Hyperglobulinaemic Purpura Associated with Splenomegalic Cirrhosis in Childhood. Contributions to the Pathogenesis of the Disease

By

J. Szamosi, Magda Osztovics and R. Backhausz

P. Heim Children's Hospital, and Institute for Serobacterological Production and Research "Human", Budapest

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Hyperglobulinaemic purpura was described and differentiated from macroglobulinaemia by Waldenström [35] as an affection of the lymphatic system where hyperglobulinaemia caused by viral infection would come first and this would damage the capillaries. Stefanini and Dameschek [33] also attribute a role to viral infection and think that the purpura is just a precursor to subsequent events.

Weise [40] collected 28 cases from the literature, including 17, in which hyperglobulinaemic purpura occurred in association with other diseases, among others with cirrhosis of the liver [6], chronic rheumatism [18], acute polyarthritis [35, 13], hepatopathy [29], and splenomegaly of uncertain aetiology [38, 36]. In the rest, the hyperglobulinaemic purpura was not associated with any other disease. Other papers to be mentioned are that by Gráf *et al.* [9] on a case of secondary purpura associated with leucaemia, as well as those by Rosenzweig *et al.* [27], Kay and Robertson [15], Klinghoffer *et al.* [16], Borovi-czeny *et al.* [4].

Report of a Case

V. M., a female patient suffering from so-called secondary hyperglobulinaemic purpura was 11 years of age when first admitted September 26, 1955. Since that time she has been readmitted several times (March 6—December 4, 1956; January 18—June 1, 1957; July 20, 1957—January 8, 1958) and has been re-examined every six months.

Previous diseases included measles, whooping cough, scarlet fever, pneumonia, hepatitis. Seven months before the first admission she had developed swelling and pain of both lower legs and ankle joints, and gingival bleedings. On admission extreme paleness, loss of weight, densely packed punctate haemorrhages and pigmentation marking the site of previous haemorrhages on both feet were noted. The gingiva was hyperaemic and bled at sites. The spleen was palpable and the liver reached 5 cm under the costal arc.

A few days following admission jaundice developed. It had been noted during the first weeks of her stay in the hospital that on taking blood samples the erythrocytes of the child agglutinated. She was blood group A_1, D pos. The direct and indirect Coombs tests were negative. The serum of the child agglutinated the erythrocytes of her own and those from a subject of the same group at a titre of 1 in 32, at +4° to 37° C.

The important laboratory findings have been tabulated. No changes were noted in bleeding and clotting time, differential blood count and erythrocyte resistance. X-rays of the chest, bones and the intestinal tract revealed no pathologic changes.

No Bence-Jones protein could be demonstrated in the urine. NPN was 25 mg per 100 ml, endogenous creatinine clearance 116 ml, average daily urine output 1000 g, dilution-concentration test 1001—1014. Except for a chronic cystitis, urologic examinations (intravenous and retrograde pyelography, cystoscopy) revealed no change.

The colloid lability tests were in accordance with the increase of globulins. The thymol flocculation test was 17—24 U; goldsol, 5; prothrombin, normal; galactose test, normal; serum alkaline phosphatase, 19 King units. Ultracentrifugation (made on three occasions) did not reveal an increase of macroglobulin. Cryoglobulin was not demonstrable. The Sia test was negative. The ionogram showed lower K (3.8 mEq) and alkali reserve (14—16 mEq) values. No signs of acidosis were noted.

During the first two years of observation th spleen was gradually increasing in size, to reach the umbilicus, whereas the liver was not enlarged. The purpura, presenting with itching, pain and swelling of the feet, occurred always with the same intensity at short intervals for $1^1/_2$ years, then its intensity diminished and the intervals became longer. It was not correlated with motor activity, exposure to heat or mechanical stimuli. Agglutination of the erythrocytes persisted unchanged throughout.

With the enlargement of the spleen a decrease took place in the leucocyte and thrombocyte counts (Table I). There was no correlation between the decrease in the thrombocyte count and the appearance of purpura.

Treatment consisted of the administration of prednisone, vitamins, liver preparations and transfusions of blood. Small doses of cortisone administered for short periods had produced no result during the first two years, then in 1957 following two long courses of prednisone purpura did not appear again, and for a while the ESR decreased; the level of total globulin and gamma globulin decreased, that of albumin increased in the serum; the level of total lipid and cholesterol increased in the serum, that of bilirubin decreased; and the plasmocyte count decreased in the bone marrow. Prior to prednisone treatment, in the sternal bone marrow (Dr. Körmendy) there was intense erythropoiesis and an increase in the number of reticulum cells (mainly of plasma cells).

The clinical picture suggested hypersplenism and hepatic changes. Splenectomy and liver biopsy were therefore done.

The operation took place December 16, 1957 (Horváth). A spleen of extreme size, an enlarged liver with nodular surface were revealed. Portal blood pressure was 360 mm water. There was no ascites. Because of the portal hypertension a portorenal shunt was made by suturing the omentum to the decapsulated left kidney, to achieve revascularization later.

Histologic study (Balogh) yielded the following evidence. In frozen sections the liver pattern was hardly discernible. The newly forming, sometimes multinuclear liver cell islets were surrounded by connective tissue and contained large numbers of Kupffer cells. The periportal connective tissue and its intrahepatic parts were thickened and hyalinised. Groups of mononuclear cells, including many mature and immature plasmocytes and a few leucocytes were seen around the bile ducts and the branches of the portal vein and hepatic artery. In the stained preparations connective tissue infiltrated by heparinocytes and leucocytes were visible. The spleen weighed 1870 g, had a tense capsule. There were many erythrocytes in the pulp. The Malpighian bodies were distant from one another, were bigger than the usual size and contained reticulum cells and many leucocytes. Some trabecules were

TABLE I

Some important laboratory findings during the observation period

Date	RBC	Hg%	WBC	Thrombocyte count	Serum-protein, Total g/100 ml	albumin (relative per cent)	$alpha_1$- globulins (relative per cent)	$alpha_2$- globulins (relative per cent)	beta-globulins (relative per cent)	gamma-globulins (relative per cent)	ESR mm/1h	Serum bilirubin mg/100 ml	Serum total lipid mg/100 ml	Serum cholesterol mg/100 ml	Treatment
Sept. 20, 1955	3,600,000	70	6200	250,000	10.8	26.0	4.98	11.45	9.77	47.80	120	4.75	160	100	
March 31, 1956	2,500,000	64	4000	102,000	10.5	17.45	4.64	10.98	23.55	43.0	150	3.0	180	100	May 17— May 29 ACTH 680 U.
June 2, 1956	3,500,000	69	6000	107,000	9.4	28.00	4.60	4.30	19.05	44.50	52	1.2	300	160	
January 28, 1957	3,000,000	52	5000	59,000	10.0	16.80	4.00	12.20	16.08	50.20	107	3.6	150	60	Feb. 1—March 25 Prednisone 470 mg. ACTH 270 U.
April 2, 1957	2,500,000	42	3800	40,000	8.7	14.5	4.64	9.1	20.46	51.3	62	3.0	290	220	
July 20, 1957	2,800,000	44	3600	40,000	10.0	15.08	4.50	10.53	18.80	51.00	96	3.8	160	90	July 29—Oct. 9 Prednisone 1215 mg
Oct. 15, 1957	3,300,000	50	4000	40,000	8.6	32.75	10.95	6.75	13.78	35.95	23	1.30	465	125	
							Splenectomy, December 16, 1957								
May 8, 1958	3,800,000	65	15,000	380,000	8.5	23.80	8.68	10.20	9.20	48.12	96	1.30	520	185	
Oct. 10, 1958	3,800,000	75	14,000	300,000	8.5	34.72	4.72	13.06	5.56	41.04	33	0.40	570	245	

thicker and there was an increased amount of fine connective tissue fibres. Mononuclear infiltration was visible near the hilum, between the almost preterminal rami.

After operation the child was well. The size of the liver decreased, purpura and jaundice did not reappear. The postoperative laboratory findings are presented in Table I.

Renal function improved parallel with the decrease of hyperproteinaemia; at present the result of the dilution-concentration test 1001—1020.

The child now at the age of 16 years attends school, but no signs of sexual maturation have appeared.

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The most outstanding feature in our case was hyperglobulinaemia, a condition which in the course of 19 years BERGSTEDT and LINGEN [1] observed in only 2 children with liver cirrhosis, while it occurred in 14 per cent of SCHMIDT's adult material [30]. It is more common with the splenomegalic form [31, 17]. SCHNEIDERBAUR [31] ascribed it to a change in reticuloendothelial function.

In our case there was an increase in the number of plasmocytes in the bone marrow and of Kupffer's cells in the liver. A similar observation has been described by SCHAFFNER *et al.* [28].

We continued to study the patient, in order to determine

a) the specificity of the serum globulins the level of which was increased; and

b) the effect of the increased globulin concentration upon the level of natural antibodies.

To determine the specificity of globulins, immuno-diffusion methods were employed. As antisera, precipitating immune serum from rabbits inoculated previously with serum taken from the patient on August 11, 1956, or with sera from normal subjects, were used. The sera from the rabbits inoculated with the patient's blood will be denoted anti-V. M.

Immunoelectrophoretic study of the anti-V. M. serum showed the presence of 7 different antibodies, notably 1 anti-albumin, 1 anti-alpha$_1$-, 1 anti-alpha$_2$-, 2 anti-beta$_1$-, 2 anti-beta$_2$- and anti-gamma-globulins.

Blood for immunological study was obtained on twelve occasions from the patient in the period of from April 23, 1956, to April 9, 1959. The antigenicity of the single serum samples was tested by the two-dimensional double diffusion technique of OUCHTERLONY. From the relative positions of the lines of precipitation in the agar plates conclusions have been drawn as to the relationship between the antigen-antibody systems.

According to the evidence obtained, the serum of our patient contained no antigen that would not occur in normal serum.

The quantitative assay for antigens involved the use of OUDIN's methods, the simple, one-dimension comparative diffusion technique and the simple, one-dimension tube method. The scheme of the comparative analysis according to OUDIN is presented in *Fig. 1.* In two small, square areas a layer of antigen-agar mixture and next to these in one rectangle (in the lower rectangles in Fig. 1) antiserum-agar layers are placed. Under such

conditions the number of precipitation zones signifies the minimum number of antigen-antibody systems, the position of a line is determined by the relative concentration of reagents. In the presence of excess antigen the line is formed in the antiserum layer and in case of an antibody excess it will be found in the antigen layer. At a given point of time in the presence of excess antigen the distance of a line from the antigen-antibody interface is directly proportional to the logarithm of the antigen concentration. The precipitation zones of the neighbouring systems show confluence along the vertical midline of the container, if they are identical in immunological specificity. In the presence of heterologous antigens the coalescence is partial. The lines of foreign systems show no coalescence.

The immune serum mixture No. 304 produced in rabbits inoculated with normal human serum was used as the antiserum, whereas the antigens were the patient's serum (V. M.), a 10 per cent solution of human gamma globulin (G), a 10 per cent solution of human albumin (A), and normal human serum (N). The experiments were performed as shown in Fig. 1 (see square 1, Fig 1).

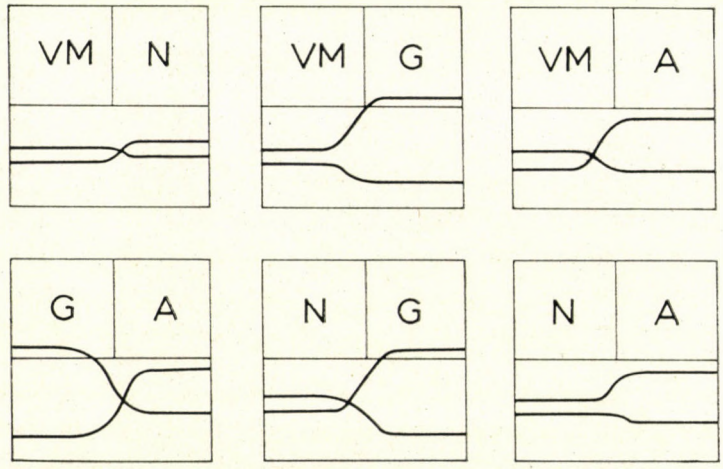

FIG. 1. Quantitative determination of antigens, according to OUDIN. Squares above: antigen-agar mixture. Rectangles below: antiserum-agar layer.
V. M. = patient's serum
G = 10 per cent solution of human gamma globulin
A = 10 per cent solution of human albumin

Comparative studies with normal serum and the patient's serum showed the same number of precipitation strips and complete interference, as a sign that in the patient's serum there was no antigen which would not be present in normal serum. The comparative method also allowed some conclusions as to the relative concentrations of the single antigens on the basis of the distance of the respective fronts from the boundary. Most

of the proteins in the patient's serum had the same concentration as that of the proteins of similar antigenicity in normal serum, *i. e.* a straight line of precipitation was visible in the antiserum-agar medium.

Significant differences were noted exclusively in connection with serum albumin and gamma globulin (square 3, Fig. 1).

In the normal serum the albumin concentration was higher and the gamma globulin concentration was lower than in the patient's serum, and therefore in the comparative test the lines intersected in the midline. The reactions set up in the same way with normal serum and the patient's serum, using a gamma globulin solution or albumin solution as the comparative reagent, are shown in squares 4, 5 and 6 in Fig. 1. The albumin solution contained a small amount of gamma globulin and the gamma globulin a small amount of albumin as contaminants. To facilitate evaluation the precipitation lines of proteins having approximately the same concentrations are not shown.

With OUDIN's simple diffusion method the diffusion coefficients for the gamma globulin solution, the normal serum gamma globulin and the protein in the patient's serum were closely similar, suggesting that the pathological protein present in the patient's serum did not differ significantly in molecular size from normal gamma globulin.

The results of this first series of experiments were interpreted as indicating that a protein of gamma globulin antigenicity had increased in the serum of the patient. The diffusion coefficient and thus apparently also the mean molecular size of this protein were not significantly different from those of normal gamma globulin.

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For determination of the antibody content, serum samples taken on 12 different occasions were used.

Anti-A and anti-B isoagglutinins, as well as the antibacterial antibodies active on the group 0 human erythrocytes sensitized with enteral antigens and old tuberculin, respectively, were tested by haemagglutination micromethods. The enteral antigens were produced from strains of *S. typhi* O, Vi, *Sh. flexneri* 2a and 3, *Sh. sonnei*, by the method of SPAUN.

The patient's serum contained no or very little of the antibodies examined. The absence of anti-B isoagglutinins in certain samples was particularly interesting, as they are known to be present in the serum of practically every A and 0 type individual more than 6 months of age. In case of a negative result by haemagglutination, in saline tests with antiglobulin serum were made, but these revealed no incomplete form of isoagglutinin.

Over a period of 3 years the patient's serum was found to contain 0.5 I. U. of staphylococcus antitoxin.

Thus, the results of this second series of experiments indicated that the pathological protein increase inhibited the formation of isoagglutinins and agglutinating bacterial antibodies.

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The cause of the purpura associated with hyperglobulinaemia is uncertain. Most authors, including WALDENSTRÖM, have ascribed it to the increase of globulin. Others [29, 12, 23] suggest an allergic mechanism, while still others [13, 22, 18] look upon the increased viscosity of serum as the factor directly damaging the vascular wall.

According to LINDEBOOM [19], the increase of globulins cannot be the cause of purpura, because in the condition under discussion hyperglobulinaemia is a constant feature, while purpura occurs intermittently. In our case the intensity and the recurrences of purpura were favourably influenced by hormonal treatment, while the hyperglobulinaemia could be influenced only temporarily.

PRIBILLA [25] and DÖRKEN [8] regard the condition as a special form of Schönlein—Henoch's disease. We made plasma protein studies in 10 of such cases and found no hyperglobulinaemia in any of them.

Biopsy specimens from the skin eruptions of patients with hyperglobulinaemic purpura [7, 15] showed an inflammation of the blood vessels. This finding might prove valuable in further research.

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Agglutination of erythrocytes *in vitro* has been observed in our case. This phenomenon occurred in 4 cases of splenomegalic cirrhosis reported by LÖWINGER *et al.* [20], who attributed it to the presence of autoagglutinin. NEUMANN and HOMMER [24] described 3 such cases in connection with acute hepatitis, and HENNEMANN and KUNCZ [11] in 2 patients with reticulosis. In the latter cases the phenomenon has been ascribed to a disturbance of protein metabolism.

In our case Coombs' test was negative, no haemolysis was demonstrable, but the agglutination of erythrocytes could be correlated with the changes in the protein pattern. After operation namely the formerly 1 in 32 titre decreased to 1 in 1, parallel with the improvement in the protein pattern. Although the presence of autoantibodies could not be ruled out, we feel inclined to consider the phenomenon a pseudoagglutination, a synpexis, consequential to the excessive increase in the concentration of gamma globulin.

DISCUSSION

WALDENSTRÖM [35] has sharply distinguished between hyperglobulinaemic purpura and macroglobulinaemia and in his recent report [39] he writes about primary and secondary macroglobulinaemia, but even the primary form does not appear to have a uniform clinical, morphological and immunological pattern.

Having observed several transitory forms between macroglobulinaemia, hyperglobulinaemic purpura, myeloma and chronic lymphadenitis, SEHNERT [32] does not consider macroglobulinaemia to be a clear-cut entity. According to BERNDT [2], macroglobulinaemia is merely a symptom which may occur in several conditions; the same has been stated

for hyperglobulinaemic purpura by MIESCHER [23]. Various transitory forms have been found by JAHNKE and SCHOLTAN [14], especially between macroglobulinaemia and myeloma. The evidence published by MACKAY *et al.* [21] suggests macroglobulinaemia to be a form of lymphosarcoma. RINGELHANN *et al.* [26] described a case with macroglobulinaemia where haematology was characteristic of leucaemia and histology of reticulosarcomatosis. In BRENNER's [5] case, too, macroglobulinaemia was associated with leucaemia. WALDENSTRÖM [38] also states that malignant tumours may produce macroglobulin, and BOLLINGER [3] and GUGLIELMO [10] similarly think that the examinations of precipitations of macroglobulins are non-specific.

We ourselves agree with those who refuse to accept both macroglobulinaemia and hyperglobulinaemic purpura to be independent entities. The number of transitory forms nearly equals that of the "true" cases. A common property is a reticuloendothelial proliferation that may equally occur in frequently relapsing infections and long-lasting chronic conditions. Proliferation of the reticulum may be similar to neoplastic growth in some cases.

Active reticuloendothelial proliferation has been demonstrated also in our case. In the bone marrow the number of the reticulum (and first of all the plasma cells) was increased, the spleen was enlarged, and the number of Kupffer cells increased. As a result, hyperproteinaemia and hypergammaglobulinaemia, respectively, were the most outstanding changes. This explains the high ESR and the pseudoagglutination. No paraprotein could be demonstrated. The serum contained neither cryoglobulin, nor marcroglobulin. Detailed immunological and immunoelectrophoretic studies have shown an increase of a protein of gamma globulin antigenicity in the patient's serum, that did not differ from the normal in regard to mean molecular size.

In our case the appearance of hyperglobulinaemia and purpura preceded that of liver cirrhosis and splenomegaly. The previous hepatitis mentioned in the history may have been responsible for the active reticuloendothelial proliferation. The disturbances in salt and water balance and the weak renal concentration capacity might all have been due to the hyperproteinaemia. No increase of NPN and no hyposthenuria were noted. Concentration was impaired just temporarily and therefore a hepatorenal syndrome was not suspected. Thrombopenia was associated with the splenomegaly.

As in the case of WALDENSTRÖM [36, 37], splenectomy proved to be effective. After operation purpura did not reappear, the albumin in serum increased. No recurrence of jaundice has been noted.

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Summary

A patient with hyperglobulinaemic purpura presenting in childhood and associated with splenomegalic cirrhosis has been kept under observation for 4½ years.

Detailed serum protein, immunological and immunoelectrophoretic studies have been made and an increase of a protein with gamma globulin antigenicity and normal molecular weight has been demonstrated in the serum of the patient.

The symptoms of the disease responded well to hormone therapy. Splenectomy produced a remission lasting now more than 2 years. An increase in the number of Kupffer cells was an outstanding feature in the histology of the liver.

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Chefarzt DR. J. SZAMOSI
Üllői ut 86
Budapest VIII., Hungary