

SOME ASPECTS OF HUMORAL IMMUNITY IN EX-ASBESTOS-WORKERS

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A study was performed in a group of ex-chrysotile-asbestos-workers who had been exposed to asbestos for more than 10 years, and had an interval of more than 20 years since their first exposure. According to radiographic lung findings, two subgroups were formed, one with radiographic asbestosis (N=12) and the other without it (N=19). The following parameters were determined and compared with those of control group: serum protein fractions (electrophoresis), immunoglobulins (radioimmunoassay), rheumatoid factor (Waller-Rose) and erythrocyte sedimentation rate (Westergren).

In workers with asbestosis the mean values of total proteins and all globulin fractions were significantly higher. In the ones without asbestosis significantly higher mean values were those of total proteins, and of alpha-1-globulin and gamma-globulin fractions. No significant differences were found between individuals with asbestosis and those without it in terms of mean immunoglobulin values (IgA, IgM and IgG), but those were significantly higher in both subgroups than in controls. All mean values of serum proteins and immunoglobulins for the group of ex-workers and the control group were within the range of normal values. Erythrocyte sedimentation rate in workers with asbestosis (\bar{X} = 37.0 mm/h) was higher than in workers without it (\bar{X} = 26.1 mm/h) or among the controls (\bar{X} = 7.72 mm/h).

In conclusion, immunoglobulin values, even if changed because of asbestos exposure, cannot explain the development of asbestosis. Erythrocyte sedimentation rate should not be neglected in routine health examinations of ex-asbestos-workers.

Mechanisms of pathogenesis of diseases related to asbestos exposure remain unexplained. This statement is corroborated by the existence of various theories of pathogenesis (1-3). Recent concepts greatly emphasize the significance of immune processes in human body during exposure to asbestos dust (4).

Apart from serious limitations (5), experimental investigations *in vitro* (6-8) and *in vivo* (9, 10) support clinical and epidemiological studies (11-13) indicating changes in

the cellular and humoral immune responses in workers exposed to asbestos. Despite certain disagreement, a view prevails that exposure to asbestos induces suppression of cellular immunity (at least to some extent) and stimulates humoral immunity (4, 7, 11–13). These considerations provide a means of explaining some elements of the pathogenesis of fibrosis and malignant disorders related to asbestos dust exposure.

Another essential point concerns the answer to the question: is there a predisposition or susceptibility of the host to asbestos dust (7) or to dust of other origin (14). The answer is also of great practical importance in occupational medicine, i.e. in the prevention of diseases related to exposure to asbestos and other dust. Studies of the HLA system and some aspects of autoimmunity (ANA) as well as of organ-nonspecific antibodies (RFs) have not provided satisfactory answers.

Descriptions (1) of some pathological entities related to exposure to asbestos dust include not only the changes in serum immunoglobulins but also the disturbed ratio of albumins and globulins (1) and higher erythrocyte sedimentation rate (15, 16). The state of the immune system in persons after cessation of asbestos exposure is gaining in importance in this context, i.e. the question whether there are any differences between the immune states of persons with progressive (or developing) pathological changes (asbestosis) after cessation of asbestos exposure and those of people without pathological changes.

In our study of the population of ex-chrysotile-asbestos workers we determined the levels of serum immunoglobulins, serum protein fractions and rheumatoid factor (Waalser-Rose) with a view to discovering possible differences from the healthy population as well as differences between workers with radiographic asbestosis and those without it.

SUBJECTS AND METHODS

This study is part of a broader study (17) into the state of health of chrysotile factory workers. The results cover a group of ex-workers selected by the following criteria: a period from the first exposure twenty years or longer, duration of exposure ten years or longer, and at the time of cessation of exposure, small irregular opacities, category of profusion 1/1, not found radiographically (18).

All workers took the following tests: chest X-ray (18), erythrocyte sedimentation rate (Westergren), total proteins (biuret method), serum protein fractions (electrophoresis on acetate cellulose), serum immunoglobulins IgA, IgM and IgG (radioimmunodiffusion) and rheumatoid factor (Waalser-Rose). Exposure to asbestos was assessed qualitatively, by duration of exposure, because of lack of data for quantitative assessment (17).

According to radiographic findings, the examined group was further subdivided: A – with radiographic asbestosis and NA – without radiographic asbestosis. Data are shown in Table 1. Mean serum proteins values are expressed in g/L; differences were tested through t-test, with SD previously determined by F-test.

The control group consisted of 36 healthy individuals matched by age and sex, without any asbestos dust exposure.

Table 1

Age, duration of exposure and period since first exposure to chrysotile asbestos in ex-workers

Examined group	Age	Duration of exposure	Period since first exposure
With small irregular opacities, subgroup A (N = 12)	54.58 ± 7.56	20.42 ± 4.78	26.17 ± 4.11
Without small irregular opacities, subgroup NA (N = 19)	56.63 ± 6.20	19.80 ± 4.78	26.21 ± 3.31

Table 2

Serum protein levels (g/L) in the examined and control groups

Serum proteins	Subgroup A		Subgroup NA		Control	
	\bar{X}	SD	\bar{X}	SD	\bar{X}	SD
Total proteins	76.83	4.41	73.06	3.30	67.17	3.98
Albumins	36.00	3.02	37.92	2.54	39.29	4.07
Alpha-1-globulins	2.48	0.52	2.50	0.54	2.09	0.36
Alpha-2-globulins	7.59	0.68	7.09	1.33	6.77	1.21
Beta-globulins	10.58	1.94	9.50	1.10	8.95	1.09
Gamma-globulins	17.79	3.22	15.77	2.63	10.65	2.98

Table 3

The values of t-test for serum proteins in the examined and control groups

Serum proteins	A : C		NA : C		A : NA	
	t-test	p <	t-test	p <	t-test	p <
Total proteins	7.09	0.001	5.17	0.001	2.594	0.02
Albumins	1.01	n. s.	1.23	n. s.	0.07	n. s.
Alpha-1-globulins	2.85	0.01	3.19	0.005	1.19	n. s.
Alpha-2-globulins	2.23	0.05	0.90	n. s.	1.19	n. s.
Beta-globulins	3.63	0.001	1.57	n. s.	3.24	0.001
Gamma-globulins	7.05	0.001	5.92	0.001	1.82	n. s.

RESULTS

Our study shows (Table 1) that 12 workers (38.7%) – subgroup A, developed radiographic asbestosis after cessation of exposure.

For workers from subgroup A (Tables 2 and 3) the means of total serum proteins were statistically significantly higher ($p < 0.001$) than for the control group and subgroup NA ($p < 0.002$). For subgroup NA, the mean serum protein values were also statistically significantly higher than for the control group ($p < 0.001$).

However, there were no statistically significant differences in the means of serum albumins within the examined subgroups or between the subgroups and the controls.

All average values of serum globulin fractions in subgroup A were statistically significantly higher than those of the controls ($p < 0.001$, except for alpha-2-globulin with $p < 0.05$). The values of serum globulin fractions for subgroups A and NA were not significantly different except for the average value of beta-globulin ($p < 0.001$). The values of serum globulin fractions for subgroup NA were statistically significantly higher (alpha-1-globulin $p < 0.005$ and gamma-globulin $p < 0.001$) than for the control group.

Average values of serum immunoglobulins for subgroups A and NA were statistically significantly higher than the control values ($p < 0.02$ to $p < 0.001$). There were no statistically significant differences between the subgroups (Tables 4 and 5).

Table 4

Serum immunoglobulin levels (IgA, IgM and IgG) in the examined and control groups

Serum immunoglobulins	Subgroup A		Subgroup NA		Control	
	\bar{X}	SD	\bar{X}	SD	\bar{X}	SD
IgA (g/L)	2.31	0.27	2.25	0.24	1.94	0.43
IgM (g/L)	1.45	0.23	1.53	0.25	1.28	0.21
IgG (g/L)	12.98	2.39	13.39	1.30	10.67	1.98

Table 5

The values of t-test for serum immunoglobulins in the examined and control groups

Serum immunoglobulins	A : C		NA : C		A : NA	
	t-test	p <	t-test	p <	t-test	p <
IgA (g/L)	2.85	0.01	2.90	0.01	0.64	n. s.
IgM (g/L)	2.49	0.02	4.04	0.001	0.88	n. s.
IgG (g/L)	3.32	0.005	5.36	0.001	0.61	n. s.

Table 6
The erythrocyte sedimentation rate in the examined and control groups

Examined groups	Erythrocyte sedimentation rate (mm/h)							
		0-9	10-19	20-29	30+	\bar{X}	SD	range
Subgroup A	n	—	—	6	6	37.0	16.78	21-73
	%			50.0	50.0			
Subgroup NA	n	2	5	7	5	26.1	16.96	3-67
	%	10.5	26.5	37.0	26.5			
Control	n	24	9	3	—	7.7	5.72	1-22
	%	66.5	25.0	8.5	—			

The average values of total serum proteins and certain fractions (albumin, globulin and immunoglobulin) were within the range of normal values (19) for the examined subgroups and the control group alike.

The only two workers with positive Waaler-Rose test (1:64 and 1:128) were in subgroup NA. The means of the erythrocyte sedimentation rate in mm/h are given in Table 6. For individuals with asbestosis ($\bar{X}=37.0$ mm/h) the means were higher than for individuals without asbestosis ($\bar{X}=26.1$ mm/h) or for the control group ($\bar{X}=7.72$ mm/h).

DISCUSSION

Previous studies (17) show that the process of fibrogenesis develops even after cessation of asbestos exposure. According to the present investigations (20) the exposure intensity was very high, the average period of latency was 26 years and the period after cessation of asbestos exposure was six years on the average.

Our results support studies (1) dealing with the disturbed albumin-globulin ratio which is the outcome, according to our investigations, of increased globulin fractions. Although we have excluded (by questionnaire and physical examinations) chronic liver diseases, nephrotic syndrome and chronic inflammatory rheumatism, we are not sure that all findings concerning serum globulin and immunoglobulin fractions can be ascribed to asbestos dust exposure, i.e. to the immune response to asbestos dust.

It should be pointed out that except for the beta-globulin values (which can be related to hyperlipoproteinaemia or partly to the immunoglobulin and complement system) no significant differences have been found between individuals with asbestosis (with progressive radiographic changes) and those without it (without progression) in terms of values of serum globulin and immunoglobulin fractions. Statistically significant differences in average values of serum immunoglobulins in workers exposed to asbestos, compared with the control group, support those studies (11,12) that emphasize stimulation of humoral immune response. Our results (with all their

limitations) show that causes of lung asbestosis should be sought among other factors as well. It is probably not the matter of one-way stimulation of humoral immune response, but most likely of the polyclonal one (1, 7).

Further comprehensive investigation in ex-workers, of the complement system, secretory IgA (in BAL), subclasses IgG and T-lymphocyte system (and cellular immune response), as well as of beta-globulin factors, will probably complete the present picture. The same applies to the possible predisposition or susceptibility of the host (HLA system, autoimmunity etc.). Although erythrocyte sedimentation rate tests are highly non-specific (11, 12, 21), the rate, as our results indicate, should not be neglected in investigations of the health state of asbestos workers, for it can be a useful guide in further studies.

Our results indicate that workers with longer duration of exposure (of high intensity) could develop asbestosis after cessation of exposure. In individuals with radiographic asbestosis, as compared with the control group, significantly higher average values of serum globulin fractions were found (although within the range of normal values). Formerly exposed workers with no sign of radiographic asbestosis had significantly higher values of alpha-1- and gamma-globulin than the controls.

Differences in values of serum immunoglobulin fractions (IgA, IgM and IgG) among individuals with and without asbestosis were statistically non-significant, but they were significantly higher compared with the control group. The findings indicate that the pathogenesis of asbestosis probably includes other factors which should be investigated as well. The mean values of serum immunoglobulins (IgA, IgM and IgG) for both subgroups and the controls remained within the range of normal values.

The results could be related to the prolonged stimulation of humoral immunity after cessation of asbestos exposure, but the investigated parameters do not reveal possible mechanisms of fibrogenesis. Erythrocyte sedimentation rate, although a non-specific test, could point to the presence or progression of pathological pleuropulmonary changes after cessation of exposure.

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Sažetak

NEKE KARAKTERISTIKE HUMORALNOG IMUNITETA KOD BIVŠIH RADNIKA INDUSTRIJE AZBESTA

Ispitana je grupa od 31 bivšeg radnika fabrike koja prerađuje hrizotilni azbest. Prema radiografskom nalazu na plućima grupa je podjeljena na dve podgrupe: A (N=12) koja pokazuje radiografsku azbestozu (koja se razvila posle prekida ekspozicije) i NA (N=19), kod koje nije radiografski utvrđena progresija niti azbestoza.

Ispitivane su vrednosti proteinskih frakcija u serumu, imunoglobulina A, M i G, RFs i brzina sedimentacije eritrocita i poređene sa kontrolom (N=36 zdravih osoba).

Vrednosti ukupnih proteina i svih globulinskih frakcija kod podgrupe A su značajno veće od onih kontrolne grupe, dok su u odnosu na podgrupu NA značajno veće vrednosti beta-globulinske frakcije. Kod podgrupe NA vrednosti ukupnih proteina, alfa-1 i gama-globulina su značajno veće od onih u kontrolnoj. Vrednosti svih određivanih serumskih imunoglobulina se međusobno

značajno ne razlikuju kod podgrupa A i NA, ali su statistički značajno veće od kontrolne grupe (iako su prosečne vrednosti podgrupa i kontrole u rangu normalnih vrednosti). Brzina sedimentacije eritrocita kod podgrupe A je veća nego kod podgrupe NA i kontrole.

U zaključku možemo reći da promenjene vrednosti imunoglobulina ne mogu objasniti patogenezu azbestoze. Sedimentaciju eritrocita ne smemo prevideti u rutinskim pregledima radnika izloženih azbestu.

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