). Hyperthyroidism was diagnosed and therapy of tiamasol was started. The antithyroid drugs were continued for 3 years. During the therapy the boy had an episode of hyperglycemia with polyuria and polydipsia. The control levels of fasting and postprandial glycaemia were normal, as was the level of HbA1c. The diabetes mellitus was excluded. We didn`t note these symptoms later.

After the next 6 months, the boy had a low level of TSH and a high level of fT4, fT3, and ATPO, as well as symptoms of hyperthyroidism. He received incorrect treatment of tiamasol and he had problems with systematic control visits in an endocrinological department. Radioiodine treatment was introduced when the patient was 12 years old. Thyroid iodine 131I uptake dose was optimal for 17 mCi. Thyrotoxicosis was present for a month – continuation of antithyroid therapy was necessary. Biochemistry and clinical manifestations of hypothyroidism were revealed after 2 months, which required the supplementation of L-thyroxin (150 µg). The level of TSH and free T4 were within the normal range, but the level of TRAb was still high (23,87IU/ml) after 7 months of the radioiodine therapy. After 2 years of this therapy, the levels of TSH and fT4 were within normal ranges, his weight – 84kg and height -164,4cm, and BMI 31,16 kg/m<sup>2</sup>, so the patient was obese, as was his mother.

## Patient 2

An 11-year-old girl with DS was admitted to an endocrinological department, because she lost 6 kg of body weight during 3 months and had problems with concentration. During physical examination the patient presented tachycardia, tremor of hands, and an enlarged volume of thyroid gland. The laboratory results showed elevated levels of free T4 -5,2 ng/l (0,86-1,8 ng/ml ) and free T3 -12,5ng/ml (2,4-6,5 pg/ml), as well as decreased level of TSH -0,07 mIU/ml (0,4-3,8mIU/ml).

After 4 weeks following the introduction of an antithyroid treatment (tiamasol) the control levels of fT4 and fT3 were normal. After 2 months, the patient`s clinical status was significantly better, without hyperthyroidism manifestation,

and normal level of free T4. One year later a tiamasol dose was reduced and L-thyroxin was added. This treatment was continued for a year. Later on tiamasol and L-thyroxin doses were reduced gradually during the next 22 months, which resulted in no drugs being administered to the patient. During control visits no abnormalities in physical examination were found, the patient presented with good clinical status, without hyperthyroidism manifestations, and thyroid hormone levels within normal range. Five months later hypothyroidism was diagnosed and L-thyroxin 25 ug was administered. Two months after the diagnosis the patient was hospitalized for the control examinations. Her body weight was 44,5kg, height – 146,5cm and BMI 20,73 kg/m<sup>2</sup>. The level of free T4 was normal, but TSH was increased (9,01mIU/ml). Tests showed elevated levels of antibody titer anti TPO (>1000,0 IU/ml) and TRAb (2,86 IU/ml), which led to the diagnosis of an active autoimmune process. Corrections of L-thyroxin therapy were required. The USG examination of the thyroid gland was typical for an autoimmune thyroid disease without the nodules.

In 18th year of the patient`s life the celiac disease was diagnosed during screening tests of the population of children with Down syndrome. The patient presented no symptoms of this disease, except for a lower body weight. Patient`s results were positive: IgAtTG, IgGDGP, and a higher level of total IgA. The histopathology of the specimen, taken during the duodenum biopsy, confirmed this enteropathy classifying in Marsh III B. A gluten-free diet was introduced. The L-tyroxin therapy is still continued.

## Discussion

Although DS patients are predisposed to autoimmune diseases, hyperthyroidism in patients with Down Syndrome is rarely reported in medical literature [6,7]. In children with 21 trisomy hyperthyroidism is more common (6,4%) than in the general pediatric population [6, 8, 9]. The main characteristics of the hyperthyroidism in DS patients include: earlier disclosure of the disease, lack of female predominance in occurrence of hyperthyroidism, and more frequent coexistence of other autoimmune diseases.[8] Diagnosis of the disease in both groups is similar: sudden onset, diagnosis on the basis of symptoms and laboratory tests [8,9]. The main differences concern the thyroid-associated orbitopathy, which is less frequent in DS (16,5%) comparing to general population (20 – 25%) [9, 10].

## Antithyroid treatment in pediatric population

Initial treatment in the population of children and adolescents is antithyroid pharmacotherapy (methimazole is recommend). Response to the treatment is good, but remission is not often achieved (20-30%) [11-13]. Chronic methimazole therapy makes it possible to control the levels of hormones but does not increase the probability of remission [11]. The chance of

remission is increased with continued administration of drugs, until the antibody titer of TRAb is within the norm.

The population of DS children is specific due to immune defects caused by trisomy 21. Therefore, an aggressive antithyroid therapy can be dangerous, and is contraindicated with concomitant infections [14]. One of the most serious side effect of using thionamids is agranulocytosis (0,1-0,5%) [15]. Other major side effects include: lupus-like syndrome (vasculitis), hepatitis, and liver failure. Occurrence of any of these side effects is an indication for an immediate discontinuation of thionamids treatment and the reason for considering RAI or surgery [5]. Small side effects (itching, hives, muscle pain, slightly higher level of liver enzymes) are observed in 25% of cases of pediatric population [4, 11].

In one of our cases this treatment resulted in clinical remission but not in immunological remission. Also, there were no side effects during the treatment. Now the female patient presents autoimmune thyroiditis and she is treated with L-thyroxin.

## Radioiodine treatment in pediatric population

Radioiodine therapy is chosen in some cases, for instance when the thionamid therapy has failed, or when there are some contraindications, or when quick remission of hyperthyroidism is required [14]. Rivkees *et al.* described the treatment of 1200 pediatric patients that started radioiodine 131I therapy after the age of 1 year old. Remission was obtained in 95% cases. The size of the thyroid gland over 80 ml is the main contraindication for this therapeutic option. Side effects are not significant and

include: temporary nausea and mild pain in the area of the thyroid gland. The most serious and rare complication is the thyroid break-through (the risk factor is a large goiter). The risk of thyroid ophthalmopathy is significant in adults and not described in the pediatric population [11].

As far as thyroid cancer is considered, the younger the patient is, the higher risk of cancer [11, 16]. Patients younger than 5 years old cannot be treated with RAI because of high risk of neoplasia [17]. Few cases of thyroid malignancy, after radioiodine treatment in children, were described: A 5-year-old patient treated with 50 Ci/g; 9-year-old patient treated with 5.4 mCi; 11-year-old patient treated with 1.25 mCi; 16-year-old patient treated with 3.2 mCi. [5] What is important, a lower dose of radioiodine poses a greater risk of cancerogenesis [5, 16]. Although radioiodine therapy in the pediatric population with Graves' disease is common in the United States, in other countries it is used only in difficult cases [18].

In our case RAI was recommended because the parents were noncompliant. In one of our cases the expected result was achieved – the male patient presented hypothyroidism that was treated by levothyroxine.

## Conclusion

Hyperthyroidism is more prevalent in patients with DS than in the general population, and has no gender predominance. It is mainly caused by Graves' disease. Sometimes anti-thyroid drugs are not effective in achieving remission and radioactive iodine as a definitive treatment is required in such cases.

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