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Resolution of Cyclic Neutropenia by Intramuscular Gamma Globulin in a Case of Common Variable Immunodeficiency with Predominantly Antibody Deficiency

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Cyclic neutropenia is a rare disorder and as the name suggests, neutropenia occurs cyclically and neutropenic nadirs are seen every 21 ± 2 days. It often presents by 5 years of age and is accompanied by recurrent illnesses that coincide with the agranulocytic period(1). Although the etiology is unknown, it has been associated with

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dysgammaglobulinemia(2). Therapy with granulocyte-colony stimulating factor (GCSF) has been successful(3).

We present a case of common variable immunodeficiency (CVI) with mainly antibody deficiency, along with a typical cyclic neutropenia. The patient was successfully treated with intramuscular gammaglobulin.

Case Report

A 1^{1/2}-year-old boy was referred for fever every 15 to 20 days since the age of 11 months. He was free of fever only for 2 months when he was 14 months old.

Three weeks prior to the present illness he had a purulent ear discharge and pneumonia with right upper lobe consolidation. His Hb was 11.1 g/dl, Hct 33.6%, WBC $9.2 \times 10^9/L$, polymorphonuclear leukocytes (PMN) 51% and nonsegmented neutrophils (NS) 3%, IgG 302 mg/dl, TgA 22 mg/dl and IgM 49 mg/dl (normal range for TgG: 423-1184 mg/dl, TgA: 35-222 mg/dl, IgM: 22-131 mg/dl).

On examination, the child was afebrile but irritable and had a swollen, red, left middle finger following an injury. He weighed 10 kg. His investigations were as follows: Hb 10.1 g/dl, Hct 30%, WBC $5.6 \times 10^9/L$, PMN 1%, NS 1%. The following day he had a temperature of 103°F. His absolute neutrophil count (ANC) was zero, at this stage (*Fig. 1*).

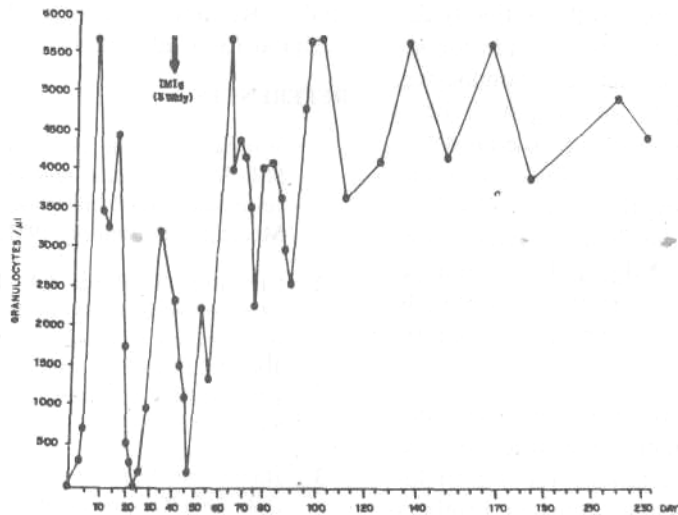


Fig. 1. Absolute neutrophil counts before and after IM immunoglobulin treatment.

The child was followed up with blood counts every other day and a cyclic neutropenia with a cycle of 24 days was unveiled. The immunologic tests showed an IgG 250 mg/dl, IgA <20 mg/dl, IgM <20 mg/dl; decreased T-cells (23%), B-cells (8%) and a decreased response to PHA. The T and B cell numbers were measured by rosette forming cells of the mononuclear cells with sheep RBC. Though he had been immunized with 3 doses of **DPT** and 5 doses of oral polio vaccines, his polio antibody titers of P₁, P₂ and P₃ were under 4 units, and antitetanus antibody 0.00147 IU/ml (normal protective level is 0.01 IU/ml by ELTSA). Anti-B titer in this Group A, Rh + child was undetectable. Serum G.CSF, 3 days prior to the ANC being zero, showed a slight elevation 'in vitro' CFU-C assay. Chest X-rays revealed an absence of thymic shadow.

IM gamma globulin (IMiG) was started on day 14 of the cycle, and repeated every 3 weeks. IMiG was initiated with a loading

dose of 0.3 g (1.8 ml) per kg of IgG globulin and thereafter 0.1 g (0.6 ml) per kg every 3 weeks as maintenance. On day 22 of that cycle, the ANC bottomed at 176 and not at zero as it had done prior to IMiG. His ANC values have subsequently never gone below 2100 and he has been completely asymptomatic since IMiG was started 3 years ago.

Three months after initiation of IMiG, T-cells became normal (52%), B-cells 18%, but a decreased response to PHA. There was no excretion of the polio virus in his stools. Serum IgG, IgA, IgM were negligible.

Discussion

Cyclic neutropenia is considered to be a regulatory disorder of marrow hematopoietic stem cells. In our patient, cyclic neutropenia responded completely to IMiG, which is of significance in trying to understand the disease. In CVI with predominantly antibody deficiency, autoimmune phenomena (especially pernicious anemia) develop(4). We postulated that an autoanti-

body in a background of the antibody deficiency syndrome was responsible for inducing the dysregulation of granulocytes. The beneficial effect of IVIg have been explained on two bases(5): (i) the mononuclear-phagocyte system (MPS) - Fc receptor blockade theory, this seems unlikely in this case because the child was given a very small amount of IMIg; and (ii) immune modulation theory; here the autoantibody level is reduced via the Ig injected by immunomodulation.

Alternately, a persistent virus in a immuno-deficient patient could have upset the smoothly regulated production of granulocytes. In two immune deficient brothers infected with Parvovirus-B19, the persistence of the virus caused a red cell aplasia(6). Therapy with IVIg which contained anti-Parvo-virus B19 antibodies, cured the red cell aplasia and normalized the Hb. Our patient may have had a persistent virus that attached granulocyte stem cells and limited their reserve. With Ig therapy, the virus may have been eliminated by antiviral antibodies in the Ig, thereby increasing the number of stem cells that enter the pool of committed myelopoiesis.

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