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Neutropenia associated with X-linked agammaglobulinaemia

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Abstract

In a series of six cases of sex-linked agammaglobulinaemia neutropenia occurred as a presenting feature in four and during the presenting illness in the other two. The six patients all had low antibody titres and absent or low immunoglobulin concentrations with normal concentrations of T cells and absent B cells. The patients were all first seen with severe, acute infection, including septic abscesses and meningitis; neutropenia resolved as the infection and immunoglobulin deficiency were treated. Haematologists should be aware that neutropenia is a common association of infection in patients with immunoglobulin deficiency.

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Sex-linked agammaglobulinaemia was first described by Bruton in 1952. The first association of the disease with neutropenia was noted by Good.[1] The association is well established but not considered common. All six patients with sex-linked agammaglobulinaemia who were diagnosed in two Manchester children's hospitals over several years had neutropenia—four at presentation and two in early follow up before treatment with gammaglobulin started. In our experience this is a common finding and deserves to be more widely known.

Methods

In all six patients the diagnosis was based on extremely low concentrations of B cells and immunoglobulins IgG, IgA, and IgM, absence of appropriate blood group isoagglutinins, a failure to produce humoral antibody in response to antigenic stimuli, and a lymph node biopsy specimen. All patients had had their tonsils removed. None had other affected family members.

Immunoglobulins were measured by immunodiffusion using Hyland immunoplates.[2] Routine ABO grouping techniques were used to detect ABO antibodies.[3] Blood counts were performed by standard automated techniques using Coulter Counters[4] and neutrophil counts were estimated manually. Cell markers were detected by fluorescence microscopical examination using labelled antisera.

Results

The patients all had low antibody titres and absent or low immunoglobulin with normal T cells and absent B cells, as described in classic sex-linked agammaglobulinaemia.[5] Measurement of standard antibodies showed that all patients were antibody deficient. Four had a positive Schick test in spite of having completed a full course of triple vaccine (diphtheria, tetanus, pertussis). Severe infection was the presenting feature in all six cases and neutropenia was found at some stage of the presenting illness. All had severe pyrexial illnesses, including septic abscesses and meningitis. The organisms isolated included *Staphylococcus aureus*, *Haemophilus influenzae*,

Table 1 Presenting symptoms and blood counts of six patients with X-linked agammaglobulinaemia

Patients	Age at onset	Presenting symptoms	Organism isolated	Presenting blood count: Hb g/l	Presenting blood count: White cells × 10⁹/l	Presenting blood count: Platelet count	Absolute neutrophil count × 10⁹/l	Bone marrow
Case 1 DOB 30.07.79	8 m	Groin abscess Septic spots	*Pseudomonas aeruginosa*	10·1	16·1	Normal	0·3	Normal granulopoeisis
Case 2 DOB 13.03.71	2 y	Meningitis	*Haemophilus influenzae*	10	6·7	Normal	0·3	Maturation arrest of granulopoeisis
Case 3 DOB 05.01.75	3 y	Fever Diarrhoea	No isolate	9·8	12·2	Normal	11·2	
	1 m later	Recurrent fever	No isolate	—	8·8	—	0·3	Maturation arrest of granulopoeisis
Case 4 DOB 05.02.70	5 m	Fever Febrile convulsions	*Haemophilus influenzae*	12·9	6·5	Normal	0·1	—
Case 5 DOB 31.05.77	10 m	Viral meningitis Ulcerated necrotic lesions	Adenovirus	12·2	7·5	Normal	0·1	Maturation arrest of granulopoeisis
Case 6 02.02.58	2 y	Febrile Convulsion pneumonia	*Staphylococcus pyogenes*	11·2	6·4	Normal	Normal	
	3 m later	Abscess		—	5·0	—	0·9	—

Table 2 Laboratory investigations of six patients with X-linked agammaglobulinaemia

Patients	Immunoglobulin (g/l)			Blood group and isoagglutinins	Lymph node biopsy	Schick test	Lymphocyte markers					
	IgG	IgM	IgA				SIg	Ia	CD20	T3	T4	T8
Case 1	1·2	0·2	0·26	Group O Anti-A/anti-B absent	—	—	0	0	—	91	49	44
Case 2	Nil	Nil	0·39	Group A Very weak anti-B	Absent germinal centres	—	0	1	0	96	52	42
Case 3	0·17	0·12	0·13	Group A Anti-B absent	Cortical depletion absent germinal centres	POS	—	4 (wk)	2 (wk)	77	54	31
Case 4	0	0	<0·05	Group O Anti-A/anti-B absent	—	POS	— DR	<2	<2	89	52	38
Case 5	2·7	0·07	0·02	—	Cortical depletion absent germinal centres	POS	0	2		95	60	42
Case 6	Nil	Nil	<0·05	—	—	POS	—	—	CD 19 0	—	—	—

Patients who were Schick-tested were previously immunised with triple vaccine

Pseudomonas aeruginosa and adenovirus. In four cases neutropenia was present at initial presentation with infection, and in the other two cases neutropenia was detailed at a second infection a few weeks later. The neutrophil counts ranged from 0·1 to 0·9 with a median of $0·3 \times 10^9$/l. The bone marrow in three of four cases showed maturation onset of granulopoiesis.

Table 1 summarises the presenting symptoms and blood count of the patients. Results of laboratory investigations are given in table 2. The time taken from initial presentation to diagnosis ranged from two to 12 months, with a mean of five months. Intramuscular gammaglobulin treatment was started (50 mg/kg/day for five days followed by 25 mg/kg/weekly as soon as the diagnosis was established, and at the time of writing the patients were being treated with intravenous immunoglobulin.

Discussion

The immunological features of X-linked agammaglobulinaemia, first described by Bruton in 1952, are well known and documented.[6] Haematologists seem to be unaware of the associated finding of neutropenia, which may be present in the acute stages of the disease, or less frequently, may be persistent. It is seldom and only briefly documented in standard haematology textbooks. It occurs in all types of hypogammaglobulinaemia, but in our experience, it is a very common feature of Bruton's disease. Good first drew attention to the prevalence of neutropenia in patients with agammaglobulinaemia in 1956.[1] Three of his eight patients had transient neutropenia. In two it was persistent. Mentzer *et al* reported profound neutropenia in a father and daughter with common variable hypogammaglobulinaemia.[7] Another case of X-linked agammaglobulinaemia and severe neutropenia was described by Buckley and Rowlands.[8] Of 11 cases of transient hypogammaglobulinaemia of infancy, one had neutropenia.[9] It is not unusual to see neutropenia in infants who have physiologically low concentrations of IgG at the age of 4 to 6 months. In the Medical Research Council's report of hypogammaglobulinaemia[10] neutropenia was recorded as being the most common haematological abnormality. It occurred in 9·4% of children, usually as a transient response to infection, and in 2·9% of adults.

We found neutropenia in all our cases. In three it was shortlived and in the other three intermittent, with occasional prolonged episodes of up to 30 days.

Previously reported mechanisms of neutropenia include myelosuppression and autoimmunity. In cases with agammaglobulinaemia McCullough noted that neutropenia rarely occurs in patients receiving gammaglobulin. He thought it was due to suppression of myelopoeisis by endotoxin.[11] A bone marrow aspiration was performed on four of our six patients. Three showed maturation arrest at the myelocyte/promylocyte stage and the fourth showed normal orderly granulopoiesis with toxic granulation of the mature forms. These changes are compatible with increased neutrophil destruction; they do not suggest depressed production.

Autoimmunity is another possible mechanism for neutropenia. In patients with normal humoral immunity anti-neutrophil antibodies may account for neutropenia,[12] but cannot be implicated in our patients who were unable to produce antibodies. Lymphocyte-mediated reactions, however, are a hypothetical possibility and have been reported by several authors. Cytotoxic cells have been implicated[13–16] and have mainly been of the T8 lymphocyte subclass. In five patients with autoimmune blood dyscrasias and primary hypogammaglobulinaemia, reported in 1981,[17] two had raised numbers of T suppressor cells. All our patients had very low numbers of or absent B cells, and the five patients tested showed normal absolute numbers of circulating T cells. One patient had a low T:B cell ratio. Immune complexes were not investigated at the time so the possibility cannot be excluded that immune complexes may have been formed with small amounts of low affinity antibody, leading to neutrophil destruction via Fc binding mechanisms.

The neutropenia in our patients was indisputably associated with humoral immune deficiency and all other causes were excluded.[18] Neutrophil function tests, when performed, were all normal. None had a family history of neutropenia. All our patients had neutropenia during episodes of severe infection, which was predominantly of bacterial origin. Bone marrow examination in four cases showed no

evidence that neutropenia was due to toxic depression of myelopoeisis. The neutropenia seems to be a result of increased destruction of neutrophils by endotoxin produced by bacteria during severe infection. In all cases the neutropenia resolved after replacement treatment. When a child presents with neutropenia and recurrent infection, it is important to consider a diagnosis of hypogammaglobulinaemia, and our experience suggests that the neutropenia will resolve completely when gammaglobulin replacement treatment is started.

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