Clinical picture of patients with the undetectable serum IgE and low serum IgE in a retrospective evaluation of patients of the Opole Regional Hospital (2013-2023)

Abstract:

Over the period 01/01/2013 until 31/08/2023, 13 907 total plasma IgE determinations were performed in the analytical laboratory of the Provincial Hospital in Opole.
Among these determinations, there were 377 results below 2.0 U/l (in 279 patients), with the ultra-extremely low results (<0.1 U/l), i.e. virtually undetectable, in 65 (in 44 patients).
The clinical picture of patients with the ultra-extremely low (undetectable) IgE (defined as <0.1 U/l) - group 1 and the low IgE (defined as <2.0 U/l), divided into 4 ranges - 0.1-0.5; 0.6 -1.0; 1.1-1.5; 1.6-1.9 U/l - the group 2, 3, 4 and 5 respectively - was compared.
Results:
Health problems, defined as a syndrome of immune dysfunction, occurred more frequently in the groups with the ultra-low (virtually undetectable) IgE (<1.0) than in the group with the low IgE (0.1 - 1.9) level, suggesting primary immune deficiency in these patients. This is also supported by the fact that the group 1 was younger than the others combined, and at the same time 'sicker' than the other groups.

In this group - 97 patients had serum IgE determinations at least twice during the analysed period - in 20 patients at least one of the repeated serum IgE results was higher than 10 U/l, in the remaining ones - in 17 patients it was in the range (2-10 U/l), in the remaining 60 patients the results of repeated serum IgE determinations did not exceed 2 U/l.

Conclusions:
For the purpose of talking about IgE deficiency as an indicator of a predisposition to neoplastic diseases, it would be necessary to carry out screening tests at least 3 times, in the identified age groups, e.g. every 10 years, from the age of 5 years.
This would make it possible to determine - whether the IgE deficiency is primary or secondary. Primary, i.e. originally predisposing to the development of neoplastic diseases and being a part of primary immunodeficiency, or secondary - as a symptom of 'depletion' of the immune system.
The incidentally detected low serum IgE needs to be verified.

Key words: ultralow/undetectable IgE plasma level (<0.1 U/l), extremely low IgE plasma level (<2.0 U/l), low IgE plasma level.

Introduction

Interest in the significance of low plasma total IgE levels has been growing in the recent years due to data demonstrating its relationship to immunodeficiency syndromes and susceptibility to neoplastic diseases (1, 2, 3, 4, 5, 6). In both cases, there is a broad concept of immune dysfunction syndrome. High levels of total IgE, in turn, are thought to improve a prognosis in the selected groups of oncology patients. Furthermore, there are emerging perspectives for the use of allegro-oncological knowledge in the oncology treatment processes and the side effects of immunotherapy of neoplastic diseases (7, 8, 9, 10).
Awareness of differences in response to treatment depending on blood IgE levels may influence the individualisation of treatment for the specific conditions (11).

The reference value for plasma IgE levels is values below 100 U/l - 2-100 U/l. In the literature, values below 2.0 - 2.5 U/l are considered low or extremely low levels of total IgE.

As the group of individuals with total IgE values below 2.0 - 2.5 U/l may be clinically significantly heterogeneous due to the presence of tissue IgE, it is suggested that IgE values below this limit should be more accurately determined (5).

In a previous study comparing a group with the ultra-extremely low IgE level (<0.1 U/l), i.e. virtually undetectable, with a group with the extremely high IgE level (>10,000 U/l), a proposal was made that the IgE values <0.1 U/l should be defined as the ultra-extremely low (or undetectable), values between 0.1 and 0.5 as the extremely low and values between 0.6 and 2.0 as the low ones (12).

In the retrospective study presented here, it was decided to compare the groups clinically - with the ultra-extremely low IgE levels (<0.1 U/l), i.e. virtually undetectable and the low IgE (defined as >0.1 to <2.0 U/l).

Material and Methodology

Within the period 01/01/2013 until 31/08/2023, 13 907 total plasma IgE determinations were performed in the analytical laboratory of the Provincial Hospital in Opole.
Assuming the data quoted above, among these determinations there were 377 results below 2.0 U/l (in 279 patients), while the ultra-extremely low results (<0.1 U/L), i.e. practically undetectable, were 65 (in 44 patients).

A comparison was decided to be made between the clinical picture of patients with the ultra-extremely low (undetectable) IgE (defined as <0.1 U/l) - the group 1 and the low IgE (defined as <2.0 U/l), divided into 4 ranges - 0.1-0.5; 0.6 -1.0; 1.1-1.5; 1.6-1.9 U/l - the groups 2, 3, 4 and 5 respectively.

Results

In order to compare the study samples, statistical analyses were performed using the IBM SPSS Statistics 29. The analyses used included Student's t-test for independent samples, one-way analysis of variance and chi-square test of independence. The significance level was taken as the threshold $\alpha = 0.05$, the effect size was interpreted according to Cohen *(Cohen, J.,1992. A power primer. Psychological Bulletin, 112(1), 155–159. https://doi.org/10.1037/0033-2909.112.1.155).*

In the first instance, differences between all compared groups were calculated for nominal variables using the chi-square test of independence (table 1) and for the age using one-way analysis of variance (figure 1). When differences were observed with the chi-square test, the significance of the differences was calculated using the Bonferroni correction for multiple pairwise comparisons. Parameters assessed were age, sex, place of hospitalisation (suggesting the most significant health problem), prevalence of bronchial asthma/chronic obstructive pulmonary disease (COPD), neoplastic disease including lymphoma, immune dysfunction syndrome, atopic dermatitis (AD), bronchiectasis, sarcoidosis, psoriasis, granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis).

Table 1. Clinical parameters evaluated in each group of patients: with the ultra-extremely low (undetectable) IgE (defined as <0.1 U/l) - the group 1 and the low IgE (defined as <2.0 U/l), divided into 4 ranges - 0.1-0.5; 0.6 -1.0; 1.1-1.5; 1.6-1.9 U/l - the groups 2, 3, 4 and 5, respectively.

Differentiation of the study groups in terms of the variables tested

Variable	Group 1	Group 2	Group 3	Group 4	Group 5	χ^2	df	p	*V*

Sex	M	18 (0.41)	23 (0.39)	19 (0.26)	33 (0.41)	24 (0.35)	4.53	4	0.339	0.12
	K	26 (0.59)	36 (0.61)	53 (0.74)	47 (0.59)	44 (0.65)				
Unit	OP	30 (0.68)	38 (0.64)	54 (0.75)	54 (0.68)	50 (0.74)	21.46	16	0.161	0.13
	OD	3 (0.07)	8 (0.14)	3 (0.04)	7 (0.09)	6 (0.09)				
	OH	8 (0.18)	9 (0.15)	13 (0.18)	10 (0.13)	6 (0.09)				
	OCW	0 (0.00)	4 (0.07)	1 (0.01)	2 (0.03)	1 (0.01)				
	Other	3 (0.07)	0 (0.00)	1 (0.01)	7 (0.09)	5 (0.07)				
Asthma/COPD	No	34 (0.77)	40 (0.68)	41 (0.57)	50 (0.63)	54 (0.79)	10.92	4	0.027	0.18
	Yes	10 (0.23)	19 (0.32)	31 (0.43)	30 (0.38)	14 (0.21)				
Neoplastic disease	No	32 (0.73)	38 (0.64)	40 (0.56)	59 (0.74)	57 (0.84)	14.90	4	0.005	0.21
	Yes	12 (0.27)	21 (0.36)	32 (0.44)	21 (0.26)	11 (0.16)				
Lymphoma	No	38 (0.86)	50 (0.85)	57 (0.79)	68 (0.85)	56 (0.82)	1.48	4	0.830	0.07
	Yes	6 (0.14)	9 (0.15)	15 (0.21)	12 (0.15)	12 (0.18)				
Immunological dysfunctions	No	4 (0.09)	7 (0.12)	10 (0.14)	55 (0.69)	59 (0.87)	144.54	4	<0.001	0.67
	Yes	40 (0.91)	52 (0.88)	62 (0.86)	25 (0.31)	9 (0.13)				
AD	No	42 (0.95)	52 (0.88)	68 (0.94)	79 (0.99)	68 (1.00)	13.25	4	0.010	0.20
	Yes	2 (0.05)	7 (0.12)	4 (0.06)	1 (0.01)	0 (0.00)				
Bronchiectasis	No	34 (0.77)	55 (0.93)	60 (0.83)	75 (0.94)	66 (0.97)	16.83	4	0.002	0.23
	Yes	10 (0.23)	4 (0.07)	12 (0.17)	5 (0.06)	2 (0.03)				
Sarkoidosis	No	42 (0.95)	54 (0.92)	67 (0.93)	72 (0.90)	64 (0.94)	1.66	4	0.799	0.07
	Yes	2 (0.05)	5 (0.08)	5 (0.07)	8 (0.10)	4 (0.06)				
Psoriasis	No	44 (1.00)	56 (0.95)	71 (0.99)	77 (0.96)	67 (0.99)	3.95	4	0.412	0.11
	Yes	0 (0.00)	3 (0.05)	1 (0.01)	3 (0.04)	1 (0.01)				
Granulomatosis with polyangiitis	No	41 (0.93)	54 (0.92)	69 (0.96)	76 (0.95)	66 (0.97)	2.35	4	0.671	0.09
	Yes	3 (0.07)	5 (0.08)	3 (0.04)	4 (0.05)	2 (0.03)				

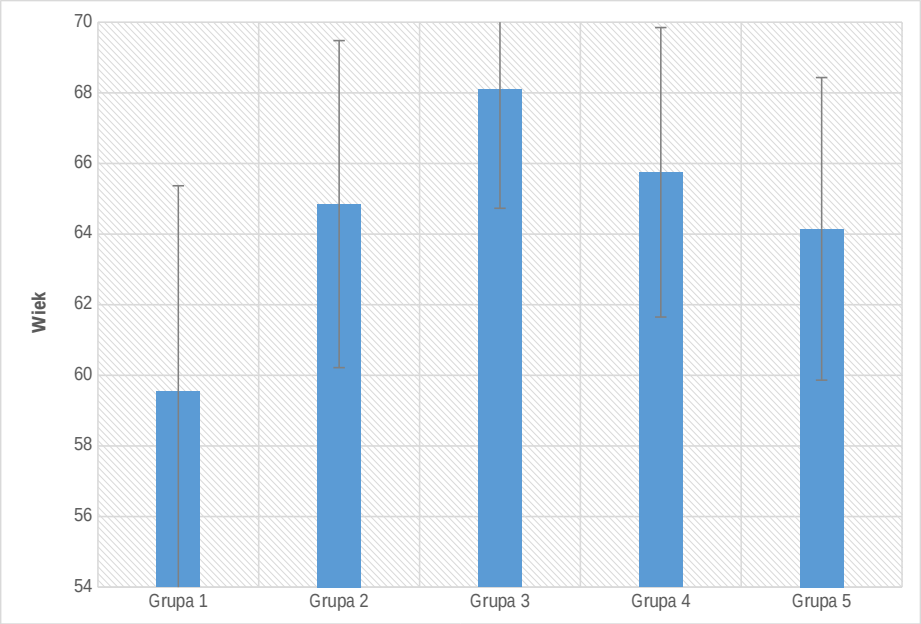
Annotation. n(%) - number of observations (percentage of observations); χ^2 - result of a chi-square test; df - number of degrees of freedom; p - statistical significance; V - effect size.

OP – pulmonology department, OD – dermatology department, OH – haematology department, OCW – internal diseases department.

Analysis of the differences in terms of individual nominal variables (Table 1), revealed a lack of statistically significant differences for sex and individual, and no differences were observed in the frequency of diseases such as lymphoma, sarcoidosis, psoriasis and granulomatosis with polyangiitis. Bronchial asthma was found to be the least frequent in group 5 (approx. 21%) compared to the group 3 (approx. 43%), where it occurred most frequently. The groups 1, 2, 4 were intermediate in terms of the number of people experiencing asthma (approx. 31%) and did not differ from the extreme groups. Similarly, neoplastic disease, irrespective of the starting point, was most common in the group 3 (approx. 44%) compared to group 5 (approx. 16%), while no differences were observed in the other groups, with the rates of neoplastic diseases ranging from 26% to 36%. Immune dysfunctions were less frequent in the groups 4 (approx. 31%) and 5 (approx. 13%) compared to the groups 1, 2 and 3, where the percentage of dysfunctions was approx. 90%. Analysing the results in terms of AD, it was found that the condition was most common in the group 2 (approx. 12%) compared to the group 5, where it was not present at all (0%), the other groups ranged from 1% to 6% and did not differ from the extreme groups. Bronchiectasis in turn, was observed most frequently in the group 1 (approx. 23%) and least frequently in group 5 (approx. 3%), while no significant differences were observed in the other groups and, on average, this condition occurred in 10% of individuals. Additional analysis also showed that there were no statistically significant differences in the age of the groups compared, $F(4.318) = 1.66$; $p = 0.160$; $\eta^2 = 0.02$ (figure 1).

Figure 1

Age differentiation in the groups compared (Key: Wiek-Age, Grupa-Group)



Annotation. Bars for errors represent 95% confidence intervals of mean scores.

In the next step, a contrast analysis was performed between the group 1 and the aggregated results of the group 2 - 5. A comparison of nominal indicators was performed using the chi-square test of independence, and the results are presented in the Table 2. A comparison of ages was performed using the Student's t-test for independent samples, and the results are presented in the figure 2.

Table 2 Clinical parameters evaluated in each patient group: with ultra-extremely low (undetected) IgE (defined as <0.1 U/l) - the group 1 and low IgE (defined as <2.0 U/l), divided into 4 ranges - 0.1-0.5; 0.6 -1.0; 1.1-1.5; 1.6-1.9 U/l - the groups 2, 3, 4 and 5 respectively (this time a total of 2-5)

Contrast analysis of the groups studied in terms of the variables tested

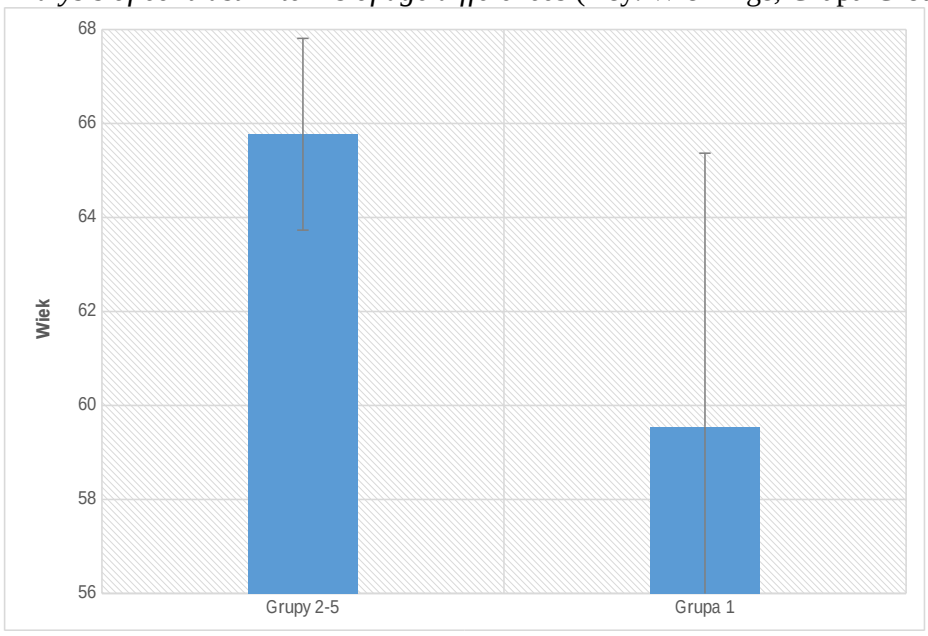
Variable		Group 1	Groups 2-5	χ^2	df	*p*	φ/*V*
Sex	Men	18 (0.41)	99 (0.35)	0.48	1	0.487	0.04
	Women	26 (0.59)	180 (0.65)				
Unit	OP	30 (0.68)	196 (0.70)	2.34	4	0.673	0.09
	OD	3 (0.07)	24 (0.09)				
	OH	8 (0.18)	38 (0.14)				
	OCW	0 (0.00)	8 (0.03)				
	Other	3 (0.07)	13 (0.05)				
Asthma	No	34 (0.77)	185 (0.66)	2.09	1	0.148	0.08
	Yes	10 (0.23)	94 (0.34)				
Neoplastic disease	No	32 (0.73)	194 (0.70)	0.18	1	0.668	0.02
	Yes	12 (0.27)	85 (0.30)				
Lymphoma	No	38 (0.86)	231 (0.83)	0.35	1	0.556	0.03
	Yes	6 (0.14)	48 (0.17)				
Immunological dysfunctions	No	4 (0.09)	131 (0.47)	22.40	1	<0.001	0.26
	Yes	40 (0.91)	148 (0.53)				
AD	No	42 (0.95)	267 (0.96)	0.01	1	0.941	<0.01
	Yes	2 (0.05)	12 (0.04)				

Bronchiectasis	No	34 (0.77)	256 (0.92)	8.69	1	0.003	0.16
	Yes	10 (0.23)	23 (0.08)				
Sarcoidosis	No	42 (0.95)	257 (0.92)	0.62	1	0.432	0.04
	Yes	2 (0.05)	22 (0.08)				
Psoriasis	No	44 (1.00)	271 (0.97)	1.29	1	0.255	0.06
	Yes	0 (0.00)	8 (0.03)				
Granulomatosis with polyangiitis	No	41 (0.93)	265 (0.95)	0.25	1	0.619	0.03
	Yes	3 (0.07)	14 (0.05)				

Annotation. *n*(%)– number of observations (percentage of observations); χ^2 - result of a chi-square test; df - number of degrees of freedom; p - statistical significance; V - effect size for the tables larger than 2x2.
Abbreviations – OP – pulmonology department, OD – dermatology department, OH – haematology department, OCW – internal diseases department

The analyses performed (Table 2), showed that only the presence of immune dysfunctions and bronchiectasis demonstrated statistically significant differences. Immune dysfunctions were present in 91% of subjects in the group 1, while in the groups 2 - 5, just over 50% of subjects were observed to have immune dysfunctions. In the case of bronchiectasis, the prevalence of this condition was observed to be significantly higher for the group 1 (approx. 23%) compared to the groups 2-5 (approx. 8%). Furthermore, it appeared that those in groups 2-5 were older by an average of six years compared to those in the group 1, $t(321) = 2.17$ 95% *CI* [0.57; 11.88]; $p = 0.031$; $d = 0.35$ (figure 2).

Figure 2
Analysis of contrast in terms of age differences (Key: Wiek-Age, Grupa-Group)



Annotation. Bars for errors represent 95% confidence intervals of mean scores.

In the material under study, serum IgE determinations were not part of routine, repeated testing. Hence, in some individuals, the serum IgE was determined once, in spite of several hospitalisations or visits to hospital outpatient clinics, in others repeatedly (97 of 323 patients).

In this group of 97 patients (with at least one IgE result <2.0 U/l) - in 20 patients at least one of the repeated serumIgE results was higher than 10 U/l (table 3), of the remainder - in 17 patients it was

in the range (2-10 U/l), in the remaining 60 the repeated serum IgE level determinations did not exceed 2 U/l.

Table 3. Characteristics of individual patients with the incidentally low serum IgE<2.0 U/l who had more than one IgE determination during the study period and at least one of the determinations was higher than 10 U/l.

	Sex/age at the time the ultra-low level of IgE was determined	Health problems according to medical records	Number of the IgE determinations and a range of values	Main (most frequent) place of hospitalisation / treatment
1	K 69	Microcellular carcinoma of the right lung, decrease in the IgE level during dissemination - can be interpreted as a symptom of depletion of the immune system	3x 0.4 – 345, chronologically: 187 – 345 0.4	OP
2	K 73	Adenocarcinoma of the right lung - subsequent progression - metastasis to the left lung and adrenal glands; chronic obstructive pulmonary disease (COPD), renal cysts - can be interpreted as a symptom of immune depletion	2x 0.5 – 218.7, chronologically: 218.7 – 0.5	OP
3	K 81	Granulomatosis with polyangiitis (Wegener granulomatosis), bronchial asthma, chronic sinusitis, venous insufficiency of the lower limbs - can be interpreted as a symptom of depletion of the immune system	9x 0.5 – 82.6, chronologically: 82.6 – 1.1 -0.5	OP
4	K 85	Non-small cell cancer of the right lung, lower limb venous thrombosis, atrial fibrillation, old age - can be interpreted as a symptom of immune system depletion	2x 0.7– 12.5, chronologically: 12.5 – 0.7	OP
5	K 86	Granulomatosis with polyangiitis (Wegener granulomatosis), tuberculosis in anamnesis, osteoporosis, degenerative changes of the musculoskeletal system, pnemocystodosis - can be interpreted as a symptom of depletion of the immune system	4x 0.7 – 92.1, chronologically: 92.1 – 3.7 - 1.1 – 0.7	OP
6	K 73	Tumour of the left lung, bronchial asthma / COPD, emphysema, generalised atherosclerosis - can be interpreted as a symptom of depletion of the immune system	2x 73.3 – 0.8	OP
7	M 86	Granulomatosis with polyangiitis (Wegener granulomatosis), purulent arthritis, multilevel discopathy - can be interpreted as a symptom of depletion of the immune system	2x 1.1- 91.1 chronologically: 92.1 – 3.7 – 1.1	OP
9	M 73	Left lung tumour. Bronchial asthma/COPD, emphysema, generalised atherosclerosis – can be interpreted as a symptom of depletion of the	2x 73.3 – 0.8	OP

		immune system		
11	M 53	Tuberculosis recurrence, COPD, emphysema, fluid in left pleural cavity - increase in the IgE level during clinical improvement phase	2x 1.3 - 144	OP
12	M 71	Post-radiation pneumonia Small cell cancer of the right lung, bronchial asthma, atrial fibrillation, circulatory failure - increase in the IgE level during clinical improvement phase	2x 1.4 – 107.7	OP
13	K 73	COPD/Bronchial asthma, psoriasis - last highest result during the period of requiring hospitalisation for exacerbation of bronchial asthma and psoriasis; high variability of IgE levels - indicates significant lability of the immune system	13x 1.4 - 1200	OP
14	M 83	Bronchiolitis, idiopathic bronchiolitis with organising pneumonia, bronchial asthma, secondary immunodeficiency, generalised atherosclerosis	7x 1.5 - 13	OP
15	K 81	COPD, emphysema, chronic respiratory failure on home oxygen therapy, Graves-Basedow disease – can be interpreted as a symptom of depletion of the immune system	7x 101.2 – 1.4	OP
16	M 56	Pulmonary sarcoidosis, chronic renal failure, chronic venous insufficiency of the lower limbs	3x 38.6-1.6-24.0	OP
17	K 81	Tumour of the right lung, COPD, t2 DM - without histopathological diagnosis of the tumour, stable clinical condition	2x 1,6 – 47,4	OP
18	M 68	Idiopathic pulmonary fibrosis, chronic respiratory failure on home oxygen therapy, bronchiectasis, t2 DM, secondary immunodeficiency, listeriosis in anamnesis - increase in the IgE level during inflammatory exacerbation of chronic respiratory failure	3x 0,9 – 16,0 – 1,6	OP
19	K 71	Adenocarcinoma of the right lung Bronchial asthma - increase in the IgE level during asthma exacerbation	2x 1,8 – 485,5	OP
20	M 48	Granulomatosis with polyangiitis (Wegener granulomatosis), granulomatous otitis media, t2 DM - decrease in the IgE level during the period of clinical improvement	4x 27,4 – 0,4	OP

OP – pulmonology department, COPD – chronic obstructive pulmonary disease, t2 DM- type 2 diabetes mellitus

Discussion:

As mentioned above - the analysis of differences in terms of individual nominal variables (Table 1), revealed a lack of statistically significant differences in respect of sex and individual, and in

addition no differences were observed in the frequency of diseases such as lymphoma, sarcoidosis, psoriasis and granulomatosis with polyangiitis. Bronchial asthma appeared to occur least frequently in the group 5 (approx. 21%) compared to the group 3 (approx. 43%), where it occurred most frequently. The groups 1, 2, 4 had intermediate numbers of people experiencing asthma (approx. 31%) and did not differ from the extreme groups. Similarly, neoplastic disease, irrespective of the starting point, was most common in the group 3 (approx. 44%) compared to the group 5 (approx. 16%), while no differences were observed in the other groups, where the percentage of neoplastic diseases ranged from 26% to 36%. Immune dysfunctions were less frequent in the groups 4 (approx. 31%) and 5 (approx. 13%) compared to the groups 1, 2 and 3, where the percentage of dysfunctions reached approximately 90%
This supports the idea that the lower the serum IgE level, the greater the probability of immune dysfunction. Bronchiectasis, on the other hand, was observed most frequently in the group 1 (approx. 23%) and least frequently in the group 5 (approx. 3%), while no significant differences were observed in the other groups and, on average, this condition occurred in 10% of individuals. The distinctly more frequent occurrence of bronchiectasis in the group 1 indicates an impairment of the immune response to bacterial infections of the respiratory tract, which resulted in prolonged inflammation of the bronchi and destruction of the bronchial wall.

An additional analysis also showed that there were no statistically significant differences in terms of the age of the groups under comparison, $F(4.318) = 1.66$; $p = 0.160$; $\eta^2 = 0{,}02$ (figure 1).

The analyses comparing the group 1 with the groups 2-5 combined (Table 2), showed that only the presence of immunological dysfunctions and bronchial dilatation showed statistically significant differences. It turned out that immune dysfunction was present in 91% of the group 1 subjects, while in the groups 2-5, just over 50% of subjects were observed to have immune dysfunction. In the case of bronchiectasis, the prevalence of this condition was observed to be significantly higher for the group 1 (approx. 23%) compared to the groups 2-5 (approx. 8%). Moreover, it appeared that people in the groups 2-5 were older by an average of six years compared to those in the group 1, $t(321) = 2.17$ 95% *CI* [0.57; 11.88]; $p = 0.031$; $d = 0.35$ (figure 2).

Health issues, defined as a syndrome of immune dysfunction, were more common in the groups with the ultra-low (virtually undetectable) IgE level (<1.0) than in the group with the low IgE level (0.1 - 1.9), suggesting primary immune deficiency in these patients. This is also supported by the fact that the group 1 was younger than the others combined, but at the same time ‘sicker’ than the other groups.

Based on these observations, one can try to answer the question:
Randomly found the low serum IgE - IgE deficiency - primary or secondary?

For the purpose of referring to IgE deficiency as an indicator of predisposition to neoplastic diseases (1, 2, 3, 4, 5, 6), screening should be carried out at least 3 times, in the specific age groups, e.g. every 10 years, beginning at 5 years of age.
This would also make it possible to determine - whether the IgE deficiency is primary or secondary. Primary, i.e. originally predisposing to the development of neoplastic diseases and forming part of the primary immunodeficiency, or secondary - as a symptom of ‘depletion’ of the immune system.
The low serum IgE determined randomly requires a verification.

In the delimited group with the low IgE level, additional skin tests can be conducted to evaluate a deficiency of the tissue Ig (13, 14).

In the material under study, determinations of the serum IgE were not part of routine, repeated testing. Thus, in some patients, the serum IgE was determined once, despite several hospitalisations

or visits to the hospital outpatient clinics, in others it was determined repeatedly (97 of 323 patients). In this group of 97 patients - in 20 patients at least one of the repeated serumIgE results was higher than 10 U/l (table 3), of the others - in 17 patients it was in the range (2-10 U/l), and in the remaining 60 patients repeated determinations of the serum IgE levels did not exceed 2 U/l.

This observation may suggest that the IgE levels <0.1 U/l, found randomly, are more suggestive of primary immunodeficiency than levels between 0.1 and 2.0 U/l, where they are more probably suggestive of secondary immunodeficiency.

Conclusion

The low serum IgE level found incidentally does not allow to conclude whether the IgE deficiency is primary or secondary (as a symptom of 'depletion' of the immune system), and can be considered a poor prognostic factor, e.g. in chronic lymphocytic leukaemia (15). Its increase in subsequent studies argues for the secondary nature of a previous low level, but it can be considered a positive prognostic factor for regression of the underlying disease.

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