

# Morphea and antithyroid antibodies

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## Abstract

**Introduction:** Morphea, also known as localized scleroderma, is an autoimmune skin disease which is characterized by excessive accumulation of collagen that leads to the thickening of the dermis and subcutaneous tissue. There is an unclear relationship between morphea and other autoimmune diseases, especially related to the thyroid gland.

**Aim:** To determine the occurrence of increased antithyroid antibodies in patients with morphea in relation to the clinical manifestations of the disease.

**Material and methods:** Forty-two Caucasian patients with different forms of morphea were included into the study. To determine the thyroid status, thyrotropin (TSH), anti-peroxidase antibodies (TPO-Ab), anti-thyroglobulin antibodies (Tg-Ab) were evaluated with the use of the electrochemiluminescence method and TSH receptor autoantibodies (TRAb) – with the use of the radioimmunoassay method.

**Results:** Increased levels of antithyroid antibodies were observed in 6 cases in relation to TPO-Ab (14.3%), in 4 cases in relation to Tg-Ab (9.5%) and in 1 patient in relation to TRAb (2.3%). There was no difference in the level of antithyroid antibodies between circumscribed and generalized forms of morphea.

**Conclusions:** Although morphea is an autoimmune disease, it does not seem to be associated with increased prevalence of positive antithyroid antibodies. We conclude that there is no need to perform routine laboratory tests for thyroid disorders in patients with morphea.

**Key words:** morphea, anti-peroxidase antibodies, localized scleroderma, antithyroid antibodies.

## Introduction

Morphea, also known as localized scleroderma, is characterized by excessive accumulation of collagen that leads to the thickening of the dermis and subcutaneous tissue. The clinical picture of the disease depends on the duration of the pathologic process. In early stages of the disease, typically indurated plaques surrounded by the erythematous rings (known as lilac rings) are observed, while in the late phase of the disease, hyperpigmented atrophic patches become usually evident [1]. The etiopathogenesis of this disease remains poorly understood [2, 3]. Morphea is classified as an autoimmune disorder, which affects the skin, but the main antigen has not been still recognized [1–4]. It is well known that the presence of one autoimmune disorder can be associated with a higher risk of other disorders, what was called by Szyper-Kravitz *et al.* as “mosaic of autoimmunity” [5].

In the literature it is emphasized that morphea coexists with other autoimmune disorders like vitiligo, primary biliary cirrhosis, autoimmune hepatitis, systemic lupus erythematosus, diabetes mellitus type I and myasthenia gravis [6–15]. The association of morphea with the most common autoimmune disease – Hashimoto’s thyroiditis was detected previously, but in limited reports, mostly regarding pediatric population [8]. The recent studies revealed that autoimmune thyroid diseases are common in patients with systemic sclerosis and their prevalence was estimated at 10.4% [14]. Although systemic sclerosis differs from morphea in numerous aspects, including clinical and immunological findings, it also presents autoimmune collagen overproduction [16, 17].

The coexistence of morphea and antithyroid antibodies in adult patients is worth considering. This subject is still unclear and has not been discussed in relation to the

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subtypes of the morphea, the activity of the disease and the number of skin lesions.

### Aim

The aim of this study was to determine the frequency of antithyroid antibodies in patients with morphea in relation to clinical manifestations of the disease.

### Material and methods

We enrolled 42 patients with histologically confirmed morphea (Caucasian women constituted 76.2% and Caucasian men 23.8% of the group). The mean age was 47.7 years (min. 18 years; max. 80 years). All morphea patients were recruited consecutively from the outpatient clinic of the Department of Dermatology in 2013–2015. The medical history of each patient was taken in detail, including gender, age, duration of the disease, comorbidities as well as family history.

The subtypes of the morphea were determined on the basis of a classification proposed by Kreuter *et al.* of circumscribed, linear, generalized, pansclerotic and mixed forms [16]. Circumscribed morphea was diagnosed if less than three plaques were observed, while generalized morphea was defined if at least four plaques on at least two of the seven anatomical sites were found (head and neck, chest and abdomen, back, right upper extremity, left upper extremity, right lower extremity, left lower extremity). The activity of the process was analyzed on the basis of clinical findings: absence of the lilac ring (violet ring on the perimeter of the lesion) for the last 3 months preceding the examination was classified as inactive [2, 16, 18].

To evaluate the thyroid function, the following tests were performed: thyrotropin (TSH), anti-peroxidase antibodies (TPO-Ab), and anti-thyroglobulin antibodies (Tg-Ab) with the use of the electrochemiluminescence method and TSH receptor autoantibodies (TRAb) – with the use of the radioimmunoassay method.

The normal ranges of the above were: TSH 0.27–4.20  $\mu$ U/ml; TPO-Ab < 34 IU/ml, Tg-Ab 10–115 IU/ml, TRAb < 2 IU/l.

### Statistical analysis

For the observed variables, appropriate descriptive statistics like mean, SD and minimum and maximum were evaluated. The analyzed parameters were compared by use of *t*-Student test. Compliance with the normal distribution was assessed by Kruskal-Wallis test.

### Results

The demographic characteristics of the analyzed group are presented in Table 1.

The mean duration of the disease was 44 months (min. 3 months, max. 180 months). The most common subtype of morphea was a circumscribed form (28 of analyzed cases – 66.6%). The mean number of plaques was 2.9 (min. 1, max. 11). The subtypes of morphea in the analyzed group are presented in Table 2. The most of the patients were in the active stage of the disease (35 subjects – 83.3%).

Increased levels of antithyroid antibodies were observed in 6 cases in relation to TPO-Ab (14.3%), in 4 cases in relation to Tg-Ab (9.5%) and in 1 patient in relation to TRAb (2.3%). Mean levels of thyroid parameters in the study group in relation to the type of morphea as well as its clinical activity (active vs. inactive) are listed in Table 3.

The TSH level was significantly higher in the patients with a circumscribed form of morphea than in the generalized subtype ( $p = 0.01$ ). There were no statistically significant differences in the levels of antithyroid antibodies between circumscribed and generalized forms of morphea. The most common autoimmune comorbidity was vitiligo, however it was diagnosed only in 3 cases. One patient suffered from celiac disease, another one from diabetes mellitus type 1.

### Discussion

As it was mentioned at the beginning, the relation between various autoimmune diseases is well known. However the real mechanisms involved in these processes are still unclear. Most of the patients show a genetic

**Table 1.** Dermographic characteristics of morphea patients

Age [years]	Total, n (%)	Male, n (%)	Female, n (%)
< 20	3 (7.1)	–	3 (9.3)
20–29	7 (16.6)	–	7 (21.9)
30–39	5 (11.9)	5 (0.3)	2 (6.2)
40–49	6 (14.3)	2 (0.2)	4 (12.5)
50–59	7 (16.6)	2 (0.2)	5 (15.6)
60–69	8 (19)	1 (0.1)	7 (21.9)
70–79	5 (11.9)	2 (0.2)	3 (9.3)
80–89	1 (2.3)	–	1 (3.1)

**Table 2.** The subtypes of morphea in analysed group

Morphea subtype	Total, n (%)	Male, n (%)	Female, n (%)
Circumscribed	28 (66.6)	7 (70)	21 (65.7)
Generalized	11 (26.2)	3 (30)	8 (25)
Linear	2 (4.8)	–	2 (6.2)
Pansclerotic	1 (2.4)	–	1 (3.1)

**Table 3.** Mean levels of thyroid parameters in morphea patients

Parameter	TPO-Ab [IU/ml]	Tg-Ab [IU/ml]	TRAb [IU/l]	TSH [ $\mu$ U/ml]
Total group	28.7	53.1	0.67	2.06
Subtypes:				
Circumscribed	75.6	76.4	0.41	2.58
Generalized	20.2	37.2	1.2	1.44
Linear	8.0	14.5	1.24	2.25
Pansclerotic	288.0	13.0	0.82	2.45
Activity:				
Active	29.9	45.0	0.67	1.99
Inactive	41.4	862.0	0.59	2.06

predisposition which interferes with environmental and hormonal factors [6]. The most common autoimmune comorbidity in our study group was vitiligo. The coexistence of both diseases (morphea and vitiligo) was previously reported in the literature [6, 7, 11], however the data were mostly limited to single case reports. For example, the association of vitiligo, morphea and Hashimoto's disease was presented by Dervis *et al.*, who described a 48-year-old woman with generalized morphea [11]. In the latest report on a large group of patients with vitiligo (1098), morphea was described in 0.2% of analyzed cases and this was a linear type [4].

In this study we did not reveal an increased frequency of positive antithyroid antibodies in morphea patients. The mean levels of analyzed thyroid parameters in the majority of the group were within normal ranges. Elevated TPO-Ab was detected in 14.3% of patients, Tg-Ab – in 9.5% and TRAb – in 2.3%. The alterations of antithyroid antibodies were presented in relation to the different subtypes of morphea. The highest level of TPO-Ab was detected in pansclerotic morphea (288 IU/ml). However, it was only one 76 year-old patient and it is difficult to draw any conclusion, while the frequency of positive antithyroid antibodies increases with age [19, 20]. It could be suggested that the elevated levels of TPO-Ab can be associated with more severe forms of morphea. Also Arif and Hassan reported a 55-year-old female with generalized morphea involving the trunk and proximal limbs who revealed hypothyroidism on laboratory screening [21]. However, on the other hand, our findings demonstrated higher TPO-Ab levels in patients with circumscribed morphea in comparison to a generalized one but with

no statistical significance. Similar findings were observed in association to Tg-Ab in patients with circumscribed and generalized morphea, while TRAb mean values were higher in generalized morphea. The analysis of TSH levels revealed values within normal ranges in all study subgroups, but a TSH mean concentration was significantly higher in circumscribed morphea than in generalized one ( $p < 0.05$ ). Our results show that there is a tendency for higher TPO-Ab and TSH in the limited form of morphea (circumscribed one). This link appears interesting, but needs to be discussed on a larger group of patients. Similarly to our observations, Lee *et al.* showed only 2 cases with diagnosed Hashimoto's disease and circumscribed morphea [22]. Both described patients had one morphea plaque, while one was with a lilac ring on examination.

To the best of our knowledge, this is the first study to assess antithyroid antibodies and thyroid function in association with activity of morphea. We suspected higher levels of antithyroid antibodies in patients with an active stage of morphea. Surprisingly, the patients with an inactive stage presented a tendency for higher TPO-Ab, Tg-Ab and TSH levels (statistical analysis not performed due to a small number of patients – 7 cases). We may speculate that long-lasting autoimmune disorder, in this case morphea, is less likely to be connected with other autoimmune diseases.

According to the literature data, the frequency of immune processes in the thyroid can be detected in up to 40–50% as evaluated by Okayasu *et al.* in autopsy studies in elderly Caucasian women [19, 23]. The National Health and Nutrition Examination Survey (NHANES III) – a vast study that assessed TSH and antithyroid anti-

bodies in 13 344 thyroid disease-free subjects revealed that Tg-Ab was detectable in 10.4 ±0.5% of subjects and TPO-Ag in 11.3 ±0.4% of subjects [20]. Approximately 18% of that population had positive Tg-Ab or TPO-Ab, what is higher than in our study. Hollowell *et al.* revealed also that positive antithyroid antibodies were more frequent in women than in men and increased with age [20]. The NHANES III survey concluded that positive Tg-Ab without an increased TPO-Ab level are not significantly associated with thyroid disease [20]. The differences in the antithyroid antibodies concentration in different populations may result from genetic and environmental factors, such as iodine uptake [24]. Pedersen *et al.* evaluated TPO-Ag and Tg-Ab concentrations in patients from mild and moderate iodine-deficient areas [24]. The overall prevalence of one or both antithyroid antibodies in this study was 18.8%. In approximately 40% of the subjects with positive antithyroid antibodies, both of them (TPO-Ab and Tg-Ab) were detectable [24]. In Poland, iodine prophylaxis based on the consumption of iodized salt with 30 mg KI/kg was introduced in 1997 and eliminated iodine deficiency in this area.

Finally, it is worth mentioning that the reference limits for antithyroid antibodies have not been clearly defined. Thus, in clinical practice it is difficult to interpret and compare different results. In our study, all the measurements were performed with unified techniques.

## Conclusions

The elevated Tg-Ab and TPO-Ab levels in the general population can appear without any clinical relevance in an even higher percentage than in our study. Thyroid dysfunction may occur in morphea patients accidentally and we do not approve expensive tests for routine evaluation of the thyroid function in this group.

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## Conflict of interest

The authors declare no conflict of interest.

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