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Acquired autoimmune hypothyroidism as a cause of severe growth deficiency in one of the twin sisters

Głęboki niedobór wzrostu w wyniku autoimmunologicznego zapalenia tarczycy u jednej z sióstr pochodzących z ciąży bliźniaczej

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Abstract
Acquired autoimmune hypothyroidism is rare in early childhood, however, it must be considered in a 4 year old child with medical history of delayed growth, increased somnolence, difficulty concentrating, and reduced activity. We report on the case of full clinical picture of severe hypothyroidism in one of the twins. Thyroid function deteriorated in one of the sisters, resulting in mental, motor and growth slowdown, remaining undiagnosed for about 2 years, while the other sister developed normally. In the reported case, severe hypothyroidism and growth deficiency were accompanied by celiac disease. Initiation of L-thyroxine therapy resulted in an immediate response that increased the growth velocity by more than 2.2 times. This confirms the dominant role of thyroid hormones over celiac disease in the growth process, as the catch up effect started before gluten free diet was introduced.
Key words:
hypothyroidism, growth deficiency, children.

Streszczenie
Nabyta autoimmunologiczna niedoczynność tarczycy występuje rzadko we wczesnym dzieciństwie, jednak należy ją rozważyć u 4-letniego dziecka z wywiadem opóźnionego wzrastania, zwiększonej senności, zaburzeniami koncentracji i obniżoną aktywnością. Opisano przypadek pełnego obrazu klinicznego ciężkiej niedoczynności tarczycy u jednej z sióstr pochodzących z ciąży bliźniaczej. Dysfunkcja tarczycy spowodowała u niej spowolnienie umysłowe, motoryczne i wzrostowe, jednocześnie pozostając nierozpoznana przez ok. 2 lata, podczas gdy jej siostra rozwijała się normalnie. W opisywanym przypadku ciężkiej niedoczynności tarczycy i niedoborowi wzrostu towarzyszyła celiakia. Rozpoczęcie terapii L-tyroksyną spowodowało natychmiastową reakcję zwiększenia tempa wzrastania o ponad 2,2 razy. Potwierdza to dominującą rolę hormonów tarczycy nad chorobą trzewną w procesie wzrastania, ponieważ efekt nadrabiania zaległości rozpoczął się przed wprowadzeniem diety bezglutenowej.
Słowa kluczowe:
dzieci, niedoczynność tarczycy, niedobór wzrostu.

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Introduction

Proper thyroid function is of great importance for normal development during childhood. Hypothyroidism should be one of the first medical suspicions in a child with medical history of reduced activity, increased somnolence, difficulty concentrating, and delayed growth. However, growth deficiency occurring as a result of acquired hypothyroidism is usually not severe, as other symptoms typical for thyroid dysfunction are present earlier, and the diagnosis should be set before growth retardation becomes distinctive [1–3]. That is why it is so surprising to find profound discrepancies in the development of two twin sisters, who had been previously developing similarly. Rapid progression of hypothyroidism, which has occurred in the course of autoimmune thyroiditis in one of the twins, has led to a severe growth delay and drastically impaired psychomotor functioning, with concurrent significantly abnormal laboratory tests results.

Case presentation

Sisters were born from dizygotic twin pregnancy, dissected by caesarean section in 37th week. First sister (SZ) weighed at birth 2800 g and second sister (SN) 3080 g. At the doctor's office, the girl SN turned up at the age of 4 years 7 months due to short stature and mental retardation. She was then 97.0 cm of height (below 3rd percentile; Fig. 1). Her mother reported a slowdown of growth and mental functions, drowsiness, and reluctance to contact her peers. In parental observation, above symptoms had been gradually increasing for about 2 years. Before that time, the psychomotor development of the sisters proceeded similarly. Physical examination revealed dryness and roughness of the skin, particularly in the area of the elbows; bradycardia with the range of heart rate from 60 to 78 per minute, poor facial expression, poor response to stimuli, and reluctance to answer questions. Thyroid gland was palpable, not enlarged, with increased cohesion. Hypothyroidism was suspected and laboratory tests were pre-ordered. Obtained results are presented in Table I. Thyroid ultrasound examination showed slightly heterogeneous gland, not enlarged, without obvious focal lesions, but with reduced echogenicity, and vascular flow within the normal range. Estimated total thyroid volume was 2,65 ml. Based on symptoms and test results, the girl was diagnosed with severe hypothyroidism and autoimmune thyroiditis. The L-thyroxine substitution therapy was started after admission to the hospital, at an initial dose of 25 μg per day (1.5 μg/kg of body weight per day), then the dose was gradually raised to 50 μg per day (3 μg/kg of body weight per day). After 5 and 8 days further evaluation of thyroid hormones was performed (Table I). The girl's condition was stable.

During initial laboratory tests the patient was also diagnosed with anemia and oral supplementation of iron, folic acid and group B vitamins were started. Despite the treatment, some blood count parameters have even decreased. Iron concentration at the beginning was 53 μg/dl, and after 3 months it was only 17 μg/dl. Detailed results of blood counts are presented in Table II.

In the course of extended diagnostics and additional blood tests, the presence of antibodies typical for celiac disease has also been found (anti-gliadin IgA and IgG – both results beyond 200 RU/ml; anti-tissue transglutaminase IgA – result beyond 200 RU/ml, IgG – weakly positive). Based on these results, the girl was directed to a gastroscopic examination. Histopathological evaluation of the collected sections allowed to set the diagnosis of celiac disease. Gluten free diet was implemented 3 months after initiation of L-thyroxine treatment.

Starting L-thyroxine therapy has changed the patient's growth velocity. At the commencement of treatment the girl SN was 97.0 cm of height (height SDS = –2.93) and after 3 months the growth was 100.1 cm (height SDS = –2.44). Growth rate before the treatment was 4.4 cm per year (velocity SDS = –1.38 SD) and after 3 months reached 9.7 cm per year (velocity SDS = +3.1 SD). These values reflect to the period before gluten free diet.

The course of the patient's SN growth is shown on the percentile chart, in comparison to her twin sister SZ (Fig. 1). At the age of 2, the growth of both twins was similar and was about 90th percentile, which was consistent with parental height (mother = 180.1 cm, above 97th percentile, father 180.3 cm, 50–75th percentile).

The development and behavior of the other twin, SZ, did not raise the parents' objections. Her height was about 90th percentile (Fig. 1). The girl did not show any signs of hypothyroidism. On palpation, the thyroid gland was not enlarged, but with increased cohesion. The presence of heterogeneous areas with normal and reduced echogenicity and normal vascular flow was found in the thyroid ultrasound examination. Estimated total thyroid volume was 3,63 ml. Thyroid hormones and thyrotropin concentrations were within the laboratory standards: TSH = 3.237 μIU/ml, FT4 = 1.11 ng/dl, FT3 = 4.06 pg/ml. However, the antibodies typical for autoimmune thyroid disease were detected: anti-TG = 29.4 IU/ml, anti-TPO = 7.3 IU/ml. The girl SZ needs further endocrine observation.

The parents gave informed consent to use the medical data of their children for the purpose of the article preparation.

Discussion

Growth during childhood is regulated in a particularly complex way and depends on multiple factors. Hormonal interactions are of great importance – not only in terms of growth hormone secretion, but also others, such as cortisol, sex hormones, or thyroid hormones [2, 4]. How significant may this influence be, we can see in the example of our patient.

Acquired autoimmune hypothyroidism is rare in young children, although it is more frequent than hyperthyroidism [3, 5]. In presented case, a particularly severe growth deficit occurred as a result of the coexistence of two unfavorable medical conditions: autoimmune hypothyroidism, and celiac disease. It should be emphasized that both, celiac disease and autoimmune

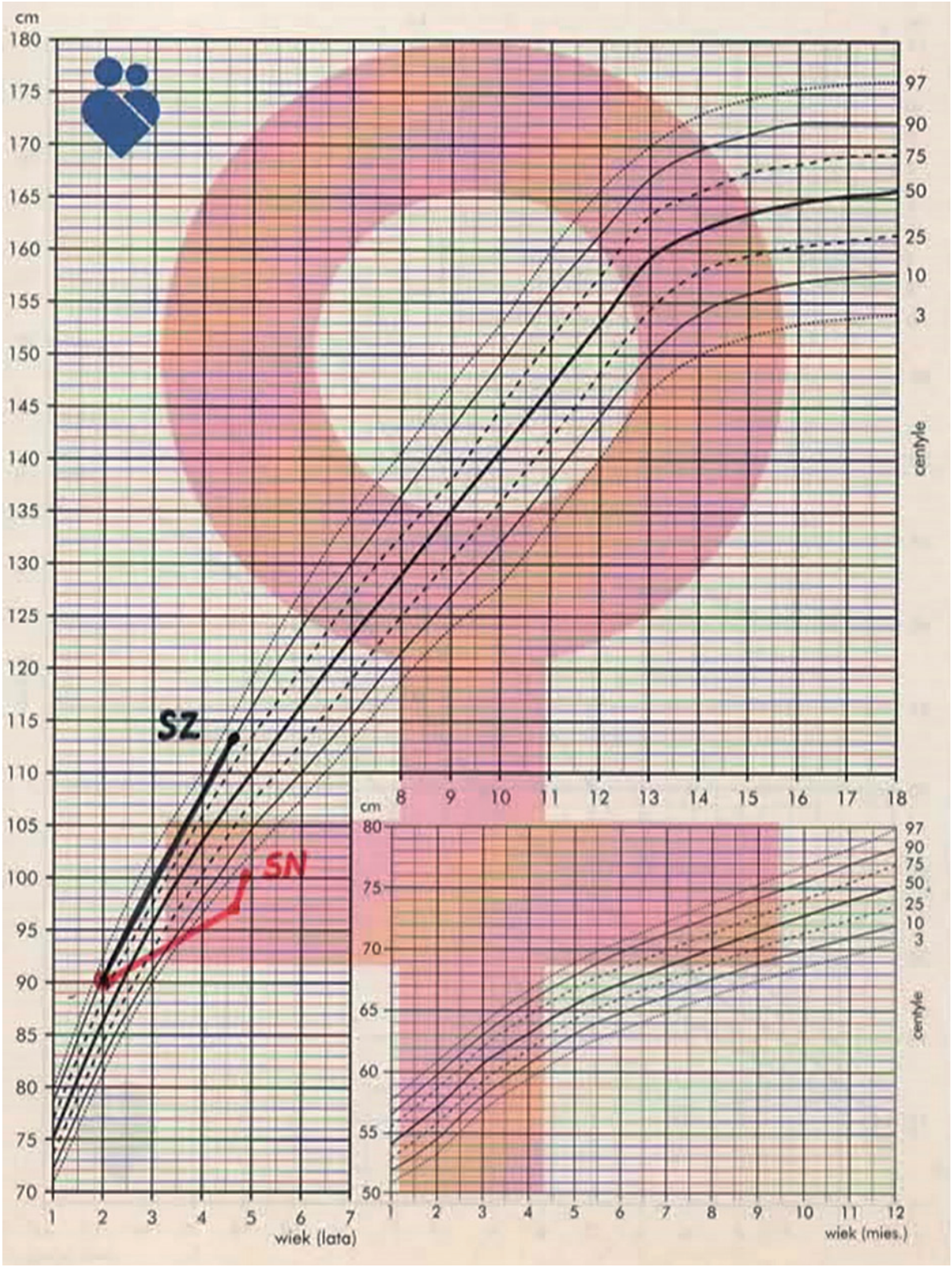

Figure 1. Growth chart of both girls – sister SN and sister SZ – showing discrepancies in their development

Table I. Laboratory tests results of patient SN at diagnosis and during treatment with L-thyroxine

Group	Baseline	5 days	8 days	3 weeks	6 weeks	3 months	Normal range
TSH [μIU/ml]	above[1] 100.000	–	above[1] 100.000	23.1	39.378	2.144	0.6–4.84
FT4 [ng/dl]	below[2] 0.40	0.48	0.53	1.16	0.97	1.03	0.96–1.77
FT3 [pg/ml]	below[2] 1.00	1.57	2.06	3.34	3.34	3.37	2.41–5.5
aTPO [IU/ml]	above[1] 1000.00	–	–	–	–	–	0–5.61
aTG [IU/ml]	97.9	–	–	–	–	–	0–4.11
Cortisol [ng/ml]	62	84	–	–	–	–	37–194
ACTH [pg/ml]	23.2	–	–	–	–	–	10.0–60.0

[1]above the range of method sensitivity; [2] below the range of method sensitivity
TSH – thyroid stimulating hormone; FT4 – free thyroxine; FT3 – free triiodothyronine; aTPO – anti-thyroperoxidase antibodies; aTG – anti-thyroglobulin antibodies; ACTH – adrenocorticotropin

Table II. Blood count of sister SN before and during substitution therapy with L-thyroxin

Group	WBC [$10^3/\mu l$]	RBC [$10^6/\mu l$]	HGB [g/dl]	MCV [fl]	MCH [pg]	PLT [$10^3/\mu l$]
at diagnosis	6.54	3.11	9.9	89.4	31.8	314
after 5 days	8.35	3.00	9.4	92.0	31.3	371
after 3 months	5.79	4.06	8.6	67.5	21.2	508

WBC – white blood cells; RBC – red blood cells; HGB – hemoglobin; MCV – mean corpuscular volume; MCH – mean corpuscular hemoglobin; PLT – blood platelets

thyroiditis, are classified as autoimmune disorders, and both diseases occur in people with genetic predisposition. When a patient with severe autoimmune hypothyroidism is due to start treatment with thyroid hormones, it is essential to be assured, that this is not the case of the autoimmune polyglandular syndrome (APS) – type 1 (skin and mucosal candidiasis, hypoparathyroidism, adrenal insufficiency and other autoimmune diseases) or type 2 (autoimmune thyroid disease, adrenal insufficiency, type 1 diabetes, other autoimmune diseases) [6–10]. This is particularly important in case of coexisting adrenal insufficiency, when alignment of thyroid hormone deficiency may lead to adrenal crisis and sudden death. In such cases, adrenal failure is masked by the metabolic slowdown caused by hypothyroidism. This necessitates the exclusion of adrenal insufficiency at the time of initiation of substitution therapy with L-thyroxine.

In patient SN, initiation of L-thyroxine therapy resulted in an immediate response that increased the growth velocity by more than 2.2 times. This growth rate was over-physiological and resulted from the catch-up mechanism – a mechanism specific for the treatment of recombinant growth hormone, mainly in patients with GH deficiency. As can be seen in the presented case, the phenomenon of catch-up growth may also affect patients with other pathologies that significantly affect metabolic processes. The more so, presented by one of the sisters catch-up effect is highly pronounced. At the moment it is difficult to determine how long this phenomenon will continue and to what extent the growth backlog will be reduced. The severity of metabolic changes occurring under the influence of treatment, resulted in the rapid consumption of the body resources, which manifested as a drop in iron concentration, despite its supply. However, it is important to remember that chronic iron deficiency anemia is one of the celiac disease's symptoms. This anemia is usually resistant to oral iron supplementation and is usually reversible during gluten-free diet [7, 11]. Hence,

the patient blood count and iron concentrations have not improved with iron oral supplementation, until a strict gluten-free diet was introduced. It is likely that a similar phenomenon also apply to other micro- and macronutrients, or vitamins involved in the processes of growth. Therefore, in such cases, it is important to consider the need for simultaneous nutritional restoration with the supply of additional energy substrates. In the future, it is worth investigating whether such additional actions will have a positive impact on extending the catch-up growth and improving the potential final height.

Conclusions

We report an extremely rare case of severe hypothyroidism in one of the twin sisters, undiagnosed for about two years. It shows the extent to which this disease affects growth of a child in comparison to the healthy twin. Also, in this case, autoimmune hypothyroidism and growth deficiency were accompanied by celiac disease. Unfavorable coincidence of these diseases has caused not only the depletion of the body's resources, but also hindered the possibility of quick supplementation of the deficiencies. Despite the short observation time, obtained growth velocity indicates the dominant role of thyroid hormones over celiac malabsorption in the process of growth, as the catch-up effect started before gluten free diet was introduced.

We do not know whether the treatment applied will allow the complete catch-up growth, or weather some part of growth deficit will remain permanent. Nature has created an intriguing situation of severe hypothyroidism in one of the twin sisters, who have been developing similarly before the disease occurred. This is a perfect opportunity to carry out such an assessment.

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