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Relationship between immunoglobulin levels, tuberculin hypersensitivity and radiological extent of disease in Greek patients with pulmonary tuberculosis

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ABSTRACT: Greek patients with pulmonary tuberculosis, who were studied before receiving any form of treatment, tended to have elevated immunoglobulin (Ig) levels in the IgG and IgA, but not the IgM, classes. This is in agreement with the findings of the majority of studies on immunoglobulin levels in other countries. The levels of IgA were particularly associated with the extent of disease and were significantly higher in smear-positive than in smear-negative patients. There was no significant relationship between the intensity of tuberculin sensitivity and immunoglobulin levels except for a weak tendency for patients with high IgA levels to have small skin reactions to tuberculin.

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It is well established that patients with active tuberculosis often have elevated levels of total immunoglobulin. In the majority of reports, levels of total IgG and IgA, but not IgM, have been elevated [1–9]. Other workers have reported an increase in IgM levels in addition to IgG and IgA [10, 11]. In a further report there was an increase in IgG but not in IgA levels, and a decrease in IgM levels [12], and in another increases were confined to the IgA class [13]. Thus, there are considerable differences in the reported changes in immunoglobulin levels in tuberculosis which may reflect varying ethnic factors or, possibly, differences in the time during the course of the disease when the assays were done. Changes in total immunoglobulin levels are nonspecific responses to the infection and may be due to adjuvant: they are not related directly to the production of specific antibody to the tubercle bacillus [4].

There is little information on the relationship of the reported rises in immunoglobulin levels to other aspects of the disease, although in two reports [9, 14] there was some association between the levels and radiological extent of disease.

The purpose of this study was to determine the pattern of elevation of immunoglobulin levels in Greek patients with pulmonary tuberculosis and to determine whether these are related to the age and sex of the patient, the intensity of the tuberculin skin test reactivity, sputum smear positivity, erythrocyte sedimentation rate (another nonspecific indicator of inflammation) and the radiological extent of disease.

Patients and methods

Fifty nine patients with pulmonary tuberculosis, 46 male and 13 female, aged 16–85 yrs (mean 43 yrs) were included. All patients were skin tested with 2 IU of RT 23 purified protein derivative (PPD) by the Mantoux method: the transverse diameter of the induration was recorded at 48 h, by the same observer in each case. Sputum was examined microscopically for acid-fast bacteria. The erythrocyte sedimentation rate (ESR) was determined on 43 patients. The radiological extent of disease was recorded as minimal, moderate or extensive (far advanced) or as pleural effusion only according to the criteria of the National Tuberculosis Association of the USA [15].

An additional group of 41 patients with pulmonary tuberculosis, 27 male and 14 female, aged 15–72 yrs (mean 33 yrs) were included for studies on serum iron and proteins. The control group consisted of 52 individuals, 27 men and 25 women, aged 22–70 yrs (mean 36 yrs).

Serum was obtained on the day of tuberculin testing and, in the case of the patients, before therapy was commenced. Levels of immunoglobulin in the IgG, IgA, and IgM classes in sera from all patients and control subjects were determined by radial immunodiffusion [16]. Sera from the additional 41 patients were assayed for iron levels, and total protein, albumin, $alpha_1$, $alpha_2$, beta and gamma globulins were estimated by electrophoretic scanning.

Data were analysed by Student's t-test (when they were parametric), Mann-Whitney test, Spearman's rank correlation test and the Chi-squared test where appropriate.

Results

The levels of immunoglobulin in the IgG, IgA, and IgM classes in the 59 patients and 52 control subjects are shown in table 1. The IgG and IgA levels were significantly higher in patients than in controls ($p<0.001$): levels of IgM were higher in the patients but not significantly so ($p>0.05$). The upper limits of normal immunoglobulin levels in the controls were defined as the mean levels ±2 SD. The numbers of patients with levels above the defined upper limits for IgG, IgA, and IgM were 19 (32%), 18 (31%) and 8 (14%), respectively.

Table 2 shows that 32 of the 59 patients had elevated immunoglobulin levels: 21 in one class, 9 in two classes and 2 in all three classes. There was a significant tendency for patients with more extensive disease to have elevated immunoglobulin levels ($\chi^2=14.5$; $p=0.001$).

Table 3 shows the immunoglobulin levels in the patients according to radiological extent of disease. There were no significant differences in IgM levels in the three groups, or in IgG and IgA between those with minimal and moderate disease. In extensive disease there was a significant increase in IgG levels ($p<0.01$) and this increase was even more evident in the case of IgA ($p<0.001$). The relationship of IgA levels to the extent of disease is shown in figure 1.

There was an association between smear-positivity and extent of disease ($\chi^2=8.86$, $p=0.013$) and IgA levels were significantly higher in the 36 smear-positive patients (mean 457 $g \cdot dl^{-1}$; SD 229) than in the 23 smear-negative patients (mean 298 $g \cdot dl^{-1}$; SD 142; $p<0.01$).

Table 1. – Immunoglobulin levels ($g \cdot dl^{-1}$) in the IgG, IgA and IgM class in patients and controls

Class	Patients				Controls			
	Mean	SD	Min	Max	Mean	SD	Min	Max
IgG	1590	638	690	3340	1076	369	380	2100
IgA	395	214	115	900	251	119	70	540
IgM	193	110	44	600	159	80	50	390

IgG, IgA, IgM: immunoglobulin G, A and M, respectively.

Table 2. – Numbers of patients with elevated immunoglobulin levels (mean±2SD of control values) according to radiological extent of disease.

Elevated class	Radiological extent			
	Minimal	Moderate	Extensive	Total
IgG only	2	1	6	9
IgA only	1 (1)	2	6	9
IgM only	-	2	1	3
IgG+IgA	-	-	6	6
IgG+IgM	1	-	1	2
IgA+IgM	-	-	1	1
All three	-	-	2	2
Total elevated	4 (1)	5	23	32
None elevated	10 (7)	11	6	27

Figures in parentheses refer to the eight patients with pleural effusion only. IgG, IgA, IgM: immunoglobulin G, A and M, respectively.

There was no significant relationship between smear-positivity and IgG or IgM levels.

There was no significant relationship between the diameter of the Mantoux test and immunoglobulin levels although there was a tendency for those patients with large Mantoux reactions to have lower IgA levels ($r=-0.25$). No sex- or age-related differences in immunoglobulin levels were found in either patients or control subjects. In the patient group there were no significant correlations between Mantoux reactivity and age, although three of the four non-reactors were elderly (70, 81 and 85 yrs). Mantoux reactivity was unrelated to smear-positivity. After removal of the non-reactors, Mantoux reactivity tended to be lower (mean 13.4 mm diameter; SD 4.31) in patients with extensive disease than in those with minimum or moderate disease (mean 15.4 mm; SD 3.63; $p<0.05$). Three of the four non-reactors had extensive disease (patients aged 29, 70 and 81 yrs) and one had minimal disease (aged 85 yrs).

The ESRs showed low, positive but statistically non-significant correlations with IgG, IgA and IgM levels ($r=0.26$, 0.29 and 0.11, respectively). The ESR levels were substantially higher in 22 patients with extensive disease (mean 62 $mm \cdot h^{-1}$; SD 26; range 16–110) than in 16 patients with minimal or moderate disease (mean 37

Table 3. – Immunoglobulin levels ($g \cdot dl^{-1}$) in the IgG, IgA and IgM classes according to radiological extent of disease

Class	Extent of disease	Patients	Mean	SD	Min	Max
IgG	Minimal	14	1476	424	880	2600
	Moderate	16	1218	495	690	2700
	Extensive	29	1851	676	860	3400
IgA	Minimal	14	312	157	120	790
	Moderate	16	260	141	115	550
	Extensive	29	510	209	125	900
IgM	Minimal	14	161	86	65	400
	Moderate	16	218	125	88	600
	Extensive	29	196	108	44	470

IgG, IgA, IgM: immunoglobulin G, A and M, respectively.

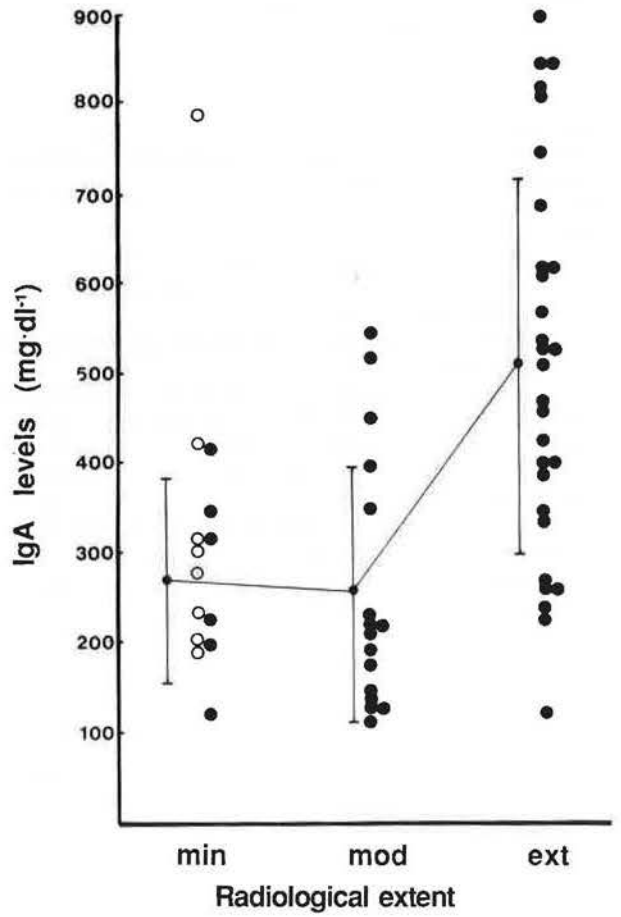

Fig. 1. – IgA levels in patients with radiologically determined minimal (MIN), moderate (MOD) and extensive (EXT) disease. Means and SD are shown. Open circles indicate those patients with pleural effusions only.

$mm.h^{-1}$ SD 22; range 8–96; $p<0.005$). Five patients with pleural effusion only had ESRs in a similar range to patients with extensive disease (mean 69 $mm \cdot h^{-1}$; SD 14; range 50–84).

Twelve of the additional 41 patients had pleural effusions only, whilst 2, 13 and 14 had minimal, moderate and extensive disease, respectively. There was a tendency for those with pleural effusion to have lower serum iron levels (mean 75.8 $ug \cdot dl^{-1}$; SD 27.3; range 30–112) than those with moderate or extensive disease (mean 93.5 $\mu g \cdot dl^{-1}$; SD 25.8; range 52–160) but this barely reached statistical significance ($p=0.05$). There was no association between extent of disease and the serum proteins as estimated by electrophoretic scanning.

Discussion

The general pattern of immunoglobulin levels in patients with pulmonary tuberculosis in Greece closely resembles that reported in the majority of previous studies, *i.e.* significant elevations in the IgG and IgA classes but not in the IgM class. Although probably due to nonspecific polyclonal B-cell activation by mycobacterial adjuvants [4] the reason for this pattern is unknown. In patients with African trypanosomiasis, such polyclonal B-cell activation leads to increase of immunoglobulin in the IgM class [17].

The relationship between ESR and extent of disease and the lack of a statistically significant correlation between the ESR and immunoglobulin levels was also noted in a study of Indonesian patients [18]. The latter is somewhat surprising as the ESR is usually regarded as reflecting changes in serum proteins, although various nutritional and metabolic factors may also

affect the ESR. It was also surprising that those patients with pleural effusions only tended to have lower serum iron levels than those with more extensive pulmonary disease.

It is of interest that IgA should show the most significant elevation in relation to the extent of disease. As IgA is principally a secretory antibody, its elevation may well be associated with presence and surface area of cavities in the lung. The tendency of IgA levels to be related to smear-positivity and, inversely, to the diameters of the tuberculin reaction probably reflect the association of these factors with extent of disease.

In conclusion, immunoglobulin levels in Greek patients follow the trend seen in most, but not all, other regions and there is a particular relationship between IgA levels and extent of disease that merits further study.

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Relation entre les niveaux d'immunoglobuline, l'hypersensibilité tuberculinique et l'étendue radiologique de la maladie, chez des patients grecs atteints de tuberculose pulmonaire. S. Michaelides, J.M. Grange.

RÉSUMÉ: Des patients grecs, atteints de tuberculose pulmonaire, étudiés avant toute forme de traitement, tendent à avoir des niveaux élevés d'immunoglobuline des classes IgG et IgA, mais non IgM. Ceci est en accord avec les observations de la majorité des études portant sur les niveaux d'immunoglobuline dans d'autres pays. Les niveaux d'IgA sont particulièrement en relation avec l'étendue de la maladie, et significativement plus élevés chez les patients positifs à l'examen direct que chez les patients négatifs à l'examen direct. On n'a pas relevé de relation significative entre l'intensité de la sensibilité à la tuberculine et les niveaux d'immunoglobuline, sauf pour une faible tendance chez les patients ayant des niveaux d'IgA élevés, d'avoir de plus petites réactions cutanées à la tuberculine.

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