BRIEF REPORT

Plasma Activity of Antihemophilic Globulin (AHG) and Other Coagulation Factors in Swiss Type of Agammaglobulinemia

By Harold M. Maurer, Orestes Valdes, Clare N. Shumway and F. Stanford Massie

The site of synthesis of antihemophilic globulin (AHG, Factor VIII) and the factors which regulate its plasma concentration are largely unknown. AHG is probably stored somewhere in the body since both adrenalin and exercise increase the circulating level within minutes. Increased AHG activity has been reported in pregnancy, come malignant diseases, trauma and post-operative states, hyperthyroidism, and in hypergammaglobulinemia due to various etiologies including multiple myeloma. In these conditions, AHG may be an acute phase reactant whose activity increases in the presence of tissue damage or hypermetabolism.

Available evidence suggests that AHG is synthesized by the reticuloendothelial system, possibly the lymphocyte or plasma cell. Pool assayed various rat tissues for AHG activity and found activity only in the spleen. Spaet concluded that there was a depression of AHG synthesis following the blockade of the reticuloendothelial system by thorotrast and India ink. Nilehn found low plasma concentrations of AHG in patients with aplastic anemia and suggested that the bone marrow might be the site of AHG production. Perfusion of normal dog's spleen with canine hemophilic blood results in increased amounts of AHG in the perfusate, whereas perfusion of the spleen from a hemophilic dog does not show a similar increase. Further, Norman et al. have shown that canine hemophilia A can be relieved by splenic homotransplantation. Splenectomy abolishes the rise in AHG activity after injection of adrenalin into normal humans. Weiss and Kochwa proposed that AHG is produced in specialized plasma cells since AHG levels are increased in patients with multiple myeloma and hypergammaglobulinemia. Recently, Zacharski et al. have shown that human leukocytes in Eagles culture medium, generated significant amounts of AHG during 24 hours incubation at 37 C. Since polymorphonuclear leukocytes survive poorly in this culture medium they concluded that the lymphocyte was responsible for synthesis of AHG.

We wish to report the level of activity of AHG and other coagulation factors...
in a patient with Swiss type of agammaglobulinemia (SAG) who shows marked functional and morphologic abnormalities of the reticuloendothelial system including virtual absence of lymphocytes and plasma cells in lymphoid tissue, bone marrow and blood.

CASE REPORT

K.B., a negro male weighing 4 pounds, 4 ounces at birth, was the product of a mating of a 16 year old girl with her great uncle. At two months of age when he weighed 5 pounds, 1 ounce, he was admitted to Medical College of Virginia Hospitals because of a urinary tract infection and failure to thrive. Physical examination disclosed a poorly developed and poorly nourished child. Liver, spleen, and lymph nodes were not felt and the tonsils were absent. The hemoglobin concentration was 15 Gm. per cent, the total white blood cell count was 7950/mm³ of which 65 per cent were neutrophils, 3 per cent lymphocytes (238/mm³), 5 per cent eosinophils and 21 per cent monocytes. The platelets appeared adequate on the peripheral smear. X-rays and fluoroscopy of the chest and nasopharynx failed to show adenoidal or thymic tissue.

Studies related to delayed hypersensitivity disclosed: a) no reactivity to 2,4-dinitrochlorobenzene in acetone; b) no rejection of a skin homograft; and c) no proliferation of lymphocytes cultured in vitro with phytohemagglutinin. The bone marrow showed normal erythropoiesis, myelopoiesis, and thrombopoiesis, marked reduction in the number of lymphocytes (4 per cent), and plasma cells were not seen. The number of histiocytes in the marrow sample appeared increased.

Studies related to humoral antibody function revealed: a) no antibody response to stimulation with E. coli antigen and diphtheria-tetanus toxoid; and c) a positive Schick test before and after immunization with Schick antigen.

His course in the hospital was marked by recurrent urinary tract infection, diarrhea, pneumonia, moniliasis and osteomyelitis due to atypical mycobacteria. With the exception of one episode of bleeding related to Vitamin K deficiency, no other bleeding problem was evident.

Post-mortem findings were compatible with SAG.

At the time the coagulation studies were performed, the absolute lymphocyte count in the blood was zero.

METHODS

Venous blood was collected with a disposable needle and plastic syringe and was mixed 9:1 with 4 per cent sodium citrate solution in a plastic tube. Plasma was separated by centrifugation at 2500 rev./min. for 15 minutes at 20 C. Supernatant plasma was transferred to plastic disposable test tubes and then maintained at 4 C. until tested, within 3 hours of venepuncture.

The coagulation methods used were: one stage prothrombin time and partial thromboplastin time with celite,¹⁷ and assays for Factors II,¹⁸ V and VII,¹⁷ VII and IX,¹⁹ X,²⁰ XI,²¹ XIII,²² fibrinogen.²³ Substrate plasma for use in the assays of Factors VII, VIII and IX was obtained from patients with known severe congenital deficiencies of these factors. The remaining assays were performed using artificially depleted plasma which was made according to the method described.

RESULTS

The results of the coagulation studies are listed in Table 1. The activities of all coagulation factors except fibrinogen were within the normal range. Fibrinogen was increased which might be related to chronic infection in the patient.

DISCUSSION

The “Swiss” type of agammaglobulinemia (SAG) is a lymphopenic immu-
Table 1.—Results of Coagulation Studies

<table>
<thead>
<tr>
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<th>Normal</th>
<th>K. B.</th>
</tr>
</thead>
<tbody>
<tr>
<td>One stage prothrombin time, sec.</td>
<td>12-15</td>
<td>15.2</td>
</tr>
<tr>
<td>Activated partial thromboplastin time, sec.</td>
<td>35-45</td>
<td>38.2</td>
</tr>
<tr>
<td>Fibrinogen (mg%)</td>
<td>200-400</td>
<td>635</td>
</tr>
<tr>
<td>Factor II (%)</td>
<td>65-145</td>
<td>80</td>
</tr>
<tr>
<td>Factor V (%)</td>
<td>50-150</td>
<td>100</td>
</tr>
<tr>
<td>Factor VII (%)</td>
<td>&gt; 75</td>
<td>100</td>
</tr>
<tr>
<td>Factor VIII (%)</td>
<td>50-200</td>
<td>130</td>
</tr>
<tr>
<td>Factor IX (%)</td>
<td>50-200</td>
<td>73</td>
</tr>
<tr>
<td>Factor X (%)</td>
<td>65-180</td>
<td>100</td>
</tr>
<tr>
<td>Factor XI (%)</td>
<td>50-148</td>
<td>68</td>
</tr>
<tr>
<td>Factor XIII (urea solubility)</td>
<td>clot insoluble</td>
<td>clot insoluble</td>
</tr>
</tbody>
</table>

The thymus in patients with this disease is extremely small (often only a few milligrams) and comprises only poorly-developed lobules of epithelial stroma cells. It contains no Hassall's corpuscles and virtually no lymphocytes. The spleen, lymph nodes, tonsils, bone marrow and gut-associated lymphoid tissues show an extreme depletion of lymphoid cells and a prominent reticular architectural pattern. Plasma cells, if present at all, are rare. A deficiency of circulating lymphocytes is consistently found; levels average fewer than 500/mm³ and are consistently below 1000/mm³. These patients fail to develop delayed allergy and reject skin homografts.

Studies of the immunologic mechanism in our patient are indicative of SAG. They show that "thymus-dependent" lymphoid function which includes the circulating small lymphocyte population and nongerminal center lymphoid aggregates in tissues and subserves the functions of cellular immunity, and nonthymus-dependent lymphoid function which comprises the germinal follicles and plasma cells and is predominantly involved in immunoglobulin and antibody production, are markedly deficient.

If, as proposed by others, AHG is synthesized or stored by the lymphocytes or plasma cells one would expect to find decreased plasma AHG activity in SAG. Normal AHG activity was found in our patient. This observation suggests that the lymphocytes and plasma cells are unlikely sites of synthesis or storage of this coagulation factor. Our data agree with the findings of Penick et al. who showed that total body radiation failed to depress AHG, and concluded that an intact lymphoid system was not needed for the maintenance of the AHG activity of plasma. The possibility that AHG is produced or stored in the histiocyte, epithelial stroma cell, or vascular endothelial cell cannot be excluded since these cells are abundant in the reticuloendothelial tissue of patients with SAG. Alternatively, one might argue that perhaps there is a specialized lymphocyte which is both radioresistant and escapes the reported disease. Are these the source of AHG? A remote possibility indeed.

Summary

Although the site of synthesis and storage of antihemophilic globulin (AHG, Factor VIII) is unknown, available evidence suggests that these processes occur...
in the reticuloendothelial system. We studied the plasma activity of AHG and other coagulation factors in a patient with Swiss type of agammaglobulinemia. Except for increased fibrinogen concentration probably related to chronic infection, the activity of all coagulation factors including AHG was within the normal range. These studies suggest that the lymphocyte and plasma cell are unlikely sites of AHG synthesis or storage.

SUMMARIO IN INTERLINGUA

Ben que le sito del synthese e del thesaurisation de globulina antihemophilic (GAH, Factor VII) non es cognoscite, le disponibile evidentia suggestiona que iste processos occurre in le systema reticuloendothelial. Nos ha studiate le activitate de GAH in le plasma e etiam altere factores de coagulation in un patiente con agammaglobulinemia del typo switze. Con le exception de un aiigrnentate concentration de fibrinogeno (que esseva probablemente relationate a infection chronic), le activitate de omne le factores de coagulation, incluse GAH, esseva intra le limites del norma. Iste studios suggestiona que le lymphocytos e le plasmocytos es sitos pauco probable pro le synthese o le thesaurisation de GAH.

REFERENCES


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