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Autosensitization to Connective Tissue Elements and Endogenous Adaptation Hormones in Mycobacterioses[1]

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In some mycobacterial diseases (leprosy, tuberculosis) strong autoimmunization aggravating clinical manifestations is observed. Thus, increased levels of antibodies to collagen (Abc) and elastin (Abe) are conducive to pneumosclerosis ([13, 14]) in pulmonary tuberculosis, and correlate to the most severe reactions such as erythema nodosum leprosum in leprosy ([6, 8]). To what extent endogenous adaptation hormones are involved in autoimmune processes remains to be elucidated, and that was the aim of our work.

MATERIAL AND METHODS

Titers of Abc and Abe were estimated by the latex agglutination test ([15]). The levels of hypophyseal somatotrophic hormone (HSH), hydrocortisone (cortisol), triiodothyronine (T3) and thyroxine (T4) were estimated in radioimmune assays ([2, 3, 9, 10]).

Thirty-seven patients with lepromatous leprosy (12 BL, 25 LL according to the Ridley-Jopling classification) from 23 to 62 years old were included in the study. Among them were 17 females and 20 males.

Sixteen of the 37 patients had focal infiltrates on their skin. On biopsy a significant number of disrupted leprosy bacilli were found (active leprosy). In 21 patients only scarred lesions of residual leprosy were observed with no leprosy bacilli on biopsy (inactive leprosy).

All active leprosy patients were given multiple drug therapy (MDT) as recommended by the World Health Organization, and the patients with inactive leprosy received monotherapy with dapsone.

In the study 32 patients from 21 to 45 years old (15 females and 17 males) with pulmonary tuberculosis were included. The active stage of the disease was recorded in 19 patients (4 with disseminated tuberculosis in the phase of infiltration and degeneration, 10 with infiltrative and 5 with fibrocavernous tuberculosis in the phase of infiltration). All of the patients of this group discharged *Mycobacterium tuberculosis* with their sputum. In 13 patients the disease process was inactive (cirrhotic or focal tuberculosis in the consolidation phase with no tuberculosis bacilli in their sputum). All of the patients with pulmonary tuberculosis were given a combined chemotherapy irrespective of the phase of their disease.

Controls were 32 healthy persons.

Data obtained were analyzed using Spearman's rank correlation and Student's *t* test.

RESULTS AND DISCUSSION

In active patients with leprosy and tuberculosis Abc and Abe titers were significantly increased (Table 1). In leprosy the Abc and Abe titers were increased in 50% and in 90% of the cases, respectively. In patients with tuberculosis Abc titers were more likely to be elevated than Abe titers. It is important that autoimmune manifestations remain in leprosy patients long after clinical regression has been achieved as judged by the maintenance of increased titers of Abc and Abe for many years. With a favorable course of pulmonary tuberculosis without excess fibrosis and emphysema of the lungs, antibody titers tended to fall toward normal during 4–6 months of therapy. In any case they were significantly lower than those at the peak of the disease ($p < 0.01$ for Abc and Abe) but they remained elevated as compared to the healthy controls. In both leprosy and tuberculosis patients high hydrocortisone and unchanged T4 levels were noted. HSH levels were significantly decreased in tuberculosis patients; in leprosy they were similar to those

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TABLE 1. *Antibodies to connective tissue elements and adaptation hormones in sera of patients with mycobacterioses and healthy subjects.*

Antibodies and hormones	Patients with		Healthy subjects
	Leprosy (mean ± S.E.M.)	Tuberculosis (mean ± S.E.M.)	
Log_{10} of Abc titer			
Active state	1.72 ± 0.06 (16)[a] $p < 0.01$[b]	2.70 ± 0.10 (19) $p < 0.001$	1.40 ± 0.10 (22)
Inactive state	2.20 ± 0.01 (21) $p < 0.001$	2.00 ± 0.10 (13) $p < 0.001$	
Log_{10} of Abe titer			
Active state	1.88 ± 0.02 (16) $p < 0.001$	1.84 ± 0.10 (19) $p < 0.001$	0.90 ± 0.11 (22)
Inactive state	2.08 ± 0.01 (21) $p < 0.001$	1.37 ± 0.10 (13) $p < 0.01$	
HSH nmole/l	30.4 ± 8.3 (10)	9.3 ± 2.6 (10) $p < 0.01$	32.1 ± 7.8 (22)
Hydrocortisone nmole/l	326.0 ± 15.0 (16)	498.0 ± 45.0 (9) $p < 0.001$	251.0 ± 24.0 (22)
T3 nmole/l	2.15 ± 0.15 (16) $p < 0.05$	1.54 ± 0.20 (6)	1.76 ± 0.12 (22)
T4 nmole/l	101.8 ± 5.2 (16)	103.5 ± 7.3 (6)	110.8 ± 3.3 (22)

[a] Figures in parentheses are numbers of observations.
[b] p = Level of confidence as compared with healthy subjects; absence of p values means $p > 0.05$.

in healthy subjects. Increased levels of T3 were observed only in leprosy patients. Our investigation did not show any significant relationship between the hormone levels and the disease activity.

In both mycobacterioses a marked dependence of the antibody titers on hydrocortisone, HSH and T3 levels was observed in a number of cases (Table 2).

Before proceeding to an assessment of the pathophysiological implications and significance of these interrelationships, it is necessary to pay attention to the following, rather important, in our opinion, methodological aspect.

The thing is that the two factors are strongly correlated to each other on equal footing, from the mathematical point of view

TABLE 2. *A correlation between blood adaptation hormone levels and titers of antibodies to connective tissue in leprosy and tuberculosis patients.*

Antibodies to connective tissue	Hormones			
	HSH	Cortisol	T3	T4
		Leprosy patients		
Abc	+0.1628 (10)[a]	−0.3224 (16)	+0.5279 (14) $p < 0.05$[b]	0.0858 (14)
Abe	−0.1869 (10)	−0.5246 (16) $p < 0.025$	+0.3639 (14)	−0.0057 (14)
		Tuberculosis patients		
Abc	−0.6575 (10) $p < 0.05$	−0.0759 (9)	−0.3188 (6)	+0.4928 (6)
Abe	−0.0875 (10)	−0.6070 (9)	−0.1159 (6)	+0.1739 (6)

[a] Figures in parentheses are numbers of observations.
[b] p = Level of confidence of correlation coefficients; absence of p values means $p > 0.05$.

([5]). As applied to our data it would mean the following: the levels of the hormones have the same impact on the titers of the antibodies as the intensity of antibody production has on the levels of the hormones. Such a correlation can be demonstrated in experiments on intact laboratory animals ([11]). On the other hand, in chronic diseases such as leprosy and tuberculosis there are numerous metabolic, organic, psychophysiologic, etc., disturbances ([7, 12, 13]) which impact on the adaptation system and, hence, the production of the relevant hormones. Here the immunologic changes are only among the numerous factors affecting the adaptation system. It means that the coefficient of a correlation between the levels of the adaptation hormones and antibody titers in the patients with mycobacterial infections represents primarily the impact of the first factor on the second. Based on our data it can be stated with confidence that there is a unidirectional impact of adaptation hormones on the production of the antibodies toward connective tissue elements.

Abe titer was inversely correlated to the hydrocortisone level in both mycobacterioses. Since the hydrocortisone level had a tendency to increase (Table 1), it might be one of the factors preventing autosensitization to connective tissue both in leprosy and tuberculosis. The correlation between the Abc titers and the hydrocortisone level was not so obvious in our investigation.

A high negative correlation was noted between Abc production and the level of HSH in tuberculosis patients, but since blood levels of HSH are markedly low (Table 1), it is not likely that it plays a significant immunoregulatory role.

In leprosy patients the Abc and, to a lesser degree, the Abe titers were directly related to T3 levels. Taking into consideration increased blood levels of the antibodies studied and T3 hormone in leprosy, one may suggest a significant role of the latter in autosensitization to connective-tissue structures in this mycobacteriosis. In tuberculosis such a relationship was insignificant, probably because of the limited number of observations, and it needs to be studied further.

The correlations found may suggest a new approach to the search for remedies and methods of preventing and curing manifestations of autosensitization to connective tissue in mycobacterial diseases. There is no need to use only glucocorticoids, especially since the mycobacterioses under investigation are intrinsically related to deep disturbances of cell-mediated immunity ([1, 4]) and may deteriorate because of the immunodepressive effect of the glucocorticoids. Production of antibodies toward connective tissue might be affected depending on the levels of endogenous thyroid hormones. It might be possible to combine medications according to individual endocrine and immune indices, hence decreasing the risk of side effects due to hormonotherapy.

SUMMARY

The contribution of some adaptation hormones to the process regulating production of autoantibodies to collagen (Abc) and elastin (Abe) was studied in leprosy (37 patients) and tuberculosis (31 patients). In both mycobacterioses the Abc and Abe titers were increased and inversely correlated with endogenous cortisol levels. In leprosy the antibody titers directly correlated with the triiodothyronine (T3) levels which were significantly higher than the values in healthy controls. A new approach to research for remedies and methods of preventing and curing autosensitization to connective tissue is suggested by combining medications according to individual endocrine and immune indices.

RESUMEN

Se estudió la contribución de algunas hormonas de adaptación al proceso de regulación de la producción de autoanticuerpos contra colágena (Abc) y elastina (Abe) en 37 pacientes con lepra y en 31 pacientes con tuberculosis. En ambas micobacteriosis, los títulos de Abc y de Abe estuvieron incrementados y correlacionaron de manera inversa con los niveles de cortisol endógeno. En la lepra, los títulos de anticuerpos correlacionaron en forma directa con los niveles de triyodotironina (T3), los cuales fueron significativamente más altos que los encontrados en los controles sanos. Se propone un nuevo enfoque para la investigación de remedios y métodos para la prevención y curación de la autosensibilización contra el tejido conectivo. Este enfoque considera la posible administración de medicamentos de acuerdo a los índices endócrino e inmunológico de cada individuo.

RÉSUMÉ

La contribution de certaines hormones d'adaptation au processus réglant la production d'auto-anticorps vis-à-vis du collagène (Aac) et de l'élastine (Ace) a été étudiée dans la lèpre (37 patients) et la tuberculose (31 patients). Dans les deux maladies, les titres Aac et Ace étaient augmentés et inversément correlés aux taux de cortisol endogène. Dans la lèpre, les titres d'anticorps étaient directement correlés avec les taux de triiodothyronine (T3), qui étaient significativement plus élevés que les valeurs observées chez les témoins en bonne santé. Une nouvelle approche à la recherche pour des remèdes et des méthodes de prévention et de traitement de l'autosensibilisation vis-à-vis du tissu conjonctif est suggérée en combinant des médicaments en fonction d'indices individuels endocrines et immunitaires.

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