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Original Article *Özgün Araştırma*

ASSESSMENT OF THYROID FUNCTION AND ULTRASONOGRAPHIC FINDINGS IN PATIENTS WITH MUCOPOLYSACCHARIDOSIS

Mukopolisakkaridozlu Hastalarda Tiroid Bezinin Fonksiyonel ve Ultrasonografik Değerlendirmesi

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ABSTRACT

Objective: The thyroid gland, with its high vascularity and low proliferation index of thyrocytes, is highly susceptible to storage diseases, however it has not been evaluated adequately in patients with in mucopolysaccharidosis (MPS). Therefore, the aim of this study is to assess the function, morphology, B-mode, and Doppler ultrasonography features of the thyroid gland in pediatric and adolescent patients with MPS and to evaluate whether the thyroid gland is involved in this disease.

Material and Methods: Thyroid hormone functions were measured in all patients, and B-mode ultrasound and color Doppler imaging were performed.

Results: Eight boys and 17 girls with MPS were included in the study. Eight patients were diagnosed with MPS I, 2 with MPS II, 3 with MPS III, 3 with MPS IVA, and 9 with MPS VI. Nineteen patients were receiving enzyme replacement therapy, while three patients diagnosed with MPS III remained untreated due to the unavailability of treatment options. Thyroid hormone levels were within normal limits for all patients. B-Mode ultrasound imaging revealed slightly heterogeneous echo texture in only 2 (8%) patients, both with MPS VI. Except for one patient with MPS VI, all color Doppler assessments were within normal limits.

Conclusion: The results of our study demonstrate that both thyroid function tests and thyroid gland morphology are normal in MPS through childhood and adolescence. Therefore, we believe that thyroid gland dysfunction does not play a crucial role in the development of symptoms such as growth retardation, dry skin, coarse facial features, and intellectual disability, which could potentially be attributed to thyroid dysfunction. Instead, we think that these findings are more likely attributed to the primary disease involvement process.

Keywords:*Glycosaminoglycan, mucopolysaccharidosis, thyroid, thyroid functions, thyroid ultrasonography*

ÖZ

Amaç: Tiroid bezi yüksek vaskülarite ve düşük tirosit çoğalma indeksine sahip olduğundan depo hastalıklarına karşı oldukça duyarlıdır ancak mukopolisakkaridoz (MPS) hastalarında yeterince değerlendirilmemiştir. Bu nedenle çalışmamızın amacı MPS'li pediatrik ve adölesan hastalarda tiroid bezinin fonksiyon, morfoloji, B-mod ve Doppler ultrasonografi özelliklerini ve tiroid bezinin bu hastalıktaki etkilenimini değerlendirmektir.

Gereç ve Yöntemler: Tüm hastaların tiroid hormon fonksiyonları ve antikorları değerlendirildi ve B-mod ultrason ve renkli Doppler ultrasonografisi ile görüntüleme yapıldı.

Bulgular: Çalışmaya MPS'li 8 erkek ve 17 kız dahil edildi. Sekiz hastaya MPS I, 2'sine MPS II, 3'üne MPS III, 3'üne MPS IVA ve 9'una MPS VI tanısı ile takipliydi. On dokuz hasta enzim replasman tedavisi alırken, MPS III tanısı alan üç hasta tedavi seçeneklerinin mevcut olmaması nedeniyle tedavi edilmedi. Tüm hastaların tiroid hormon düzeyleri normal sınırlardaydı. B-Mode ultrason görüntülemede, her ikisi de MPS VI tanılı olan yalnızca 2 (%8) hastada hafif heterojen eko dokusunu saptandı. MPS VI tanısı ile izlenen bir hasta dışında tüm renkli Doppler değerlendirmeleri normal sınırlardaydı.

Sonuç: Çalışmamızın sonuçları MPS'de çocukluk ve ergenlik döneminde hem tiroid bezi fonksiyon testlerinin hem de tiroid bezi morfolojisinin normal olduğunu göstermektedir. Bu nedenle büyüme geriliği, cilt kuruluğu, kaba yüz hatları, zihinsel yetersizlik gibi potansiyel olarak tiroid fonksiyon bozukluğunda görülebilecek semptomların gelişiminde tiroid bezi fonksiyon bozukluğunun önemli bir rol oynamadığına inanıyoruz. Bunun yerine, bu bulguların daha çok birincil hastalık tutulum sürecine bağlı olduğunu düşünmekteyiz.

Anahtar Kelimeler: *Glikozaminoglikan, mukopolisakkaridoz, tiroid, tiroid fonksiyonları, tiroid ultrasonografisi*

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INTRODUCTION

Mucopolysaccharidoses (MPS) are lysosomal storage disorders resulting from a deficiency of hydrolase enzymes required for the stepwise breakdown of glycosaminoglycans (GAGs). GAGs are long and unbranched polysaccharides and have many functions in the body, including lubrication of joints, cell growth, regulation of proliferation and adhesion to cell surfaces in molecules. There are four groups of GAGs. These are heparin/heparan sulfate, chondroitin sulfate/dermatan sulfate, keratan sulfate, and hyaluronic acid. MPS could be classified into 8 types and 12 subtypes (MPS I, MPS II, MPS III, MPS IV, MPS VI, MPS VII, MPS IX, MPS X) according to enzyme deficiencies and the GAGs accumulated. The actual incidence of MPS is difficult to know because many cases may be misdiagnosed or go undiagnosed. It is estimated total incidence of all types of MPS of approximately 1 in 20,000-25,000 live births. Populations with a high consanguineous marriage rate may experience a significantly higher incidence. The accumulation of GAGs causes a heterogeneous multisystemic disease that may include dysostosis multiplex, coarse facial features, growth retardation, hepatosplenomegaly, hernia, cardiovascular disorders, corneal clouding, hearing loss, central nervous system impairment, behavioral abnormalities and pulmonary compromise (1-3). Urinary GAGs, enzymatic assays and molecular analysis are used for diagnosis. The aim of treatment is to slow the progression of the disease and improve the quality of life. The two main treatments for MPS are enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT). Unfortunately, there is no ERT for MPS III, MPS IX and MPS X yet. Additionally, medical or surgical treatment may be required depending on the organs involved. Knowledge of MPS pathophysiology has changed in recent years. For a long time, it was thought that GAGs accumulation only disrupts the cell hydration and structural scaffold. However, we are now aware that GAGs accumulation also causes impairment of autophagy, apoptosis, vesicular traffic, mitochondrial function, and calcium homeostasis, leading to oxidative stress and activation of inflammation (4).

Growth retardation and skeletal deformities are the most common clinical manifestations of MPS. Existing studies have predominantly focused on skeletal and cardiac involvement. It is revealed that there are also metabolic and endocrinology abnormalities such as metabolic syndrome, hyperlipidemia, growth hormone deficiency, precocious puberty, hypothyroidism and hyperthyroidism with a clearer understanding of the pathogenesis. Unfortunately, there are very few studies investigating endocrinologic involvement in this disease, despite reports of GAGs accumulation in the thyroid gland and ovaries. The thyroid gland, with its high vascularity and low proliferation index of thyrocytes, is highly susceptible to storage diseases, however it has not been evaluated adequately in patients with MPS (5). Therefore, we hypothesized that growth retardation, abnormalities of bone metabolism, and issues of cognitive development, which are prevalent in these patients, may be partially attributed to thyroid gland involvement. The aim of this study is to assess the function, morphology, B-mode, and Doppler ultrasonography features of the thyroid gland in pediatric and adolescent patients with MPS and to evaluate whether the thyroid gland is involved.

MATERIALS AND METHODS

Children diagnosed with MPS, who were followed up in the pediatric metabolic disease clinic of our institution, were enrolled in this study. The study was approved by the local Ethics Committee on March 16, 2023, with the approval number 2023/06-04. The diagnoses of MPS were established based on urinary GAGs, enzymatic assays and molecular analysis for all patients. Data on age at the onset of ERT, current age, gender and type of MPS were recorded. Prior to the ultrasound examination (USG), thyroid stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4) levels were measured in all patients. Anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) antibodies were also evaluated for autoimmune thyroiditis.

Evaluation of thyroid morphology using B-Mode Ultrasound and color Doppler Imaging

The examination involved B-mode and color Doppler imaging using a linear transducer probe (7.5–10 MHz) with a GE Logiq P9 medical system ultrasound machine (GE Healthcare, Chicago, IL, USA). To ensure consistency and minimize operator variability, all assessments were conducted by the same pediatric radiologist, maintaining uniform scanner settings (B-mode, Color gain, scale, PRF). This approach aimed to eliminate potential bias related to the clinical appearance of MPS. Thyroid gland imaging was performed with the patient in a supine position and the neck slightly extended. Both transverse and longitudinal planes were used for examination, and sonographic measurements of size encompassed transversal dimensions (width and depth) and longitudinal dimensions (length). The thyroid gland volume for each lobe was calculated using the ellipsoid formula, and the total thyroid volume was derived by summing the volumes of both lobes. Notable observations included echo texture (normal-brighter than surrounding muscles, hypoechoic-darker than surrounding muscles), homogeneity (homogeneous or heterogeneous), and the presence of septations, nodules, or any deviations from the typical appearance of the thyroid gland. On color Doppler, the vascularity of both

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lobes was evaluated using a visual scale as previously reported by Schulz et al (6). The average examination time for thyroid imaging was 5±1 minutes.

Statistical Analysis

The data were analyzed using the IBM SPSS 25 (IBM Inc., Armonk, NY, USA) program. Descriptive statistics (mean, standard deviation, median) were provided for numerical variables.

RESULTS

25 children (8 male and 17 female) from 19 families diagnosed with MPS were included in this study. Parental consanguinity was present in all the cases. The mean age was 8.2±4.2 years (range:2.4-15.9). Mean age at the beginning of ERT was 3.4-2.9 years (range:0.6-12.5) for patients receiving ERT. Eight patients were diagnosed with MPS I, two with MPS II, three with MPS III, three with MPS IVA and nine with MPS VI. 19 of them were receiving ERT. ERT was initiated one month prior to the study in three patients. Three cases diagnosed with MPS III remained untreated due to the unavailability of treatment options. TSH, FT3, FT4, anti-TG and anti-TPO antibodies were within normal limits in all the patients, and none of them were receiving any treatment for hypothyroidism and hyperthyroidism. B-Mode ultrasound imaging revealed slightly heterogeneous echo texture in only 2 (8%) patients, both with MPS VI. The abnormal sonographic patterns observed in two patients were independent of their current age, age at the beginning or duration of ERT, or thyroid hormone levels. The remaining patients exhibited normal imaging patterns in thyroid ultrasound. Total thyroid volume was 3.4±1.9 ml (range:1.2-8.4 ml). Except for one patient with MPS VI, all the patients' color Doppler assessments were within normal limits (color Doppler pattern 0). The patient with MPS VI's thyroid gland vascularization was slightly increased; consistent with color Doppler pattern 1. Patient characteristics, including demographic, clinical and radiological parameters, were presented in Table 1.

Table 1: Demographic, clinical and ultrasonographic features of patients

Patient number	Gender	MPS type	Age (years)	Age of treatment (years)	Thyroid gland volume	Standard deviation	Echogenicity	Vascularization
1	Female	I	9.4	1.5	2	-1.11	Normal	Normal
2	Female	I	11.2	1.4	2.78	-1.29	Normal	Normal
3	Male	I	3.2	3.2	1.4	-0.18	Normal	Normal
4	Male	I	3.2	3.2	1.45	-0.16	Normal	Normal
5	Female	I	10.8	6.2	3.61	-0.06	Normal	Normal
6	Male	I	2.4	1.5	1.2	0.18	Normal	Normal
7	Female	I	3.9	21	1.22	-0.51	Normal	Normal
8	Female	I	9.2	2.1	1.2	0.18	Normal	Normal
9	Male	II	9.4	1.5	6.54	1.97	Normal	Normal
10	Male	II	14.1	5.3	6.32	-0.40	Normal	Normal
11	Female	III	6.7	NTO	4.01	1.39	Normal	Normal
12	Male	III	4.0	NTO	1.34	-0.33	Normal	Normal
13	Female	III	3.1	NTO	3.1	2.30	Normal	Normal
14	Female	IVA	12.1	9.5	4.52	-0.18	Normal	Normal
15	Female	IVA	15.0	12.5	8.46	0.65	Normal	Normal
16	Female	IVA	2.8	2.1	1.4	0.75	Normal	Normal
17	Female	VI	12.9	3.8	2.66	-1.36	Normal	Normal
18	Female	VI	10.7	1.9	2.26	-0.99	Normal	Normal
19	Male	VI	6.3	0.6	1.9	-0.71	Normal	Normal
20	Female	VI	15.9	4.4	5.74	-0.69	Slightly heterogenous	Normal
21	Female	VI	9.8	3.1	3.7	0.07	Slightly heterogenous	Normal
22	Male	VI	3.3	0.8	3.5	1.99	Normal	Normal
23	Female	VI	4.9	4.9	1.72	0.24	Normal	Normal
24	Female	VI	9.7	0.6	5.87	1.50	Normal	Normal
25	Female	VI	10.8	4	3.82	0.09	Normal	Slightly increased

NTO: No treatment options

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DISCUSSION

The presence of GAGs accumulation in the thyroid gland has been highlighted in pathological series of cases with MPS (7,8). However, in our study, we only observed slight heterogeneity in the thyroid gland parenchyma on B-Mode ultrasound in two (patients 20 and 21), and mild vascularization increase in one patient (patient 25). Although hypothyroidism is seldom observed in the clinical follow-up of MPS, our study was designed under the assumption that confirmed pathological accumulation could potentially influence sonographic evaluations. Indeed, in cystinosis, which is another lysosomal disease, it has been mentioned that there are echo texture changes in thyroid ultrasound examination, and the thyroid gland elastography values differ from normal individuals (9). Also, in other studies on Fabry disease which is a more common lysosomal disease than cystinosis, the thyroid gland was found to appear more hypoechoic and subclinical hypothyroidism is frequently observed (10,11). The ultrasonographic changes and involvement of thyroid tissue in storage diseases are often attributed to the low mitotic activity of thyroid cells, as thyrocytes typically divide only about 6 to 7 times throughout their life cycle and the high vascularity of the organ (12). Therefore, it is expected that thyrocytes are more susceptible to storage. However, our study did not confirm our preliminary hypothesis. On the contrary, based on the data we obtained, it is conceivable to propose that GAGs accumulation in the thyroid gland in MPS does not manifest in sonographic findings or laboratory results of thyroid functions and does not lead to clinically significant changes, at least during childhood and adolescence. Hence, symptoms like growth retardation, coarse facial appearance, fatigue, weakness, insulin resistance and decreased mental capacity, which are more prevalent in individuals with MPS compared to the general population, are likely connected to factors other than thyroid dysfunction. This is reinforced by the observation that thyroid function tests were within the normal range in all our cases. There are only few studies with limited number of patients addressing this issue in the literature. Furtak et al. evaluated thyroid function and morphology in lysosomal storage diseases. The study included only 3 patients with MPS, and it was mentioned that the thyroid gland showed mild heterogeneity in two patients with MPS II who were receiving ERT. This result was assumed to be related to the longer duration of ERT treatment in these cases (13). Although some of our cases have been receiving ERT for a longer period than the mentioned study, except for two cases, all other cases had normal thyroid echogenicity. In the same study, Furtak et al. reported a minimal decrease in TSH values in the control laboratory tests of these cases, suggesting that this could be related to treatment response or secondary hypopituitarism (13). However, we believe that the data is insufficient to link this decrease in TSH with improvement in functions, as both FT4 and FT3 were normal both before and after treatment. Additionally, attributing the improvement in thyroid functions to explain parenchymal heterogeneity in the thyroid gland is not plausible. This is because parenchymal heterogeneity is linked directly to the inflammation of the thyroid gland, and a reduction in the accumulation of non-metabolized GAGs is more likely to lead to a decrease in inflammation and result in a homogenous appearance of thyroid tissue.

Normal thyroid function and normal findings in ultrasonographic evaluation in the vast majority of patients might also be associated with beneficial and preventive function of ERT. On the contrary, Polgreen et al. reported a higher rate (27%) of clinical and subclinical hypothyroidism in patients with MPS I who underwent hematopoietic stem cell transplantation (14). However, they refrained from making interpretations on whether this situation was related to the total body irradiation applied before hematopoietic stem cell transplantation or the nature of the disease. Considering that thyroid functions were normal in our patients, both those receiving and not receiving ERT (3 cases), we can assume that the findings of Polgreen et al. may be attributed to the total body irradiation, rather than the nature of the disease.

Another reason for our finding of relatively normal thyroid function and morphology could be associated with the lysosome count in thyroid cells. The accumulation of GAGs frequently occurs in cells of the reticuloendothelial system, which typically have a high lysosome count. Therefore, the lack of an impact on the function and morphology of the thyroid gland, which led to the invalidation of our hypothesis, might be attributed to lysosome count.

Autoantibody and autoimmune diseases due to pro-inflammatory cytokine release have been reported in Gaucher and Fabry disease (15). However, there is no study about antibody and autoimmune disease in the literature on MPS. In our study, thyroid autoantibodies were negative.

It is essential to note that our study represents the most comprehensive evaluation of thyroid gland morphology in patients with MPS. The most important limitation of our study is the relatively low number of patients. MPS are a group of complex diseases, and it is possible to consider each subtype as a distinct entity. However, given that MPS belongs to the rare disease group, we believe that this limitation can be somewhat overlooked. Another important limitation is the absence of a prospective design and the recording of findings in cases at a single time point. Certainly, a long-term and

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prospective study could contribute to the evaluation of thyroid functions in later ages. The third limitation is that the images were evaluated by a single radiologist. While a single radiologist evaluated the sonographic findings for all cases, the inability of the evaluating radiologist to be blinded to this condition due to the phenotypic appearance of the disease could potentially introduce bias. However, obtaining results opposite to the initial hypothesis suggests that bias may not have played a significant role. The fourth limitation of the study is the lack of obtained thyrotropin-releasing hormone values. Even though it may not be essential for the main objective, given the scarcity of studies on this topic, it could have provided useful insights into the evaluation of secondary hypothyroidism in these patients.

Mucopolysaccharidosis is a complex disease that requires a continuous and multidisciplinary approach for management. The results of our study demonstrate that both thyroid function tests and thyroid gland morphology are normal in MPS through childhood and adolescence. Therefore, we believe that thyroid gland dysfunction does not play a crucial role in the development of symptoms such as growth retardation, dry skin, coarse facial features and intellectual disability, which could potentially be attributed to thyroid dysfunction. Instead, we think that these findings are more likely attributed to the primary disease involvement process. However long-term studies with more patients are needed.

Conflict of Interest: The authors have indicated no conflicts of interest regarding the content of this article.

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