

STUDY ON THE SERUM LEVELS OF IMMUNOGLOBULINS IgG, IgM, IgA IN MALIGNANT HEMOPATHIES

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The immune response of the organism is associated with definite immunoglobulin types' formation (8, 9). The antibodies, resp. immunoglobulins turn to be factors of the natural and acquired protection of the organism. In the past few years, the surge of interest in their serum level changes in various affections has led to the more extensive application of immunologic methods for their determination and follow up (4, 5). Researches by many authors, and personal observations as well, show that quantitative changes in the serum levels of immunoglobulins occur in blood diseases too (1, 2, 3, 6, 7, 11, 12).

In this reports the results of purposeful studies on 122 patients with malignant hemopathies, undergoing treatment at the hematological clinic of the Medical Faculty — Varna, over the period 1971—1973, are described. Our aim has been to establish to what degree do quantitative changes in the serum level of immunoglobulins reflect the modifications in humoral immunity of the organism in various blood affections.

Material and Methods

The changes in serum level of the immunoglobulins IgG, IgM and IgA were traced out in the listed below systemic blood diseases: leukemia — total 55 patients (45.08 per cent), of them with acute leukemia — 22, chronic lymphatic leukemia — 21, chronic myelogenous leukemia — 12; in patients with malignant lymphoblastoma — totalling 31 (25.42 per cent), of them with lymphogranulomatosis — 21, lymphosarcoma — 4, retiotheliosarcoma — 6; in patients with reticulosis — totalling 22 (18.03 per cent), of them with myeloma — 9, benign reticulosis (infectious mononucleosis) — 3, idiopathic reticulosis — 10; in patients with hemorrhagic diathesis — totalling 8 (6.55 per cent), of them with hemophilia — 4, thrombocytopenia — 4; and in 6 patients (4.92 per cent) with polycythemia vera (erythremia).

According to sex the patients are distributed as follows: men — 84 (68.85 per cent), women — 38 (31.15 per cent), all with ages ranging from 16 to 88 years. Quantitative determination of the serum immunoglobulins was made after the method of Mancini and co-authors (10). Monospecific sera, obtained from the Center of Infectious and Parasitic Diseases in Sofia, Behringwerke (F. R. Germany) and Hyland (USA) were used. The mean values of serum immunoglobulins in 300 healthy subjects — blood donors from the district blood-transfusion station — Varna, served as controls. The

changes in the serum levels of immunoglobulins were checked in the early stage of the disease (onset), in the course of treatment, after treatment was completed, and during the recurrence period. In addition, the patients were subjected to the following paraclinical examinations: peripheral blood picture (hemoglobin, erythrocytes, leukocytes and differential count), erythrocyte sedimentation rate, hepatic flocculation tests (Weltmann and thymol turbidity test), total proteins and proteinogram, transaminases, alkaline phosphatase and fibrinogen.

Results and Discussion

The changes found in the serum levels of immunoglobulins in the various types of systemic blood diseases are summed up and presented in Figure 1.

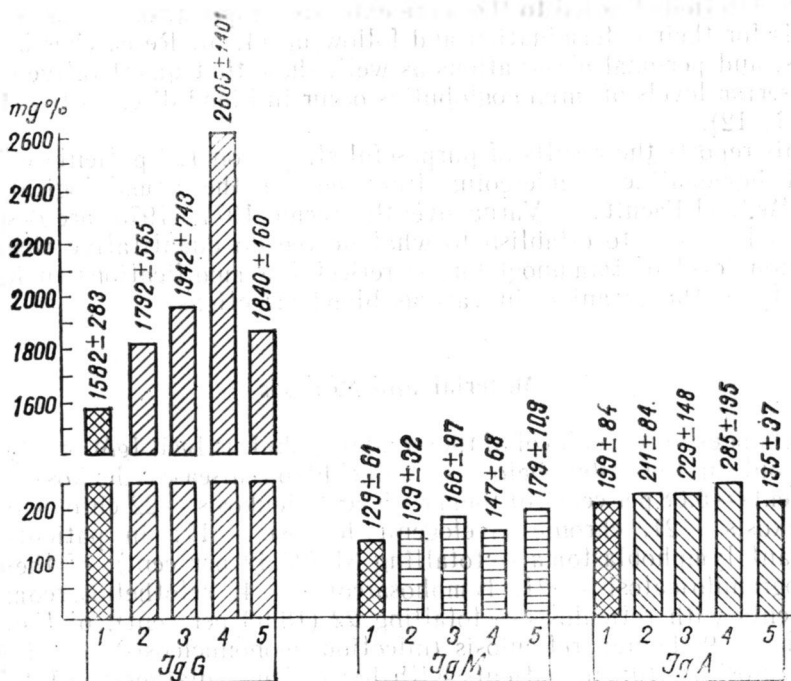


Fig. 1. Serum immunoglobulin changes in blood diseases.

1 - controls, 2 - leukemia, 3 - malignant lymphoblastomatosis, 4 - reticulosis, 5 - hemorrhagic diathesis.

In the leukemia group, the serum immunoglobulins show an overall increase in levels, better pronounced in class IgG and IgM ($p < 0.01$). In class IgA the rise is less pronounced as compared to IgA values in the controls ($p > 0.3$). By type of leukemia affection, the changes in immunoglobulins display the following peculiarities: in the acute leukemia group the mean

values of the three immunoglobulin classes are significantly increased ($p < 0.01$). In chronic lymphatic leukemia the mean values of IgG are moderately increased ($p < 0.05$), while the other two immunoglobulin classes — IgM and IgA — exhibit a fall of the serum level. The lowering is mostly marked in IgM (95 ± 10 mg, $p < 0.01$), while in IgA it is but slightly pro-

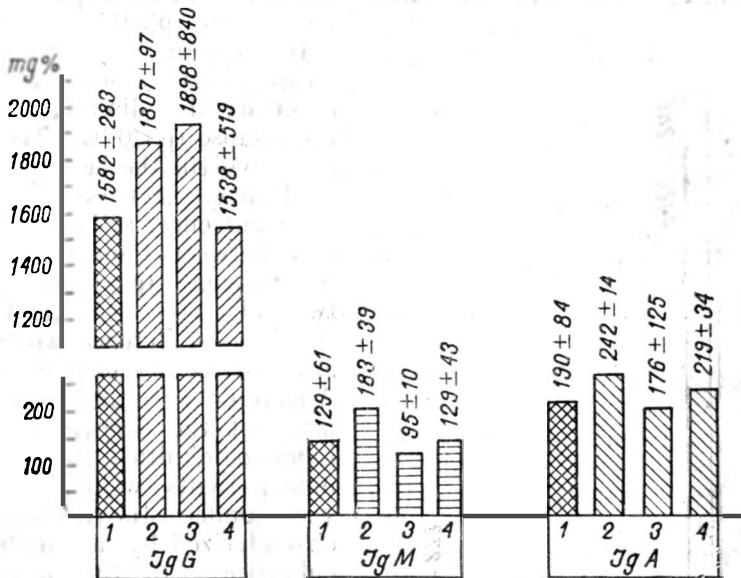


Fig. 2. Changes in the serum levels of immunoglobulins in leukosis.

nounced (176 ± 125 mg, $p > 0.3$). The data referred to are illustrated in Figure 2. In chronic myelogenous leukemia, the mean values are almost equal to those of the controls ($p > 0.8$). According to stage of the leukemia affection, the changes in immunoglobulins are characterized by the following peculiarities: in the early stages of the disease, the level of IgG class displays an insignificant rise in all three forms of leukemia (acute, chronic myelogenous and chronic lymphatic) — $p > 0.3$. At the onset of acute leukoses, the second class IgM is significantly increased as compared to controls (182 ± 94 mg %, $p < 0.01$). A rise in the mean values of IgA is also found in the same type of leukoses (249 ± 101 mg %, $p < 0.05$). In the early stage of chronic lymphatic leukemia, the serum level of IgM and IgA is reduced compared with the controls, with the difference in class IgM being significant (97 ± 21 mg %, $p < 0.01$). In chronic myelogenous leukemia, the changes in serum levels of the three immunoglobulin classes display values close to those of the controls. In the other stages of acute leukemia and chronic leukemia (before treatment, in the course of treatment, after treatment and during relapses) no essential changes in IgG and IgA are established ($p > 0.3$). Only IgM displays a reliable reduction of its level during the evolution of the disease, mostly manifested in chronic lymphatic leukemia (95 ± 67 mg %, $p < 0.01$).

$p < 0.01$). During recurrence, a reduction of IgA level is also established in chronic lymphatic leukosis (88 ± 39 mg %, $p < 0.01$).

Among the group of malignant lymphoblastomas, no essential changes in the three immunoglobulin classes are established, both relative to the summed up data concerning the entire group, and to the type and stage of the disease ($p > 0.3 - p > 0.9$).

In the reticulosis group, an increase of IgG is noted both at the onset of the disease, and during the relapse ($p < 0.05$). The IgG serum level in the beginning reveals a stronger increase than during the recurrence, although the difference between their mean values is insignificant ($p > 0.2$); the other two classes — IgM and IgA — show no difference worth noting as compared to controls ($p > 0.6$). A more detailed discussion will be made of the changes in the three immunoglobulin classes in the nine patients with myeloma disease under study, since they are characterized by a number of peculiarities. In the myeloma disease, the greatest increase recorded concerns the IgG class, both at the onset and during the recurrence of the condition (3269 ± 1849 mg % and 4480 ± 2286 mg %, $p < 0.01$). In the other two classes — IgM and IgA — the changes are insignificant in comparison with the controls ($p > 0.7$) (Fig. 3). Among the patients with myeloma, the gamma-myeloma type cases predominate (8 out of a total of 9 cases). The values of immunoglobulins for the three classes in the cited above

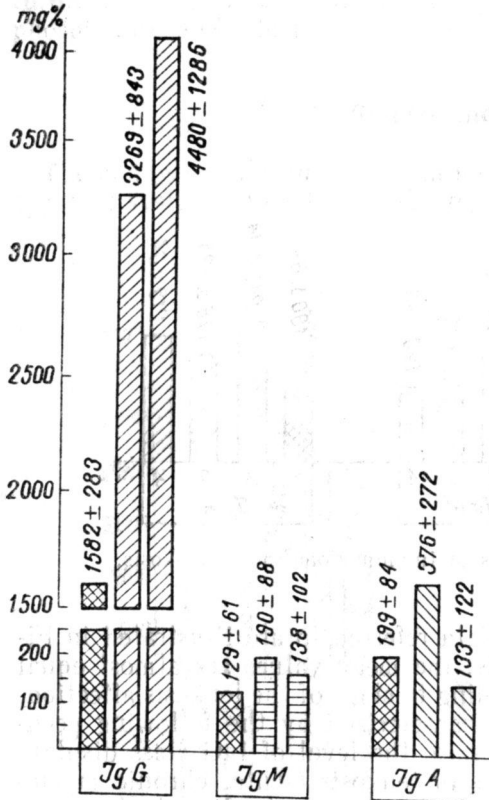


Fig. 3. Changes in serum immunoglobulins in myeloma disease.

patients with gamma-myeloma disease disclose a number of differences: three of the patients have increased IgG and IgA values, with the IgA being significantly increased up to 640 mg % ($p < 0.01$). In three of the patients there is a rise of the macroglobulin fraction, judged from the IgM increase.

Only in one of the myeloma patients rather low IgA values are found, as well as absence of the remaining two immunoglobulin classes. The plasma levels of IgG and IgA immunoglobulins in two cases with myeloma, followed up in dynamics, display a considerable reduction of their mean values following cytostatic therapy ($p < 0.05$). The highest IgG values (5800

mg %) are recorded in one of the patients with beta myeloma. The data submitted point to the fact that in part of the myeloma patients, it is a matter of monoclonal gammopathy, and in another part — of polyclonal gammopathy.

In the group of hemorrhagic diathesis (essential thrombocytopenia and hemophilia), a reliably increased IgG value is established both at the onset of the disease, and during the relapse ($p < 0.01$), with the difference between the mean immunoglobulin values in either of the cases being insignificant ($p > 0.03$). The other two classes — IgM and IgA — similarly do not show essential difference ($p > 0.3$). Among the polycythemia vera patients, certain fluctuations are established in all three classes of immunoglobulins with unessential differences as compared to controls ($p > 0.7$).

Interpretation of the changes in the other paraclinical indicators failed to affirm a definite interdependence between changes in their values and changes in the plasma immunoglobulins. Due to space restrictions, we are not in a position to deal more extensively with this particular issue in the present report.

The changes in the plasma level of immunoglobulins established among patients with malignant hemopathies may be classified, according to Waldenström, with the monoclonal and polyclonal gammopathies (7). They are produced as the result of chronic stimulation of the reticuloendothelial system, involving a great number of cellular lines (clones according to the clonal-selection theory of Burnett), with concomitant increase of all, or of a great number of the different immunoglobulin classes. In malignant hemopathies, after estimating the state of humoral immunity, due consideration should be given to the corticosteroid therapy applied in many of the diseases. As well known, corticosteroids inhibit both the function of the reticuloendothelial system, and the excess antibody production. Thus, the lower plasma level of IgM and IgA in chronic lymphatic leukosis might be explained. On the other hand, the strongly pronounced increase of IgA in some malignant hemopathies may be assumed as an expression of autoimmunization processes also, since it is universally known that IgA is a carrier of autoantibodies in the organism (8).

Conclusions

1. The level of plasma immunoglobulins from the three classes (IgG, IgM and IgA) in malignant hemopathies shows changes of the type of monoclonal and polyclonal gammopathies ($p < 0.01$).

2. In acute leukosis, the immunoglobulins are moderately increased; in chronic lymphatic leukosis, IgM and IgA display a reduction as compared to controls, and in chronic myelogenous leukosis the values of the three immunoglobulin classes prove to be close to those of the controls.

3. Among the patients with reticulosis, the IgG class shows a substantial increase in cases with myeloma, as much in the course of the disease, as in the relapse period.

4. In the other malignant hemopathies, the changes in the mean values of the plasma immunoglobulin levels for the three Ig classes are close to those of the controls, and do not show significant variations.

REFERENCES

1. Йорданова, Е., М. Радков, Р. Мишкова. Имунни изследвания при анемии, доклад на III научно-практ. конф. по хематология, Мед. ф-тет — Варна. —
2. Монеева, Р., Ф. Файнштейн, М. Хохлова, Э. Терентьева и др. Сравнительное изучение так называемой доброкачественной «моноклоновой» гаммопатии парапротеинемических ретикулезов, резюме от Мат. 44 науч. сес. ЦОЛИПК—СССР, М., 17—18, 5, 1973. —
3. Радков, М., Е. Йорданова. *Епид., микр. и инф. бол.*, 10, 1973, 1, 75—78. —
4. Христохо, Р. Возможность широка примена на радиарната имунодифузия. Сборник на труд. от VIII конгр. на лекарите от Македония, 2—4. 10. 1970, Охрид. —
5. Вгауп, Н. J. *Die Therapiewoche*, 17, 47, 1967, 1926. —
6. De Bass, C., F. Aiuti, A. Cirelli. *Boll. Soc. Ital. Biol. Sper.*, 40, 1964, 1977. —
7. Fine, J. M. *Rev. Prat.*, 18, 1968, 11, 1965—1967. —
8. Fleischmann, J. B. *Ann. Rev. Biochem.*, 35, 1966, 835. —
9. Klemm, D. *Med. Klinik*, 61, 1966, 1835. —
10. Mancini, G., A. Carbonara, J. Heremans. *Immunochemistry*, 2, 1965, 236. —
11. Mukhadze, M. G. II Meeting of the European and African Division of the International Society of Hematology, Prague, 27—29. 8. 1973, CSSR. —
12. Najman, A., A. Gerbal, C. Ropars. *Nouv. Rev. d'Hemat.*, 11, 1971, 3, 365—371.

ИССЛЕДОВАНИЕ СЫВОРОТОЧНЫХ УРОВНЕЙ ИММУНОГЛОБУЛИНОВ IgG, IgM И IgA ПРИ ЗЛОКАЧЕСТВЕННЫХ ГЕМОПАТИЯХ

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РЕЗЮМЕ

Чтобы проследить изменения в сывороточных уровнях иммуноглобулинов IgG, IgM и IgA при злокачественных гемопатиях, исследованы 122 больных, леченных в гематологической клинике Медицинского факультета — Варна, за период 1971—1973 г. Путем метода количественного определения иммуноглобулинов посредством радиальной иммунодиффузии по Манчини прослежены 55 больных лейкозом, 31 больной злокачественными лимфобластомами, 22 — ретикулезами, 8 — гемморегическими диатезами и 6 больных с истинной полицитемией. В результате исследования получены данные, которые указывают на наличие изменений в сывороточном уровне иммуноглобулинов при злокачественных гемопатиях типа моноклональных и поликлональных гемопатий, лучше всего выраженных у больных лейкозами и миеломной болезнью. При остром лейкозе иммуноглобулины всех трех классов умеренно увеличены, при хроническом лимфатическом лейкозе IgM и IgA — уменьшены, а при миелогенном хроническом лейкозе устанавливаются незначительные изменения иммуноглобулинов. Сильное увеличение иммуноглобулинов класса IgG устанавливается у больных миеломной болезнью, как во время болезни, так и при рецидиве.