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Assessment of the function and morphology of the thyroid gland in paediatric patients treated with enzyme replacement therapy due to selected storage diseases – preliminary results of our own research and a review of the literature

Ocena funkcji i morfologii tarczycy u dzieci leczonych enzymatyczną terapią zastępczą z powodu wybranych chorób spichrzeniowych – wstępne wyniki badań własnych i przegląd piśmiennictwa

[1, 2]Aleksandra Furtak, [1, 2]Anna Wędrychowicz, [2]Dorota Roztoczyńska, [1, 2]Dominika Januś, [3]Karolina Orchel-Szastak, [3, 4]Przemko Kwinta, [1, 2]Jerzy B. Starzyk

[1]Department of Pediatric and Adolescent Endocrinology, Chair of Pediatrics, Pediatric Institute, Medical College, Jagiellonian University in Cracow, Poland
[2]Department of Pediatric and Adolescent Endocrinology, University Children's Hospital in Cracow, Poland
[3]Department of Pediatric, University Children's Hospital in Cracow, Poland
[4]Department of Pediatric, Chair of Pediatrics, Pediatric Institute, Medical College, Jagiellonian University in Cracow, Poland

Abstract

Introduction: Some storage diseases, caused by a deficiency of a specific enzyme, which results in the systemic accumulation of non-metabolized substances, can be treated with enzyme replacement therapy (ERT), which can protect many organs, including the endocrine system.

The aim of the study was to assess the function and morphology of the thyroid gland in children with storage diseases treated with ERT, and to review the literature.

Material and methods: Eight patients were included in the study: 3 with Fabry disease (age: 17; 9.9; 10 years), 3 with Hunter's disease (12.3; 4.1; 9,3), and 2 with Pompe disease (6.8; 9,5). Thyroid function and morphology were assessed in each patient during ERT, and 4 of them were reassessed 27 months later.

Results: One patient with Fabry disease had been treated for hypothyroidism due to autoimmune thyroiditis diagnosed before the study. The remaining patients had normal thyroid tests and negative anti-thyroid antibodies at first and second evaluation; however, in all reassessed patients a decrease in TSH value was noted.

Among the remaining patients with Fabry disease, one had normal and a second had heterogeneous echogenicity of the thyroid during first assessment. In the second patient, normalisation of echogenicity was observed at reassessment.

Both patients with Pompe disease assessed once had slightly heterogeneous thyroid echogenicity.

In 3 patients with Hunter's disease in the first ultrasound examination, no abnormalities were found. In re-evaluation, 2 of them showed heterogeneous thyroid echogenicity.

Conclusions: We conclude that patients with storage diseases should undergo assessment of thyroid function and morphology before and during ERT.

Key words:
storage diseases, enzyme replacement therapy, thyroid.

Streszczenie

Wprowadzenie: Niektóre z chorób spichrzeniowych, spowodowanych niedoborem określonych enzymów, prowadzących do nieprawidłowego metabolizowania substratów i wtórnego gromadzenia się ich w wielu tkankach, można leczyć za pomocą enzymatycznej terapii zastępczej (ETZ), która chroni przed dysfunkcją narządów, również endokrynnych.

Cel pracy: Celem pracy była ocena funkcji i morfologii gruczołu tarczowego u dzieci z chorobami spichrzeniowymi leczonych ETZ oraz przegląd piśmiennictwa.

Materiał i metody: Badaniami objęto ośmiu pacjentów: trzech pacjentów z chorobą Fabry'ego (w wieku 17; 9,9; 10 lat), trzech z chorobą Huntera (12,3; 4,1; 9,9), dwóch z chorobą Pompego (6,8; 9,5). U każdego pacjenta oceniono czynność i morfologię tarczycy w trakcie ETZ, ponadto u czterech z nich dokonano reoceny po 27 miesiącach.

Anna Wędrychowicz
Department of Pediatric and Adolescent Endocrinology
University Children's Hospital
Wielicka 265,
30-663, Cracow, Poland
e-mail: anna.wedrychowicz@uj.edu.pl

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Wyniki: Jeden pacjent z chorobą Fabry'ego był leczony z powodu niedoczynności tarczycy w przebiegu autoimmunizacyjnej choroby tarczycy zdiagnozowanej przed badaniem. U wszystkich pozostałych stwierdzono prawidłowe wyniki hormonów osi tarczycowej i ujemne przeciwciała przeciwtarczycowe, jakkolwiek u wszystkich ponownie ocenianych obserwowano obniżenie poziomu TSH.
U kolejnego pacjenta z chorobą Fabry'ego w badaniu ultrasonograficznym stwierdzono niejednorodność miąższu gruczołu, z jego normalizacją po 27 miesiącach. U trzeciego z nich echogeniczność tarczycy była prawidłowa w pojedynczym badaniu USG.
U obu pacjentów z chorobą Pompego uwidoczniono niejednorodną echogeniczność miąższu tarczycy ze współwystępowaniem pojedynczych torbieli koloidalnych.
U trzech pacjentów z chorobą Huntera w pierwszym badaniu USG nie stwierdzano żadnych nieprawidłowości, po 27 miesiącach u dwóch z nich stwierdzono niejednorodną echogeniczność miąższu tarczycy.
Wnioski: Pacjenci z rzadkimi chorobami spichrzeniowymi powinni mieć ocenianą funkcję i morfologię tarczycy zarówno przed, jak i w trakcie ETZ.
Słowa kluczowe:
tarczyca, choroby spichrzeniowe, enzymatyczna terapia zastępcza.

Introduction

Storage diseases are genetically determined disorders caused by a deficiency of a specific enzyme and the related systemic accumulation of non-metabolized substances [1]. Today, many conditions can be treated causally using enzyme replacement therapy (ERT). ERT was first developed for Gaucher disease in the 1990s. ERT for mucopolysaccharidoses (MPSs) were developed from the beginning of the 2000s: MPS type I (2003), type VI (2005), type II (2006), type IVA (2014), and type VII (2017) [3]. ERT in Fabry disease was first used in 2001; it includes 2 forms ERT. First specific treatment of Pompe disease with ERT was in 2006. Although the target therapy of these diseases was introduced in the last 2 decades, there are some published data about the impact of ERT on the dysfunction of almost all organs and systems [2]. However, the function and morphology of endocrine glands, including the thyroid gland in storage diseases, and the influence of ERT on their function has not been thoroughly investigated. Given the high degree of vascularisation and the low proliferation index of endocrine glands, they appear to be prone to an accumulation of non-metabolized substances that can disrupt their function or morphology.

Aim of the study

The aim of the study is to provide a pilot study assessing the function and morphology of the thyroid gland in paediatric patients treated with ERT due to rare metabolic/storage/lysosomal diseases, and to present the current review of the literature regarding this issue.

Material and methods

Eight patients with metabolic diseases treated with ERT, and under the constant care of the Department of Paediatrics, were included in the study. Three patients with Fabry disease, 3 patients with Hunter's disease, and 2 patients with Pompe disease. Seven patients did not have any known thyroid disorders according to their medical history, and one patient (no. 2) had autoimmune thyroid disease recognized before Fabry disease. Thyroid function and morphology were assessed for each patient during ERT, and 3 patients with Hunter's disease and one with Fabry disease were reassessed after 27 months of therapy. Detailed clinical characteristics of the patients are presented in Table I.

The Local Ethics Committee approved the study (opinion no. 1072.6120.57.2019 of 28 March 2019). All parents of patients and all participants over 16 years old gave their written informed consent.

Each patient included to the study had thyroid function and morphology assessed. Four of eight patients (all with Hunter disease and one with Fabry disease) had thyroid function assessed twice, with about 27 months' interval. Thyroid gland function was assessed by measuring serum levels of TSH (thyrotropin hormone), fT3 (triiodothyronine), fT4 (thyroxine), ATPO (thyroid peroxidase antibodies), TRAb (anti-TSH receptor antibodies), and aTG (anti-thyroglobulin antibodies). TSH, fT3, and fT4 parameters were determined using direct chemiluminescence kits from Siemens (USA). ATPO, aTG, and TRAb parameters were determined using an immunochemical method with isotope label sets from Brahms (Germany). The following reference values were used: TSH 0.3–4.0 μIU/ml; fT3 3.0–8.1 pmol/l; fT4 10.0–25.0 pmol/l; ATPO $<$ 60.0 IU/ml; TRAb $<$ 1.0 IU/ml; aTG $<$ 60 U/ml.

Each patient included in the study had an ultrasound examination of the thyroid gland using a Samsung HS40 with a 3–16 linear transducer. All patients were examined in the supine position with hyperextended neck, using a high-frequency linear-array transducer. All patients were examined by the same researcher, and in doubtful cases this was followed by verification from another researcher – a specialist doctor. Scanning was done both in transverse and longitudinal planes. Real-time imaging of thyroid lesions was performed using both grey-scale and colour Doppler techniques. Thyroid gland ultrasound examination included measurements of both thyroid lobes in 3 dimensions and thickness of the thyroid isthmus. In addition, echogenicity of the thyroid parenchyma, vascularisation of the gland, and the presence of focal lesions were assessed. Echogenicity of the thyroid gland was assessed by comparing and assessing the relationships with surrounding structures: the sternocleidomastoid and strap muscles anteriorly; trachea, oesophagus, and longus colli muscles posteriorly; and common carotid arteries and jugular veins bilaterally. A significant reduction of thyroid

Table I. Clinical characteristics of patients with storage disorders included in the study

Patient	Sex (1 girl; 2 boys)	Age (years)	Weight (kg)	Height (cm)	Weight to height (%)	Disorder	Duration of disease (months from diagnosis)	Therapy	Duration of therapy (months)	Others
1	2	17	41	155.5	(–) 9	Fabry	21	FABRAZYME	7	Somatotropin insufficiency (rhGH therapy from 13 to 15 years old and from 16 years to now)
1*	2	19	65	172.5	(+) 6	Fabry	48	FABRAZYME	33	Somatotropin insufficiency (rhGH therapy from 13 to 15 years old and from 16 years to now)
2	2	9.9	30	140	(–) 12	Fabry	22	FABRAZYME	20	AITD, L-thyroxine substitution
3	2	10	31	136	(–) 2	Fabry	39	FABRAZYME	6	FAS
4	1	6.8	21	110	(+) 10	Pompe	84	MYOZYME	81	Hearing loss, developmental delay, decreased muscle tone and strength
5	2	9.5	25	133	(–) 11	Pompe	26	MYOZYME	25	
6	2	12.3	32	138	(+) 2	Hunter	148	ELAPRASE	146	Allergy
6*	2	14.5	59	164	(+) 18	Hunter	175	ELAPRASE	173	Allergy
7	2	4.1	30	125	(+) 20	Hunter	46	ELAPRASE	43	Hydrocephalus; ventriculoperitoneal valve
7*	2	6.2	45	146	(+) 18	Hunter	73	ELAPRASE	70	Hydrocephalus; ventriculoperitoneal valve; epilepsy
8	2	9.3	35	136.5	(+) 12	Hunter	84	ELAPRASE	79	Allergy
8*	2	11.5	43	146	(+) 13	Hunter	107	ELAPRASE	102	Allergy

*reassessment after about 27 months
AITD – autoimmune thyroid diseases; FAS – foetal alcohol syndrome

echogenicity was understood as a hypoechoic pattern of thyroid gland in comparison to submandibular gland and to neck muscles. A slight reduction in thyroid echogenicity was understood as hypoechoic thyroid parenchymal pattern in comparison to the submandibular gland, and hyperechoic in comparison to neck muscles.

Results

Eight patients with storage disease were included in the study, as well as 3 patients with Fabry disease, 3 patients with Hunter's disease, and 2 patients with Pompe disease.

Detailed characteristics of the assessed thyroid function and morphology are presented in Tables II and III.

Among the patients with Fabry disease, one (no. 2) was treated for hypothyroidism in the course of autoimmune thyroid disease (AITD) diagnosed 4 years before Fabry disease was recognized; he had normal thyroid axis hormone results (during L-thyroxine substitution, 50 ug per day) and positive anti-thyroid antibodies. Ultrasound revealed heterogeneous echogenicity and lymph node in the isthmus. This patient is under endocrinological care, and according to data from his doctor, he recently required a reduction of the substitution dose of L-thyroxine (from 62.5 μg to 50 μg per day). Among the remaining 2 patients with Fabry disease, one patient (no. 3) had normal thyroid axis hormone results, negative anti-thyroid antibodies, and normal ultrasound image on a single assessment; the other patient (no. 1) had normal thyroid axis hormone results and negative anti-thyroid antibodies on the first assessment and after 27 months. But we found decrease in TSH concentration (from 2,8 to 2,36 uIU/ml). Ultrasound revealed a slightly heterogeneous echogenicity of the thyroid gland parenchyma with the coexistence of single colloid cysts on the first assessment (after 7 months of therapy), but after the next 27 months the echogenicity of the thyroid was normal (after 34 months of therapy). This patient was the oldest in the group. The diagnosis of the disease was made late, and the time between diagnosis and ERT was long (14 months).

Two patients with Pompe disease (no. 4, 5) were assessed only once and had normal thyroid tests and negative anti-thyroid antibodies. Ultrasound revealed a slightly heterogeneous echogenicity of the thyroid gland parenchyma with coexistence of single colloid cysts and the presence of a lymph node in the isthmus in one (no. 5) of the two patients.

Three patients with Hunter's disease (no. 6, 7, 8) had normal thyroid tests and negative anti-thyroid antibodies at first evaluation and 27 months later. But in all 3 patients, we found a decrease in TSH concentration by an average of 0.4 μIU/ml (from 0.34 to 0.52). In the first ultrasound examination, no abnormalities were found in these patients; after 27 months, 2 of them (no. 6, 8) showed slightly heterogeneous echogenicity of the thyroid parenchyma (one – no. 7 – was not reassessed).

Table II. The results of the parameters assessing the function of the thyroid gland in patients with different storage diseases (Patient 1–3 with Fabry disease, Patient 4–5 with Pompe disease, Patients 6–8 with Hunter's syndrome)

Patient	TSH (uIU/ml) N: 0.3–4.0	FT3 (pmol/l) N: 3.0–8.1	FT4 (pmol/l) N:10.0–25.0	ATPO (IU/ml) N: < 60.0	aTG (U/ml) N: < 60	TRAb (IU/ml) N: < 1.0
1	2.8	6	13.8	< 30	< 20	< 0.3
1*	2.36	5.7	14.5	< 30	< 20	
2	1.766	6.8	21.1	521	106	
3	2.4	7.1	13	< 30	< 20	
4	3.53	6.8	16.2	< 30	< 20	0.4
5	1.07	6.5	15.9	< 30	< 20	
6	1.44	6	13	< 30	< 20	< 0.3
6*	0.922	6.5	13.2	< 30	< 20	
7	2.83	7.3	12.7	< 30	< 20	< 0.3
7*	2.47	6.2	11.3	< 30	< 20	0.7
8	2.18	5.2	15.4	< 30	< 20	< 0.3
8*	1.84	5.7	13.2	< 30	< 20	

* reassessment after about 27 months

Table III. Results of ultrasound examination of the thyroid gland in patients with different storage diseases (Patients 1–3 with Fabry disease, Patients 4–5 with Pompe disease, Patients 6–8 with Hunter' s syndrome)

Patient	Right lobe (mm)	Left lobe (mm)	Isthmus (mm)	Volume (ml)	Echogenicity	Vascularization	Focal changes
1	15.2 × 15 × 36.7	17 × 13.4 × 40.3	2.3	8.77	Heterogeneous	Normal	Colloid cysts – left lobe
1*	16 × 18 × 52	16 × 18 × 48	2.2	14.4	Normal	Normal	No
2	9.4 × 11.2 × 32	9.9 × 10.3 × 33.3	1.36	3.38	Heterogeneous	Normal	Lymph node in the isthmus/ AITD like
3	10.5 × 11.6 × 37	10.2 × 9.5 × 32	1.5	3.8	Normal	Normal	No
4	13 × 12 × 34	12 × 15 × 37	1.9	5.98	Heterogeneous	Normal	Colloid cyst 7.8 × 2.8 mm – left lobe
5	9.5 × 9.4 × 33.7	9.8 × 9.6 × 26.2	1.9	2.73	Heterogeneous	Normal	Lymph node in isthmus
6	15 × 12 × 31	13 × 10 × 32	2	4.87	Normal	Normal	No
6*	16 × 16.5 × 42	16 × 18 × 40	1.6	11.3	Heterogeneous	Normal	No
7	9 × 12 × 34	10 × 13 × 35	1.5	4.11	Normal	Normal	No
8	17 × 12 × 36	17 × 12 × 36	1.9	7.34	Normal	Normal	No
8*	18 × 13 × 38	18 × 15 × 38	1.9	9.57	Heterogeneous	Normal	No

* reassessment after about 27 months

Review and discussion

Storage diseases are a heterogeneous group of diseases; therefore, a probable, different effect on the function and morphology of the thyroid gland should be expected. Our group included patients with various diseases, representing the most common storage diseases that are treated with ERT. Currently in Poland there is a possibility of ERT in patients with MPS type I, type II, and type VI and in those with Pompe, Fabry, and Gaucher disease. Treatment is reimbursed for patients with MPS type I (around 2016), type II and Pompe (around 2015), Fabry (2019), and Gaucher (1995) disease. Table IV reports basic information on the diseases, enzyme defects, and pharmacological and commercial names of the recombinant enzymes. Currently, 3 patients with MPS type II, 3 patients with Fabry disease, 2 patients with Gaucher disease. and 2 patients with Pompe disease remain under the care of the Department of Paediatrics.

Type II mucopolysaccharidosis (MPS II, Hunter's syndrome, Online Mendelian Inheritance in Man number (OMIM) 309900) is characterized by the absence or severe deficiency of the activity of iduronate 2-sulfatase (I2S), the enzyme catalysing the degradation of heparan sulphate and dermatan sulphate, resulting in the build-up of these GAGs (glycosaminoglycans) in lysosomes [4, 5]. Type II MPS is one of the most common mucopolysaccharidoses, with an incidence of 1 per 140,000–156,000 live births in Europe [5, 6]. Type II MPS is a progressive disease. Postnatal patients usually do not present any phenotypic features and symptoms of the disease. The first symptoms, usually non-specific, appear between 18 months and 4 years of age, depending on the severity of the disease [5, 7]. There are 2 main phenotypes in MPS type II: severe, including strongly expressed somatic symptoms with progressive neurodegeneration, and mild – with normal intelligence and survival to adulthood. Symptoms of MPS type II include organomegaly (enlargement of the liver and tongue), dysostosis multiplex changes in the skeletal system due to abnormal bone formation, and characteristic facial features (thickened facial features, prominent forehead). As a result of the disease, hearing and vision (corneal clouding, damage to the optic nerve) is often impaired. The respiratory and cardiovascular systems are also affected (defects of the heart valves, cardiomegaly, and cardiomyopathy), and as the disease progresses, joint mobility becomes restricted and numerous contractures appear, or

Table IV. Information of the metabolic/storage/lysosomal diseases, enzyme defects, and pharmacological and commercial names of the recombinant enzymes

Disease	Deficient enzyme	Recombinant enzyme	Brand name
MPS I	α-L-iduronidase	Laronidase	Aldurazyme
MPS II	Iduronate 2-Sulfatase	Idursulfase α Idursulfase β	Elaprase Hunterase
MPS IVA	Galactosamine-6-sulfatase	Elosulfase	Vimizim*
MPS VI	Arylsulfatase B	Galsulfase	Naglazyme
MPS VII	β-glucuronidase	Vestronidase	Mepsevii*
Pompe	α-glucosidase	α alglucosidase	Myozyme
Fabry	α-galactosidase A	Agalsidase α Agalsidase β	Replagal Fabrazyme
Gaucher	Glucocerebrosidase	Imiglucerase Velaglucerase	Cerezyme Vpriv

* not available in Poland

nerve entrapment occurs, such as in carpal tunnel syndrome [8, 9]. As demonstrated in autopsy examinations, the accumulation of glycosaminoglycans also affects the endocrine organs; their presence was found in pancreatic cells, adrenal cortex cells, Leydig cells, epithelial cells of thyroid follicles, and chromophobic cells of the pituitary gland [10, 11].

Therapy of MPS type II uses idursulfase, which is a purified form of the enzyme lysosomal iduronate 2-sulfatase (I2S), produced by recombinant DNA technology in a continuous human cell line. Intravenous ERT with idursulfase provides exogenous enzyme for selective uptake into cells via mannose-6-phosphate receptors on the cell surface. Upon internalisation, the enzyme is transferred and localised within lysosomes, where it catabolises accumulated GAGs [5]. The recombinant enzyme called Elaprase [Shire Human Genetic Therapies, Inc., Cambridge, MA, USA] was approved for use in Europe in January 2007 [12]. Intravenous ERT with idursulfase reaches most tissues and is effective in treating many somatic symptoms of the disease. Idursulfase does not cross the blood-brain barrier, making the treatment of neurological symptoms occurring in MPS type II ineffective [5]. The lack of penetration of the recombinant enzyme into the central nervous system may also affect the occurrence of symptoms of hypothalamic-pituitary insufficiency and, consequently, secondary or tertiary hypothyroidism, despite the use of ERT.

In the literature, there are generally no data about dysfunction of the thyroid gland in patients with MPS type II and the influence of ERT on the function and morphology of the thyroid gland. Single reports concern tertiary hypothyroidism accompanying growth hormone deficiency and secondary adrenal insufficiency in a patient with MRI ectopy of the posterior pituitary gland [13]. There is also one description of a patient with MPS type II and hyperthyroidism, but there was no correlation between the pathogenesis of hyperthyroidism and MPS type II [14].

In our study, 3 patients with MPS type II (no. 6, 7, 8) had normal thyroid tests and negative anti-thyroid antibodies at first evaluation and 27 months later. But in all 3 patients, we found a decrease in TSH concentration by an average of 0.4 μIU/ml (from 0.34 to 0.52) during the observation period. The fT3 and fT4 concentrations were comparable. In the first ultrasound examination, no abnormalities were found in these patients; after 27 months, 2 of them (no. 6, 8) showed slightly heterogeneous echogenicity of the thyroid parenchyma (one – no. 7 – was not reassessed) (Tables II, III).

The duration of disease and ERT therapy of these patients was significantly longer than for the rest of the patients (Table I). Based on our observations, it can be assumed that ERT has a supposed beneficial, protective effect on the function of the thyroid gland, but it does not necessarily protect against the accumulation of non-metabolized substances in the thyroid tissues. Attention is drawn to the reduction in TSH levels observed in all patients, which may suggest an improvement of thyroid function as well as the deterioration of pituitary function because of the lack of ERT penetration through the blood-brain barrier.

Fabry disease (OMIM 301500) is an X-linked inherited disorder of glycosphingolipid catabolism resulting from the deficiency or absence of the lysosomal enzyme alpha-galactosidase A (alpha-gal A) [15, 16]. The lack or deficiency of alpha-galactosidase A activity leads to progressive accumulation of globotriaosylceramide in the endothelium and tissue cells of various organs [15, 17]. Fabry disease is progressive, and the mean age of onset of symptoms is 6–8 years in men

and 9 years in women [15, 17]. The most common initial symptoms include chronic neuropathic pain, heat and cold intolerance, and fatigue. Over time, storage of globotriaosylceramide results in various symptoms such as angiokeratoma, tinnitus, hearing loss, dizziness, transient ischaemic attacks, strokes, cardiomyopathy, left ventricular hypertrophy, cardiac arrhythmias, gastrointestinal disorders, obstructive pulmonary disease, proteinuria, progressive kidney disease, panic attacks, depression, and adaptive disorders [15–17].

The treatment of Fabry disease uses agalsidase beta (Fabrazyme®; Genzyme Corporation, Cambridge, MA), which is a form of human alpha-galactosidase A produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell culture. The amino acid sequence of the recombinant form as well as the nucleotide sequence encoding it are identical to the natural form of alpha-galactosidase A.

There are several reports in the literature about the function and morphology of the thyroid gland in patients with Fabry disease. However, they only apply to adults. Hauser *et al.* assessed thyroid function in 11 patients (6 women, 5 men; mean age 45 ±11 years) with Fabry disease who did not receive ERT. In the study group, 4 patients (36.4%) had subclinical hypothyroidism (normal fT4 concentration and elevated serum TSH concentration), and the remaining 7 patients had normal thyroid function. None of the patients had ATPO, aTG, or TRAb antibodies. Ultrasound examination of the thyroid gland revealed no abnormalities, including features of autoimmune thyroiditis [16]. Katsuyoshi *et al.* in a 48-year-old patient with Fabry disease and primary hypothyroidism, showed a significant accumulation of ceramide trihexoside (CTH) and ceramide dihexoside (CDH) in the thyroid gland cells based on biopsy, and thin-layer chromatography of the lipid extract of the thyroid gland of this patient revealed excessive excretion of CTH and CDH [18]. Faggiano *et al.* assessed the function and morphology of the thyroid gland in 18 patients with Fabry disease (9 women and 9 men, age 21–64 years), including 10 patients receiving ERT. It showed a significantly higher baseline TSH concentration in Fabry disease patients compared to healthy controls (1.6 ±0.2 vs. 1.1 ± 0.1 mU/l; $p < 0.01$). Moreover, they showed that the mean increase in TSH concentration after TRH stimulation was lower in the Fabry disease group compared to the control group (395 ±59% vs. 624 ±73%; $p < 0.05$). The mean increase in TSH concentration after TRH stimulation was significantly correlated with the activity of alpha-galactosidase in the plasma. The mean concentration of fT3 and fT4 was similar in patients and controls. Antithyroid antibodies (ATPO, aTG) were positive in 3 Fabry patients (16.7%) and 2 controls (11.1%). Ultrasound examination revealed mild hypoechogenicity of the thyroid gland parenchyma in 12 patients with Fabry disease (66.7%) and 3 controls (16.7%; $p < 0.05$) [19]. A very interesting study was conducted by Faggiano *et al*. They assessed the function and morphology of the thyroid gland in 14 patients with Fabry disease (7 women, 7 men, aged 21-62 years) before and during 3 years of treatment with ERT. They showed that TSH levels were higher in patients before ERT than after (1.9 ±0.2 vs. 1.2 ±0.2 mU/l, $p < 0.01$). In addition, they indicated the hypoechogenicity of the thyroid gland parenchyma observed in ultrasound in 71% of patients before ERT compared to 43% after ERT. They ruled out autoimmune pathogenesis [20]. In conclusion, all available reports on the function and morphology of the thyroid gland in Fabry disease patients emphasize the higher incidence of subclinical hypothyroidism, the pathogenesis of which may depend on the accumulation of lipids inside the thyroid gland, compared to the general population. This phenomenon can be explained by the strong vascularization of the thyroid gland, which, combined with a low thyrocyte proliferation index, estimated at 6-7 lifetime mitoses, makes the thyroid gland highly susceptible to the concentration of non-metabolized substances [16–21]. The available studies show differences in the ultrasound images of the thyroid gland. According to the authors, who did not find any abnormalities in the ultrasound examination of the thyroid gland, their absence could have resulted from insufficient accumulation of glycosphingolipids in the thyroid gland to be detected by ultrasound [16]. However, most observations indicate a reduced and heterogeneous echogenicity of the thyroid gland parenchyma in patients with Fabry disease [19, 20].

Our study included 3 patients with Fabry (no. 1, 2, 3) disease treated with ERT. One (no. 2) was treated for hypothyroidism in the course of autoimmune thyroid disease (AITD) diagnosed 4 years before Fabry disease was recognized; he had normal thyroid axis hormone results (during L-thyroxine substitution, 50 μg per day) and positive anti-thyroid antibodies, and ultrasound revealed heterogeneous echogenicity and a lymph node in the isthmus. This patient is under constant endocrinologist care; according to the data from the main doctor, he recently required a reduction of the substitution dose of l-thyroxine (from 62.5 μg to 50 μg per day). Among the remaining 2 patients with Fabry disease, one patient (no. 3) had normal thyroid axis hormone results, negative anti-thyroid antibodies, and normal ultrasound image on a single assessment; the other patient (no. 1) had normal thyroid axis hormone results and negative anti-thyroid antibodies on the first assessment and after 27 months. However, we found a decrease in TSH concentration (from 2.8 to 2.36 uIU/ml) with a comparable concentration of fT4 (13.8 vs. 14.5). Interestingly, the concentration of TSH in our patient before the use of ERT was significantly higher than after 7 months of using ERT (4.08 vs. 2.8 uIU/ml), with a comparable concentration of fT4 (13.2 vs. 13.8 pmol/l). Ultrasound revealed a slightly heterogeneous echogenicity of the thyroid gland parenchyma with coexistence of single colloid cysts on the first assessment (after 7 months of therapy), but after the next 27 months the echogenicity of the thyroid was normal (after 34 months of therapy). This patient was the oldest in the group. The diagnosis of the disease was made late, and the time between diagnosis and ERT was long (14 months).

There are limited data available on the effect of therapy on thyroid function and morphology in patients with Fabry disease. The available results and our observations are consistent with a clear decrease in TSH concentration after ERT application, which may confirm the beneficial effect of ERT on thyroid function, as well as the beneficial effect of ERT on the ultrasound image of the thyroid gland, which is visible in the reduction of

its hypoechogenicity, as demonstrated by Faggiano *et al*. [20]. The observation of thyroid function and the beneficial effects of ERT seem to be significant for patients with Fabry disease also due to the negative impact of subclinical hypothyroidism on the patient's general condition and on the incidence of neuromuscular symptoms and cardiovascular risk [16].

Type II glycogenosis (GSD II, Pompe Disease, OMIM 232300) is a rare, progressive, and fatal metabolic myopathy caused by a deficiency of natural lysosomal hydrolase, acid alpha-glucosidase (GAA), which breaks down glycogen in lysosomes into glucose. As a result of the deficiency of this enzyme, glycogen accumulates in various tissues, especially in the heart, respiratory, and skeletal muscles, leading to the development of hypertrophic cardiomyopathy and progressive muscle weakness, including respiratory disorders [22]. Pompe disease can occur in what is known as the early form, which is rapidly progressive and has a very short life expectancy, or in a slower progressive late form. Early-onset Pompe disease is characterized by the accumulation of large amounts of glycogen in the myocardium and skeletal muscles, which always leads to the development of rapidly progressive cardiomyopathy, generalized muscle weakness, and hypotension. Usually, death from heart failure and/or respiratory failure occurs before the age of one year. The late-stage Pompe disease progresses much more slowly than the early-stage form. It is usually characterized by residual acid α-glucosidase activity preventing the development of cardiomyopathy. Patients with late-onset Pompe disease typically experience progressive myopathy, predominantly of the proximal pelvic girdle and shoulder girdle, and varying degrees of respiratory involvement, eventually leading to profound impairment and/or the need for respiratory support. An atypical form of Pompe disease has also been described, progressing more slowly than the early form. It is characterized by a lower severity of cardiomyopathy and, consequently, a longer survival period.

In the treatment of Pompe disease, alglucosidase alpha [Myozyme; Sanofi Genzyme, Cambridge, MA] is used. It is a copy of human acid alpha-glucosidase, produced by recombinant DNA technology with the use of Chinese hamster ovary (CHO) cells [22]. Due to the blood-brain barrier and the size of the enzyme molecule, penetration into the central nervous system is unlikely.

To our knowledge, data about the function and morphology of the thyroid gland in patients with Pompe disease are very limited. Hui *et al*. found the accumulation of glycogen in thyroid follicular cells derived from the dissection material of 2 infants with Pompe disease [23]. Schneider *et al*. found coexistence of hypothyroidism in 5 out of 10 patients with late-onset Pompe disease (the age at diagnosis of Pompe disease was 15 to 66 years) [24]. Schneider *et al*. also emphasize a very important aspect linking the incidence of hypothyroidism and Pompe disease. Glycogen accumulated in the lysosomes of thyroid follicular cells interferes with the proper functioning of the enzymes involved in the release of thyroxine and triiodothyronine from thyroglobulin [24]. From the point of view of patients' quality of life, reports on certain biochemical features common to hypothyroidism and Pompe disease are extremely important. Hurwitz *et al*. described a decreased activity of -glucosidase in myopathy accompanying hypothyroidism [25]. Spiro *et al*. described the accumulation of glycogen in the muscles of patients with hypothyroidism [26]. These data further underscore the importance of diagnosing and treating thyroid dysfunction in patients with Pompe disease.

Our study included 2 patients with Pompe disease (no. 4, 5) treated with ERT. They were assessed, and only one and had normal thyroid tests and negative anti-thyroid antibodies. Ultrasound revealed a slightly heterogeneous echogenicity of the thyroid gland parenchyma with coexistence of single colloid cysts and the presence of a lymph node in the isthmus in one (no. 5) of the two patients.

Heterogeneous echogenicity, and above all hypoechogenicity of the thyroid gland, usually unrelated to the presence of anti-thyroid antibodies, often occurs in obese children and adolescents. Radetti *et al*. conducted a study involving about 200 overweight and obese children and found that in 37.6% of them, ultrasound of the thyroid gland suggests Hashimoto's disease, with the simultaneous lack of anti-thyroid antibodies. In this group, TSH and BMI -SDS correlated significantly; moreover, the TSH concentration was correlated with the severity of abnormalities in the ultrasound examination of the thyroid gland [27]. In our study, we can rule out the influence of obesity on the ultrasound image of the thyroid gland. Patients who found heterogeneous echogenicity of the thyroid gland had correct body weight. Interestingly, obesity (20% excess body weight for height) occurred in one of our patients with a normal ultrasound image of the thyroid gland. The cause of changes in the ultrasound image of the thyroid gland in obese patients may be the presence of generalized inflammation caused by the increased concentration of pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 secreted by adipose tissue [28–31].

Conclusions

Based on a review of the literature and our preliminary results, the accumulation of non-metabolized substances in rare storage diseases undoubtedly also affects the endocrine glands, including the thyroid gland. This can lead to disturbances in the morphology and then the function of these glands and, consequently, deterioration of the patients' health. In our group, all patients (including the AITD patient) had normal levels of TSH, fT3, and fT4. Our attention was drawn to the reduction in TSH levels in patients with MPS II after 27 months of observation, which could be associated with an improvement of thyroid function as well as the deterioration of pituitary function. Therefore, the patients should be monitored for the purpose of diagnosing possible secondary hypothyroidism; due to the limitations resulting from the penetration of drug molecules into the central nervous system, ERT does not protect against the development of hypothalamic-pituitary disorders.

At the same time, we observed the appearance of heterogeneous echogenicity of the thyroid gland on ultrasound in 2 MPS II patients after 27 months. On the other hand, in a patient with Fabry disease, the ultrasound image of the thyroid gland normalized after 27 months of ERT.

The limiting factors of this work and its conclusions are certainly the small group of patients and the short follow-up time. Based on our preliminary results in a small group of children treated with ERT and on the review of the current literature, we conclude that patients with rare storage diseases should undergo endocrine function testing, both before and during ERT.

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