ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. LXIV, N 1, 8 SECTIO D 2009

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Rheumatoid arthritis and autoimmune thyroid disorders – literature data and authors' observations

Rheumatoid arthritis (RA) is a chronic autoimmune process leading to joint destruction. It affects about 1% of the general population. RA occurs as an isolated entity or coexists with other diseases with abnormal immune response and production of organ-specific and non-specific antibodies. In autoaggression diseases, the genetic, environmental factors and immune abnormalities are essential. The commonest autoimmune thyroid diseases (ATD) include Hashimotos and Graves diseases. Systemic and organ specific diseases of autoaggression often overlap in these patients. Three types of autoimmune polyglandular syndromes are distinguished: APS-1, APS-2, APS-3 (1, 2). The cases of RA are described in type 2 and 3 (3). ATD conditions the diagnosis of the third type (almost 100%) and is common in type 2 (about 70%) (3). Only 4% of patients with type 1 develop ATD, yet never at the onset of the disease (4).

The aim of the present study was to analyse the relations between RA and ATD based on literature data and our own observations.

MATERIAL AND METHODS

The analysis involved 125 consecutive patients with RA diagnosed according to ARA criteria of 1987 (106 females and 19 males) hospitalized in the Department of Rheumatology and Systemic Connective Tissue Diseases, Medical University of Lublin during three successive months. The data regarding coexistence of thyroid diseases, including ATD, were obtained retrospectively based on available medical records and anamneses from previous hospitalizations. The patients with thyroid pathologies were divided into two groups: those with autoimmune thyroid disease and the remaining ones. The diagnosis of ATD was based on detection of antithyroid antibodies and levels of TSH and thyroid hormones (TH). The ultrasound examination or fine-needle aspiration biopsy of the thyroid gland (FNAB) was required to confirm the diagnosis.

RESULTS

Present or past thyroid dysfunctions were observed in 38 patients (30.4%). ATD was found in 4 out of 125 patients (3.2%). The characteristics of patients according to sex, age, duration of RA, ATD and its diagnosis are presented in Table 1. All diagnoses of ATD were established in female patients. The mean age was 59 years (49–69). The characteristics of the remaining patients with thyroid pathologies, including their age, sex and duration of RA are presented in Table 2.

Table 1. RA patients diagnosed with ATD. Abbreviations explained in the text

No	Patient	Sex	Age	RA duration (years)	ATD	Thyroid function	Diagnosis based on:
1	HR	F	69	2	Hashimoto's disease	euthyreosis	clinical picture, TSH, TH, anti-TPO and anti-TG-present, US thyroid changes typical of ATD
2	MG	F	62	6	ATD	euthyreosis, on diagnosis- hyperthyroidism	clinical picture, TSH, TH, anti-TPO and anti-TG-present, US thyroid changes typical of ATD
3	ET	F	56	25	ATD	euthyreosis	clinical picture, TSH, TH, anti-TPO and anti-TG-present, US thyroid changes typical of ATD, histopathological examinations of the thyroid
4	HM	F	49	7	ATD	euthyreosis	clinical picture, TSH, TH, anti-TPO, anti-TG-present, US thyroid changes typical of ATD

In patient 1 and 2, the diagnosis of ATD was confirmed by the endocrinologist; no fine-needle aspiration biopsy – FNAB was required. In patient 3, the diagnosis was also confirmed by the endocrinologist; FNAB was performed several months earlier due to US-detected nodules. In patient 4, the diagnosis was confirmed by ultrasound examination of the thyroid gland and redetermination of antithyroid antibodies at normal levels of TSH.

Table 2. RA patients diagnosed with thyroid pathologies without confirmed diagnoses of ATD

No	Patient	Sex	Age	RA duration (years)	Thyroid pathology
1	HO	F	67	25	autonomic adenoma of the right lobe treated with radioiodine
2	TG	F	72	8	nodular goiter in euthyreosis
3	MK	F	77	19	elevated TSH detected earlier
4	AS	F	43	15	earlier detected anti-TG-present
5	SK	F	66	2	nodular goiter in euthyreosis
6	AB	F	64	15	post-strumectomy condition, glandular tissue regeneration with hyperthyroidism treated with radioiodine in the past
7	LM	F	65	8	nodular retrosternal goiter in euthyreosis
8	MS	F	63	10	nodular goiter (hypothyroidism)
9	MS	F	55	30	according to the patient, the history of thyroid goiter
10	KT	F	69	12	anti-TPO-present
11	JN	F	57	28	post-partial strumectomy condition, hyperreactive nodular goiter under therapy, amyloidosis
12	KD	F	52	5	earlier detected anti-TPO-present
13	TS	F	55	17	nodular goiter of the thyroid, hypothyroidism controlled with therapy
14	SŚ	M	54	7	post-strumectomy condition due to nodular goiter, controlled hypothyroidism
15	JK	F	58	6	subclinical hyperthyroidism in the past
16	HZ	F	53	21	hypothyroidism controlled with therapy, earlier detected anti-TPO-present
17	AB	F	64	19	colloid goiter (FNAB), hyperactive and treated with radioiodine
18	JW	F	76	20	nodular goiter at euthyreosis stage

19	MM	F	65	19	colloid goiter (FNAB), earlier detected anti-TG-present
20	EB	F	43	6	nodular goiter at the subclinical hyperactivity stage
21	TM	F	49	12	hyperthyroidism under therapy
22	LD	F	51	over 20	nodular goiter under observation
23	EW	F	42	1	hypothyroidism under therapy
24	RW	F	32	2	earlier detected anti-TPO-present
25	GW	F	37	6	earlier detected anti-TPO-present
26	HS	F	57	13	nodular goiter in euthyreosis
27	ZS	F	57	32	nodular goiter in euthyreosis
28	JB	F	67	5	hyperthyroidism in the past
29	MG	F	29	2	controlled hypothyroidism
30	PT	M	19	1 year, history of JIA	earlier detected anti-TPO-present
31	AD	F	21	3 years, history of JIA	controlled hypothyroidism, earlier detected anti-TPO-present
32	EG	F	59	4	hyperthyroidism, anti-TPO-present
33	KK	F	50	15	subclinical hyperthyroidism, present anti-TPO
34	JW	F	77	16	according to the history taken, the patient was treated for thyroid disease in the past

In all patients with increased values of antithyroid antibodies (11 patients in Table 2, number: 4, 10, 12, 16, 19, 24, 25, 30–33), their determinations were repeated. They did not fulfil the criteria for ATD due to normal values of antithyroid antibodies in most cases, but diagnosis of ATD can not be excluded.

DISCUSSION

Our observations reveal higher ATD predisposition in RA patients. The final diagnosis of ATD was established in 4 (3.2%) out of 125 patients whereas anti-thyroid antibodies (anti-TPO and/or anti-TG) were observed in 15 (12%) individuals. However, it should be taken into account that the analysis was conducted retrospectively and therefore, the real number of ATD and RA coexistence would likely be higher as each patient, irrespective of clinical symptoms, underwent widened diagnostic procedures to confirm or exclude the thyroid disease. The normal function of the thyroid gland does not rule out the diagnosis of ATD when anti-TPO or anti-TG is increased. The antithyroid antibodies may be presented for a long time before the clinical course of the ATD diagnosis. Moreover, the diseases in question may manifest independently in various periods of life, which is likely to indicate that our findings may not be final (2, 5). On the other hand, it is discussed whether RA and Hashimoto's disease are the same entity with various organ localization (6). The literature reports often stress higher prevalence of antithyroid antibodies and thyroid dysfunction, including autoimmune inflammations, in RA patients. Furthermore, higher frequency of antithyroid antibodies has been described in patients with juvenile idiopathic arthritis (JIA) (7), and syndromes of overlapping with ATD (8, 9). The data reported by many authors differ markedly due to differences in research methods, which were already pointed out by Masi et al. in 1965 (10). Biro et al., in their prospective study encompassing 1,517 patients with systemic connective tissue disease, demonstrated ATD in 9 out of 185 RA patients (4.9%) (11). Caron et al. found ATD in 16.2% of RA patients (12). According to Silman et al., this percentage was 6%, yet the analysis involved multicase families with RA (13). The presence of antithyroid antibodies in RA patients is also higher compared to the remaining ones (14). Innocencio and co-workers found anti-TG and/or anti-TPO antibodies

in 32% of 25 patients and in 4% of 113 controls (15). According to Andonopoulus et al., anti-TPO was present in 12.9% (101 patients) and 8.6% of controls (16). Similar findings were reported by Magnus et al. (17). Three-fold higher prevalence of thyroid dysfunction was also demonstrated by Shiroky et al. in female patients with RA (30%) compared to female controls with non-inflammatory rheumatic diseases (11%) (18). They demonstrated that the majority of dysfunctions was related to hypothyroidism and accompanying Hashimoto's disease although antithyroid antibodies were not determined. The fact that the studies were carried out in different populations should be taken into consideration while interpreting the results mentioned above.

On the other hand, ATDs also overlap with other autoimmune diseases, such as pernicious anaemia, Addison's disease, immune-mediated thrombocytopenia, leucoderma, type 1 diabetes and others. Thyroid diseases of autoaggression may precede or follow systemic autoimmune diseases (5). Our group of patients included 6 (4.8%) patients with the diagnosis of diabetes, 2 with type 1. Biro et al. evaluated the prevalence of systemic autoimmune diseases in patients with ATD stressing that there are few literature data concerning this issue (11). In their study, 9 out of 426 (2.1%) patients were diagnosed with RA – more often in patients with Hashimoto's disease (3.5%) than those with Graves' disease (1.2%). Przybylik-Mazurek et al. found 4 patients with RA (1.6%) amongst 324 examined patients with the diagnosis of ATD – all of them with coexisting Hashimoto's disease (19). Punzi et al. found 33 patients with chronic lymphocytic thyroiditis and coexisting poly- and oligo-arthritis (20). After the > 6-year observation, RA was revealed in 8 out of 16 patients with polyarthritis and in none of those with oligoarthritis. According to the authors, mild oligoarthritis seems to have ATD-independent course. Systemic autoaggression in patients with ATD is evidenced in the report about 58/168 patients (35%) with detected antinuclear antibodies (ANA) compared to 7 /75 (9%) healthy volunteers (21). In the interpretation of autoantibody findings, including antithyroid ones, the earlier course of therapy should be taken into account. In patients treated with etanercept, ATD may be induced although initially no manifestations of the thyroid disease were present (22). The profile of antithyroid antibodies may change after the TNF-alfa blocker therapy (23).

There are numerous reports about higher prevalence of the Sjogren's syndrome and other autoimmune diseases in patients with ATD. In 1998, Gaches et al. (5) demonstrated that systemic lupus erythematosus and Sjogren's syndrome were most commonly observed in ATD patients. This fact indicates that patients with thyroid dysfunctions should be evaluated for systemic autoimmune diseases.

In conclusion, overlapping of autoimmune diseases was frequently demonstrated and is undisputable. The literature reports stress the role of genetic susceptibility to autoaggression, and genetic predisposition increasing the risk of autoaggression in response to environmental stimuli. The incidence of certain antigens of tissues compatibility (HLA) is known to be higher compared to the remaining population. Apart from genetic factors, immune dysfunction, metabolic, hormonal and environmental factors play an essential role in the development of autoaggression diseases. The examples are found in the studies concerning CTLA4 polymorphism in patients with autoimmune endocrinopathy and RA (24–26). It is disputed whether RA patients should be screened for ATD. Determinations of THS may not be sufficient, particularly in patients receiving glycocorticosteroids (27). RA patients should be continuously followed up and once new clinical symptoms develop, appropriately evaluated for thyroid diseases.

CONCLUSIONS

1. RA patients should be followed up for thyroid dysfunctions, including coexisting ATD.
2. Amongst RA patients, women are particularly predisposed to ATD.
3. Epidemiological data, clinical observations and genetic studies confirm the relation between RA and ATD.

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SUMMARY

Rheumatoid arthritis (RA) and some thyroid diseases are of autoimmune origin. Their co-existence has been evaluated and discussed in numerous studies since the beginning of the 60's. Higher prevalence of antithyroid antibodies and autoimmune thyroid diseases (ATD) has been demonstrated in patients with RA. The objective of this study was to analyze the relations between RA and ATD based on literature data and our own observations. Analysis involved 125 consecutive patients with RA (according to ARA criteria, 1987) hospitalized in the Department of Rheumatology and Systemic Connective Tissue Diseases, Medical University of Lublin during three successive months. Patients were observed for thyroid diseases, ATD in particular. The findings showed the coexistence of ATD in 4 out of 125 (3.2%) patients with RA; various present and past thyroid dysfunctions were found in 38 (30.4%) patients. Many aspects of ATD and RA overlapping were demonstrated. Patients with RA should be evaluated for coexisting autoimmune thyroid diseases.

Współwystępowanie reumatoidalnego zapalenia stawów i autoimmunologicznych chorób tarczycy – przegląd piśmiennictwa oraz obserwacje własne

Reumatoidalne zapalenie stawów (RZS) i niektóre choroby tarczycy mają podłoże autoimmunologiczne. Ich współwystępowanie było oceniane w badaniach już od początku lat 60. ubiegłego wieku i nadal jest przedmiotem dyskusji. Wielokrotnie udowodniono zwiększoną

częstość występowania przeciwciał przeciwtarczycowych i autoimmunologicznych chorób tarczycy (ACT) u chorych na RZS. W pracy na podstawie danych z piśmiennictwa i obserwacji własnych postanowiono przeanalizować zależności pomiędzy RZS a ACT. Analizie poddano 125 chorych na RZS (ARA, 1987) hospitalizowanych w Klinice Reumatologii i Układowych Chorób Tkanki Łącznej Uniwersytetu Medycznego w Lublinie w okresie trzech kolejnych miesięcy. Chorzy byli obserwowani pod kątem występowania chorób tarczycy, w tym szczególnie ACT. Na podstawie przeprowadzonej analizy stwierdzono współistnienie ACT u 4 ze 125 (3,2 %) chorych na RZS, natomiast różnorodne zaburzenia funkcji tarczycy obecnie lub w przeszłości łącznie u 38 (30,4 %) chorych. Wykazano wiele aspektów współwystępowania ACT i RZS. Chorzy na RZS powinni być obserwowani w kierunku współwystępowania autoimmunologicznych chorób tarczycy.