C1 esterase inhibitor deficiency in X-linked hypogammaglobulinaemia: an anomaly fostering anaphylactoid reactions following intramuscular gammaglobulin administration

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Summary: A patient with apparent X-linked agammaglobulinaemia was found to be inordinately susceptible to anaphylactoid reactions to intramuscular injections of gammaglobulin. The patient was found also to have low levels of C1 esterase inhibitor (C1 INH). The possibility that the C1 INH deficiency in this patient, whether genetic or acquired, fostered the susceptibility to the production of anaphylactoid reactions after gammaglobulin injections urges further studies of the association of C1 INH deficiency and anaphylactoid reactions to gammaglobulin injections. The possibility that C1 INH levels like C1q levels may be low in hypogammaglobulinaemic patients as a consequence of increased catabolism of this regulator of the complement system when IgG levels are low is considered.

Introduction

Congenital and acquired deficiencies of components of the complement system are associated with recurrent infections and collagen diseases (Day *et al.*, 1977). In the sex-linked and common variable form of hypogammaglobulinaemia, low levels of C1q often occur which are attributable to an increased catabolism of C1q when serum IgG levels are low (Kohler & Muller-Eberhard, 1972; Atkinson *et al.*, 1978; Gewurz *et al.*, 1968; Ballow *et al.*, 1973). Inherited C1q deficiencies have been associated with both increased susceptibility to infection and mesenchymal disease (Berkel *et al.*, 1981).

C1 esterase inhibitor (C1 INH) is a serum protein which inhibits activated components of several systems including complement, plasmin, kallikrein and the clotting factors XII and XI (Frank *et al.*, 1976). Deficiency of this inhibitor is usually genetically determined as an autosomal dominant (Frank *et al.*, 1976) but may sometimes be acquired. Either deficiency leads to susceptibility to attacks of angio-neurotic oedema (Day *et al.*, 1976). In both the inherited disease and the acquired form of C1 INH deficiency, patients are liable to episodes of subcutan-

eous, laryngeal or mesenteric oedema which result from release of kinin-like peptides (C2-kinin) and the generation of C3a anaphylatoxin due to triggering of complement activation (Frank *et al.*, 1976). Trauma, infection, menstruation and physical stress have been implicated in triggering these attacks.

Patients with hypogammaglobulinaemia are maintained on gammaglobulin administration to prevent infections. Systemic reactions to gammaglobulin injections occur in about 10% of patients and mostly resemble anaphylactic reactions. However, reactions have been reported to be significantly less frequent in hypogammaglobulinaemic boys with affected male relatives (Soothill, 1971). The adverse effects following gammaglobulin administration are usually due to activation of complement by aggregated IgG but may also occasionally be attributable to the presence of antibodies to small amounts of contaminating serum proteins (Frank *et al.*, 1976; Wahn *et al.*, 1984; Day *et al.*, 1984).

The aggregates of gammaglobulin, or the immune complexes formed, rarely cause symptoms after intramuscular injections of gammaglobulin unless they reach the circulation rapidly, or unless there is a functional failure of inhibitors of the complement cascade (Asherson & Webster, 1980).

Here we describe a patient with X-linked hypogammaglobulinaemia who suffered from repeated anaphylactoid reactions following gammaglobulin injections given by the intramuscular route. The patient

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was found to have C1 esterase inhibitor deficiency. To the best of our knowledge, this association has not been described before.

Case report

This 27 year old white male was being followed in the Immunodeficiency Clinic of the Memorial Sloan-Kettering Cancer Center and had been diagnosed as having X-linked infantile (Bruton's) agammaglobulinaemia on the basis of very low levels of all circulating immunoglobulins, absence of B-cells in the blood and bone marrow, and presence of pre-B lymphocytes in the bone marrow. Over the last few years he had been given 20 ml of 16.5% gammaglobulin by the intramuscular route once every 2 weeks. During this period the patient experienced recurrent episodes of severe anaphylactoid reactions which resolved completely within 2–3 hours, usually following administration of adrenaline. The anaphylactic reactions always developed a very short time after gammaglobulin administration and included shortness of breath, wheezing, tachycardia and hypotension. The patient had a brother who had also been diagnosed as having Bruton's agammaglobulinaemia, but who had died at 22 years of age with a fulminant bacterial infection. The latter patient had never experienced attacks following injections of gammaglobulin even though, like his sibling, he had been treated by intramuscular injections of gammaglobulin on a regular basis. There was no history of angioneurotic oedema or anaphylactic reactions among other family members.

Physical examination was unremarkable and routine laboratory findings were normal, except for the globulin level which was low (0.9 g/dl). Immunoglobulin levels (while the patient was on gam-

maglobulin treatment) were: IgG 240–271 mg/dl (normal range 700–1400), IgA 0–26 mg/dl (normal range 100–400), IgM 0–28 mg/dl (normal range 60–240) and IgE 9 IU/ml (normal range 0–100). Salivary IgA was not detectable. E-rosette forming cells (T-cells) were 80% (normal) and latex ingesting cells (monocytes) were 11% (normal). Staining by immunofluorescence for cells with surface immunoglobulins (B-cells) was negative. *In vitro* lymphocyte responses to phyto mitogens (PHA, Con-A, PWM) or antigens (*Candida*, *E. coli*, *Staphylococcus aureus*) were normal. Lymphocyte stimulation with several viral antigens (adenovirus, herpes virus and cytomegalovirus) resulted in normal positive responses. Mixed lymphocyte culture response to a pool of allogeneic cells was normal.

Analysis of subpopulations of T-cells by monoclonal antibodies revealed a normal percentage of total T-cells (OKT3 positive lymphocytes) – 61% (normal range 57%–69%), T-helper cells (OKT4 positive) cells – 48% (normal range; 39%–58%) and T-suppressor cells – 28% (normal range; 17%–30%). Neither isohaemagglutinins nor autoantibodies (antinuclear antibody or rheumatoid factor) were found in the serum and no anti-IgA antibodies could be detected.

Complement studies

Total haemolytic activity of complement (CH₅₀) and functional activity of C2 and C4 were determined by methods previously described (Day *et al.*, 1973). C1q and C3 levels were measured by immunodiffusion using monospecific antisera prepared against the purified components (Day *et al.*, 1973). Immune complexes were quantified by the Raji cell assay (Theofilopoulos *et al.*, 1976). C1 esterase inhibitor

Table I Complement components study of patient and father

	C1 INH (U/ml)	CH ₅₀ (U/ml)	C1q (µg nitrogen/ml)	C3 (mg/dl)	C2 (CH ₅₀ U/ml _{serum})	C4 (CH ₅₀ U/ml _{serum})	Immune complexes (µg/ml _{serum})§
Patient							
Test No. 1*	5.7 (13.6)†	70	21	84	ND‡	ND	<16
2	3.5 (9.5)	113	10	122	1499	257,855	<16
3	1.0 (6.0)	146	17	104	1318	428,743	<16
Father	6.5 (6.0)	116	31	119	ND	ND	<16
Normal range	6.0–13.6	50–110	17–23	80–180	850–1850	144,500–347,500	<16

*Test No. 1: 14 days after gammaglobulin injection. Test No. 2: 6 days after gammaglobulin injection. Test No. 3: 14 days after gammaglobulin injection. On this day, patient was given gammaglobulin injection i.m. and developed a severe anaphylactic reaction.

†Numbers in parentheses indicate the level of normal control for that day test.

‡ND = not done.

§µg equivalent human aggregated gammaglobulin/ml.

activity was measured functionally according to methods previously described (Day *et al.*, 1976). The results of these studies are summarized in Table I. Of all the family members, only the father of the patient was available for study and his C' system was normal in every respect. The patient's total haemolytic complement (CH₅₀), C4 and C2 levels (measured functionally), C3 (measured immunochemically) and circulating immune complexes were within normal limits (Table I). C1 INH and C1q, however, were decreased in the patient's sera.

Discussion

This patient with apparent X-linked agammaglobulinemia had a much greater frequency of severe clinically significant reactions to intramuscular gammaglobulin than is usually seen in X-linked recessive agammaglobulinemia or hypogammaglobulinemic patients (Soothill, 1971). In fact, the reactions were so severe as to ultimately prevent the use of intramuscular gammaglobulin preparations in this patient's treatment. These reactions were associated with consistently low levels of C1 INH. As is frequently seen in hypogammaglobulinemic patients, levels of C1q were also sometimes low. The C1 INH deficiency could not be shown to be of an hereditary form; however, conclusive family studies could not be carried out. Nonetheless, it seems attractive to postulate that, as in other forms of acquired C1 INH

deficiencies, increased consumption or catabolism of C1 INH was responsible for the low levels in this patient. On the basis of the findings in this patient, studies of C1 INH levels in agamma- and hypogammaglobulinaemic patients seem in order, especially to determine whether a propensity to anaphylactoid reactions to gammaglobulin relate in a more general way to low levels of C1 INH. The possibility exists that C1 INH levels, like C1q levels, may be lower than normal in hypogammaglobulinemic patients due to increased catabolism of C1 INH (Kohler & Muller-Eberhard, 1972; Atkinson *et al.*, 1978). Further studies of C1 INH in hypogammaglobulinemic patients seem indicated for this reason alone. Alternatively, C1 production may have been depressed in our patient, leading to a failure to clear aggregates of gammaglobulin in the preparation.

Although there are clear deficiencies in our study of this patient (e.g. metabolism of C1 INH was not evaluated), clinical circumstances precluded further analysis. Nonetheless, the association, for the first time, of low levels of C1 INH and susceptibility to anaphylactoid reactions to gammaglobulin are provocative, and should generate definitive additional studies of these relationships.

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