A New Entity of Antibody Deficiency Syndrome, to Which "Congenital Dysgammaglobulinemia" Might Be Suggested

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Recently we experienced a case which was clinically similar to agammaglobulinemia¹⁾ or fatal granulomatous disease²⁾ but definitely different from them in laboratory findings. It was a new entity of antibody deficiency syndrome, to which we may as well give the simple name: "Congenital Dysgammaglobulinemia."

CASE REPORT

H.K., a boy, was born on October 9, 1957, and of an uneventful, full-term pregnancy and spontaneous delivery. The birth weight was 3,008 g. The parents and siblings were healthy. Small-pox and diphtheria vaccinations were performed at the age from 2 to 3 months. The latter resulted in normal primary response. Since affected by pneumonia at four months of age, the child had frequently suffered from upper respiratory tract infections or bronchitis with delayed recovery though he was treated with antibiotics each time. With the chief complaints of hepatosplenomegaly and enlargement of generalized lymph nodes, the child was admitted to our Hospital at the age of one year and two months. Blood examination at that time revealed no abnormality. The liver and kidney functions were within normal limits. Under an inconclusive diagnosis, the child's condition was slightly improved by the treatment with antibiotics and the patient was discharged after hospitalization of about one month. Respiratory infections, however, were as frequently repeated as ever after leaving hospital. Both hepatosplenomegaly and enlargement of lymph nodes tended to gradual increase again. The child was readmitted to our Hospital at the age of 2 years and 9 months for a medical re-examination. Physical examinations, on the second admission, showed a poorly nourished, pale boy with hepatosplenomegaly and generalized enlargement of lymph nodes. The abdomen was distended without fluctuation or varicosis. The non-tender liver

with smooth surface was palpable 2 cm below the costal margin on the right mid-clavicular line and the spleen was palpable 7.5 cm below the left costal margin. The retroauricular lymph nodes were enlarged to 2×2.5 cm in diameter, several cervical lymph nodes to 0.5×0.5 cm, supraclavicular lymph nodes to 0.5×1.0 cm and axillar lymph nodes to 3×2 cm on both sides, respectively. These lymphadenopathic nodes were non-tender. No petechia or ecchymosis was present. There was no remarkable findings on the physical examination of the chest.

TABLE I. Blood Picture of Our Own Case

1960		Jul. 23	Aug. 10	Sep. 8	Oct. 12
R.B.C. $10^4/\text{mm}^3$		210	203	349	475
Hb. g/dl.		5.9	6.5	10.5	12.8
Ht. %		21	20		41
C.I.		0.94	1.07	1.00	0.88
V.I.		1.11	1.10		0.96
Reticul. %		12			6
W.B.C.		6300	4600	8400	13000
Differential	B. %	0	0	0	0
	E. %	6	6	0	3
	L. %	49	49	31	55
	N. %	39	34	68	41
	M. %	6	11	1	1

Laboratory data :— Blood examination disclosed a normocytic, normochromic anemia without leukemic cells or any other abnormal cells (Cf. Table I). The bone marrow showed an erythrocytic hyperplasia, indicating 0.89 of G : E-index, a decrease of plasma cells (0.6%), and the absence of leukemic cells or other abnormal cells such as Gaucher's cells. The bleeding time was 4 minutes and the coagulation time was 6 minutes. BSR on three occasions was increased. Wassermann's reaction was negative. The fasting blood sugar was 92 mg per 100 ml. The urine was negative for protein and sugar. Bence-Jones protein test in urine was negative on several occasions. The liver function tests, including thymol turbidity test, cobalt test, Takata's reaction and BSP test, were all within normal limits. E.C.G. revealed no abnormality and x-ray examinations for chest, head and extremities showed normal findings. There was no abnormality on fundoscopic examination. Cultures from throat yielded staphylococcus aureus, streptococcus viridans and pneumococcus. The electrophoretic analysis of serum protein showed a remarkable increase of gammaglobulin fraction (Cf. Table II).

Immunologic data : — During the second hospitalization, it was suspected

TABLE II. Electrophoretic Pattern of Serum Protein of Our Own Case

	1960	Aug. 9	Aug. 19	Oct. 13	Dec. 2
Total Protein (g/dl.)		7.50	7.80	7.60	7.95
Albumin	"	3.17	2.98	3.90	3.50
Globulin	"	4.33	4.82	3.70	4.45
α	"	0.80	0.99	0.85	0.80
β	"	1.36	1.42	1.05	1.20
γ	"	2.17	2.41	1.80	2.45
A/G ratio		0.73	0.62	1.05	0.79
Remarks		Before treatment, hepatosplenomegaly, lymphadenopathy and continued fever	After inoculation of typhoid and paratyphoid vaccines	On discharge, general conditions and lymphadenopathy improved after treatment	Recurrence of upper respiratory infections and bronchitis with lymphadenopathy

that the patient might possibly have an immunologic defect because of susceptibility to infections. So the following studies were carried out.

The patient was of blood group A. However, an extremely low level of β -isohemagglutinin in the serum was demonstrated (Cf. Table III). According to Ou³⁾, the average of β -isohemagglutinin titer was 1:70.2, ranging from 1:512 to 1:8, in 29 children of blood group A aged from 2 to 5 years. Therefore, the low titer demonstrated in the present case (Cf. Table III) was considered to be decidedly abnormal. The child, who had a BCG-inoculation about one year previously, was negative both for tuberculin reaction and for Middlebrook-Dubos reaction⁴⁾. Typhoid and paratyphoid vaccines were injected to the patient twice with the interval of a week and the Widal reaction was investigated one, two, and four weeks after each vaccination and of course just before it. The results of the Widal reaction in the present case were all negative, while those obtained from

TABLE III. Isohemagglutinin Titer in Serum of Our Own Case

Dilution of Sera		1:1	1:2	1:4	1:8	1:16	1:32	1:64	1:128
Time in Minutes									
10	P*	-	-	-	-	-	-	-	-
	C:**	+	+	+	+	±	-	-	-
15	P	-	-	-	-	-	-	-	-
	C	+	+	+	+	±	-	-	-
30	P	±	-	-	-	-	-	-	-
	C	+	+	+	+	+	+	-	-

* P : Patient

** C : Control; healthy child of the same age as the patient

healthy children of the same age as the patient were positive in dilution of 1 : 50 to 1 : 100 in two and four weeks following the vaccinations. Viral antibodies against mumps, HVJ (Hemagglutinating Virus of Japan), and HA₂ (Hemadsorption Virus Type 2) were not demonstrated in the serum of the patient either. The value for C-reactive protein, which was supposed to be involved in antibody production, was always completely negative in the patient on repeated examinations, despite of the occurrence of staphylococcus, streptococcus, pneumococcus, etc. in the throat swab. Indeed each of above-mentioned results—each for itself—might not always be a positive proof for decreased ability of antibody production. But the above results, taken in all, will mean that the patient has a defect of antibody production.

Biopsy finding of lymph nodes (Cf. Fig. 1):—A biopsy of enlarged lymph nodes revealed a proliferation of reticulum cells and a thinning of cortex, but no evidence of malignancy such as leukemia, sarcoma, Hodgkin's disease, etc. was seen. Plasma cells were scarcely found in the sections.

(a) A remarkable proliferation of reticulum cells is noticed, but plasma cells are scarcely found.

(b) Thinning of cortex is found.

Fig. 1. Biopsy findings of a lymph node in our own case.

Clinical course:—The child ran a feverish course (37.5 to 38.5°C) and the enlarged liver and spleen and the lymph nodes swollen ahead, showed a tendency to gradual enlargement in spite of antibiotics therapy. Though a successive blood transfusion for one week was effectual for an improvement of

the anemia, it did not influence either the hepatosplenomegaly or the lymphadenopathy. Then the administration of prednisolone was begun with an initial dose of 20 mg a day, followed by gradual reduction of dose for one month (total dose: 290 mg), resulting in an improvement of general condition — drop in temperature, increase of appetite, etc. Hepatosplenomegaly and lymphadenopathy, however, showed little change. Thereafter intramuscular injections of normal human gammaglobulin (Takeda) were carried out with a view to improve the alleged antibody deficiency syndrome. A remarkable decrease in size of enlarged lymph nodes was observed by a daily injection of 0.3 g of it for successive ten days. But decrease in size of the spleen and liver took place more slowly. Then the treatment with prednisolone alone was continued without recurrence of the above symptoms and signs until the 84th hospital day when the patient was discharged under a comparatively good condition.

On discharge, the enlarged lymph nodes of all the body had decreased in size; they were much smaller than on admission. The liver was palpable 1 cm, and the spleen was palpable 6.5 cm below the costal margin. The gammaglobulin content decreased and A/G ratio increased to a certain degree as compared with these figures on admission (Cf. Table II).

After discharge — now no medical treatment was performed, — the child had had upper respiratory tract infections and bronchitis again during one month following the discharge. During this time, the enlargement of lymph nodes had recurred, accompanied with rise of gammaglobulin content in serum (Cf. Table II). With a renewed treatment with gammaglobulin, prednisolone and antibiotics, an amelioration of the above affections and symptoms ensued.

DISCUSSION

Such a disease as the case reported here resembles one of the following diseases in symptomatology. The differential diagnosis will be discussed among them.

Fatal granulomatous disease:— This disease described by Berendes *et al.*²⁾ in 1957 has the following feature; (a) frequent attacks of infections, (b) chronic lymphadenopathy which tends to suppurate gradually, (c) hepatosplenomegaly, (d) eczematoid dermatitis and blepharoconjunctivitis, (e) hypergammaglobulinemia, (f) pulmonary infiltration, (g) granulomatous nodes of the liver or lymph nodes on biopsy, (h) chronic, progressive course, resulting in death between 6 months and 3 years after the onset, (i) occurring predominantly in male occasionally with hereditary incidence, (j) fever reminding one of sepsis, and (k) anemia, sometimes with eosinophilia.

The present case had the items (a), (c), (e), (j) and (k) in common, with the disease in question, however, there was no tendency to suppuration of lymph nodes in our own case through the whole course of 1½ years. In addition, it is different from the above disorder in that lymphadenopathic nodes of our own

patient showed a decrease in size following the treatment, and in that there was no evidence of pulmonary infiltration (j) on x-ray films of the present case. A biopsy of lymph nodes of our own patient revealed no granuloma but only a reactive reticulosis. On the other hand, the inability for antibody production and the defect of isohemagglutinin both of which are probably characteristics of our own case — do not occur in fatal granulomatous disease. It was, therefore, concluded that the present disease was different from fatal granulomatous disease, although both of them showed some similarities in symptomatology.

Congenital a- or hypo-gammaglobulinemia :— Since the first description by Bruton¹¹ in 1952, many studies⁵⁻¹⁴ have been published concerning this disorder. The features of the disease are as follows ; (a) frequent attacks of infection beginning between 9 months and 2 years of age, (b) staphylococcus, streptococcus, pneumococcus, meningococcus, etc. as common organisms causing infections, (c) a normal primary response against vaccination in early infancy in two thirds of the patients, (d) low concentration of gammaglobulin in plasma, mostly below 50 mg per 100 ml, (e) absence or extremely low titers of isohemagglutinin in serum, (f) failure to develop antibodies against specific antigen, (g) a hyperplasia of reticulum cells, thinning of cortex and decrease of plasma cells and lymphocytes — all of which will be revealed on biopsy of lymph nodes, and (h) predominant occurrence in male and transmission by a sex-linked recessive trait.

A definite difference between this disorder and our own case lies in concentration of gammaglobulin in plasma. It is, however, curious that there is an agreement of findings between these two disorders except gammaglobulin content. Especially the case of hypogammaglobulinemia reported by Dolan *et al.*¹⁴ was like our own patient accompanied with anemia and hepatosplenomegaly. Accordingly, it seems to be likely that increased gammaglobulin in our own case might be immunologically abnormal one, as will be discussed later.

Multiple myeloma :— In multiple myeloma, hypergammaglobulinemia is occasionally present¹⁵ and susceptibility to recurrent infections, diminishing of antibody response to antigenic challenge and absence of isohemagglutinins have been described. Bence-Jones protein, which is inevitably present in urine of multiple myeloma, was not found in urine of the present case, in spite of repeated examinations. Multiple myeloma can further be excluded by age incidence, bone marrow picture and x-ray findings of the bone, in addition to the absence of Bence-Jones protein already mentioned.

Janeway's cases and Hallman's cases (Cf. Table IV) :— The cases reported by Janeway¹⁶ in 1954 and the cases by Hallman¹⁷ in 1956 were similar to our own case, too. This case, however, was different from Janeway's cases in regard to inability of antibody production and decrease of plasma cells in lymph nodes as shown in Table IV. Hallman's report is devoid of description as to ability for antibody production and isohemagglutinin.

TABLE IV. Comparison among Janeway's, Hallman's Cases and Our Own Case

	Janeway's cases	Hallman's cases	Present case
Susceptibility to infections	+	+	+
Hepatosplenomegaly	+	+	+
Lymphadenopathy	+	—	+
Anemia	?	+	+
Fever	?	+	+
Hypergammaglobulinemia	+	+	+
Biopsy of lymph nodes	mononuclear infiltration and prominence of plasma cells	mononuclear infiltration	Proliferation of reticulum cells, thinning of cortex and decrease of plasma cells
Antibody response against antigenic stimulation	normal	?	absent
Isohemagglutinin titer	No description	No description	extremely low
Effect by γ -globulin	No description	+	+

Although it is generally accepted that gammaglobulin represents the major parts of antibody, it remains yet uncertain whether or not all of gammaglobulin is antibody. It may be reasonable to presume that an elevation of gammaglobulin demonstrated in the present case is a reflection of immune responses to recurrent infections. Nevertheless, an extremely poor response to antigenic stimulation (see p. 301), just as observed in agammaglobulinemia, was demonstrated in the present case. The fact that a small-pox vaccination in early infancy resulted in normal primary response in the present case might be due to the normal gammaglobulin which had been derived from mother and remained to stay during his early infancy. This could be explained on the basis of half life of gammaglobulin¹⁸⁻²⁰. An inference may be drawn from the above-mentioned results that the increased gammaglobulin in question in our own case would not be an antibody gammaglobulin but rather be a nonspecific, nonantibody gammaglobulin. It is, therefore, possible to presume that there was a disturbance in productive process of antibody gammaglobulin in the reticuloendothelial system, a site of gammaglobulin production, in the present case, causing an overproduction — a futile overproduction of nonantibody gammaglobulin. The finding that no antibody production took place against specific antigen while increase of gammaglobulin was observed in the present case (Cf. Table II) will probably support the above inference. Though the present case, from viewpoint of gammaglobulin content in serum, is quite different from a case of agammaglobulinemia, both disorders seem to have an immunological similarity in that both are unable to develop antibody. Since plasma cell is thought to be closely associated

with production of antibody gammaglobulin²¹⁻²⁷), hypergammaglobulinemia ought to be usually accompanied with increase of plasma cells in the reticuloendothelial system. In the present case, however, there was no expected proliferation of plasma cells either in lymph nodes or bone marrow; on the contrary, a more or less striking decrease of these cells was seen (Cf. Fig. 1). It is a question that nonantibody gammaglobulin — in contrast to antibody gammaglobulin — has been produced by plasma cells in the present case. Grant²⁸) stated that splenomegaly in agammaglobulinemia might be due to a reactive hyperplasia of the spleen which is probably one of sites of gammaglobulin formation. Then it may not be too much to say that also in our own case of deficiency of antibody gammaglobulin hepatosplenomegaly and lymphadenopathy occurred by way of compensation.

Now basing upon the above-mentioned presumption that the present case might have a disturbance in productive process of antibody gammaglobulin, we should like to suggest the term "Congenital Dysgammaglobulinemia" for this particular entity of antibody deficiency syndrome in contrast to the syndrome of agammaglobulinemia. The relationship between agammaglobulinemia and "dysgammaglobulinemia" is illustrated schematically as shown in Fig. 2 (Cf. Fig. 2). In normal individuals, antigen due to infection stimulates the reticuloendothelial system to produce both antibody gammaglobulin and nonantibody

Fig. 2. Schematic illustration of dysgammaglobulinemia and agammaglobulinemia.

gammaglobulin, only the former playing a role of prevention from infection. In agammaglobulinemia production of both antibody gammaglobulin and non-antibody gammaglobulin might be affected. On the other hand, the production of antibody gammaglobulin alone was probably affected in "dysgammaglobulinemia", resulting in overproduction of nonantibody gammaglobulin and susceptibility to infection. It might be due to its inhibitory action upon overproduction of nonantibody gammaglobulin that prednisolone was effective in our own case. The remarkable effect induced by normal gammaglobulin in the present case might be explained in such a way that normal gammaglobulin, induced by injection, alleviated the stimulated reticuloendothelial system, resulting in inhibition from overproduction of nonantibody gammaglobulin.

The ultracentrifugal analysis of serum protein in the present case indicates the results as shown in Table V (Cf. Table V). The molecular weights of A-component and G-component were within normal limits, and no macroglobulin or cryoglobulin was noticed. An increase of G-component may be a reflexion of elevated gammaglobulin. M-fraction, which should show approximately only 2%

TABLE V. Ultracentrifugal Analysis of Serum Protein

Component	Sedimentation constant	Molecular weight	Percentage in quantity
A	3.9	43,000	48 %
G	6.7	87,000	40 %
M	15.0	250,000	12 %

in normal, increased markedly. Although the significance of M-component is difficult to understand, it is probable that the increase of this component in the present case might be accompanied with a disorder of gammaglobulin production in the reticuloendothelial system. Smith²⁹⁾ described that there was no significant difference in amino acid composition between normal gammaglobulin and antibody. It may be impossible to distinguish nonantibody gammaglobulin from antibody gammaglobulin by the difference of the molecular weights, since the difference between both gammaglobulin is thought to exist in a derangement of molecular structure. Since the mechanism or site involved in antibody production is not yet fully understood at present, many questions concerning same remain to be solved.

SUMMARY

A case characterized by susceptibility to recurrent infections, hepatosplenomegaly and lymphadenopathy, was described in detail. Examination revealed an increased level of gammaglobulin in serum, in spite of an extremely poor capacity for antibody production. The term "Congenital Dysgammaglo-

bulinemia", — a possible disturbance in productive process of antibody gamma-globulin in the reticuloendothelial system, — was applied to this probably new entity of antibody deficiency syndrome.

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