

IMMUNOGLOBULIN DEFICIENCY

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ABSTRACT

Twenty three patients with primary immunoglobulin(Ig) deficiency were seen during the last ten years. Nine had hypogammaglobulinemia (hypo-Ig) and the rest, selective Ig deficiency. Most were in pediatric age group. There was preponderance of males with only one female. Clinical symptoms pertaining to gastrointestinal and sinupulmonary infections were most common. Complete absence of B cells was not observed in any patient with hypogammaglobulinemia. They could be typed as physiological in one patient, X-linked immunodeficiency in 2 patients and common variable immunodeficiency in the remaining six. Three patients with selective IgA deficiency were above 20 years of age. Two had only secretory IgA deficiency, confirmed by jejunal fluid examination and the rest had both secretory and serum IgA deficiency. Low IgM was seen in one patient. We see a spectrum of immunoglobulin deficiencies varying from subtle defects like absence of secretory IgA only, to severe depletion of all immunoglobulins. Therapy is still not ideal due to economic reasons.

Key words: Immunoglobulin deficiency, Hypogammaglobulinemia, Selective immunoglobulin deficiency.

Primary humoral immunodeficiency (PID) results from defects in the response to antigens by the B cells or their precursors. The severity of the clinical symptoms depends on the magnitude of the disease and on the type of immunoglobulin produced. Conditions affecting at the differentiation stage result in hypogammaglobulinemia. The later stages of cellular maturation result in specific immunoglobulin defect(1,2). Humoral immunodeficiency in this country although occasionally reported is not rare. Diagnosis of PID gains importance as most conditions are treatable. We report the cases of humoral immunodeficiency seen by us at this centre over the last ten years.

Material and Methods

During the last 10 years, 177 children with repeated infections requiring hospitalization(3) were investigated for the immune status mostly during the infection free period. Cases diagnosed as having PID during active infection were investigated during remission and the diagnosis was confirmed. Indications for investigations were dependent on the clinical profile. The WHO recommendation(4) was used for classification.

Routine investigations were done by the standard methods as already described(5). These included total leucocyte count, peripheral blood smear examina-

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tion, serum protein electrophoresis, quantitation of immunoglobulins (Hoechst), T cells and their subsets, response to lectin (PHA), phagocytosis and intracellular killing, NBT reduction and chemotaxis. Other fact finding tests such as jejunal biopsy and immunohistology were done where required.

Age matched controls were simultaneously studied with each child. Most of them were Out Patient children with mild infections.

Results

Seventy seven patients with varying type of defects were seen during the last ten years. Out of these 23 had a spectrum of humoral immune defects. Nine had panhypogammaglobulinemia and 14 had selective immunoglobulin deficiencies; of the remaining 54, twenty nine had combined defect, 15 neutrophil dysfunction and 10 cell mediated immunity. Immunoglobulin levels of IgG below 400 mg/dl and IgA <100 mg/dl were considered panhypogammaglobulinemia.

Of the 9 patients of hypogammaglobulinemia, 8 were male and one female (*Table I*). The most frequent clinical feature included bronchopneumonia and chronic diarrhea. Other features included thrombocytopenia (1 case), PUO with hepatosplenomegaly (1 case) and associated candida infection (4 cases). The patients with low immunoglobulins could be tentatively classified as (i) delayed transient hypogammaglobulinemia (Case No. 3), (ii) X-linked hypogammaglobulinemia (Case Nos. 2 and 8) and (iii) Common-variable immunodeficiencies (Case Nos. 1, 4, 7 and 9). Immunoglobulin therapy was given to three patients who could afford it. Case Nos. 5 and 7 were given intra-muscular immunoglobulins while Case No. 8 was

on intravenous therapy. However, often finances were a handicap and at periods no treatment was given. There was no change in immunoglobulin levels after therapy, but improvement was judged by the clinical symptoms.

Case No. 3 was a 3-year-male complaining 2.5 years of ill health. The immunoglobulin levels were IgG 400 mg/dl, IgA 46 mg/dl and IgM 65 mg/dl. The T cell number and functions were normal. His immunoglobulins levels improved over the next two years and by the time he was five years old they were within normal range. No treatment was given. This was an example of delayed maturation of immune response.

Case No. 6 was 15-year-old male who was deaf and mute and the only male progeny was diagnosed as celiac disease. Serum immunoglobulins were IgG 130 mg/dl, IgA 10 mg/dl and IgM 40 mg/dl. There was lymphopenia (900 mm^3). The B cells were 6% and T cells were 56%. Skin response to PPD was low (6 mm) but *in vitro* migration inhibition response to BCG was normal while response to PHA was reduced. The boy was on irregular treatment with intramuscular gammaglobulins; continued to suffer from gastrointestinal and pulmonary complaints and died of acute bronchopneumonia eight years later. On autopsy, the thymus was not traceable, the hilar, pancreatic and mesentric lymphnodes were enlarged. They showed abortive attempt at follicular hyperplasia. The lymphocytes were depleted and occasional plasma cells were seen. Identical picture was seen in Payer's patches. Immunoperoxidase staining of the intestinal sections revealed that the infiltrating lymphocytes stained only for IgM (*Fig 1*). This was considered as either manifestation of switch defect or defect in

TABLE I—Profile of Patients with Hypogammaglobulinemia.

S.No.	Age of onset (yrs)	Sex	Symptoms	Immunoglobulins			B cells (% lymphocytes)
				G (mg/dl)	A (mg/dl)	M (mg/dl)	
1.	4	M	Rec. bronchopneumonia	250	45	62	ND
2.	10/12	M	Collapse lung, thrombocytopenia	340	nil	140	ND
3.	3	M	Rec. bronchopneumonia	400	46	65	15%
4.	2	M	PUO, hepatosplenomegaly	240	20	nil	16%
5.	18	M	Rec. diarrhea, pneumonia, giardiasis	302	nil	40	6%
6.	15	M	-do-	130	10	40	13%
7.	8	F	-do-	180	15	10	30%
8.	8/12	M	Pneumonia, oral candidiasis	200	nil	68	7%
9.	5	M	Rec giardiasis	238	65	190	27%

PUO = Pyrexia of unknown origin; Rec. = Recurrent; ND = Not done.

the interleukin responsible for isotype switching.

An 8-year-old female the youngest of nine healthy siblings presented with history of recurrent giardiasis and diarrhea alter-

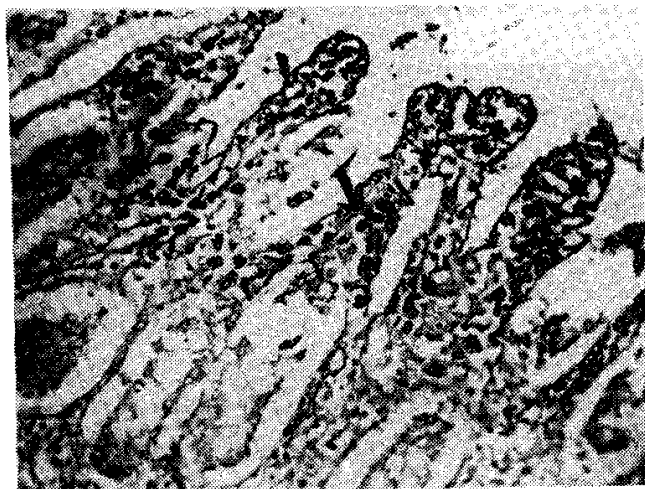


Fig. 1. Immunohistology showing IgM (arrow) staining cells in lamina propria. No staining could be demonstrated with anti-IgA.

nating with bronchopneumonia and stunted growth, serum immunoglobulins were IgG 180 mg/dl, IgA-15 mg/dl and IgM 10 mg/dl. Neutrophil function tests were in normal range and jejunal biopsy revealed nodular lymphoid hyperplasia. Immunoperoxidase staining showed few IgM and kappa positive cells. She died after seven years of bronchopneumonia. Her symptoms kept waxing and waning even though on immunoglobulin therapy.

Another child presented at the age of 8 months with bronchopneumonia and oral candidiasis. Quantitation of immunoglobulins confirmed hypogammaglobulinemia (G nil, A nil and M 120 mg/dl), T cells were 50% and B cells were 7% by Flow-cytometry (Leu 4/Leu 12). Bone marrow also showed 7% B cells. T cell and neutrophil functions were normal. Two male sibs and a maternal uncle died in infancy

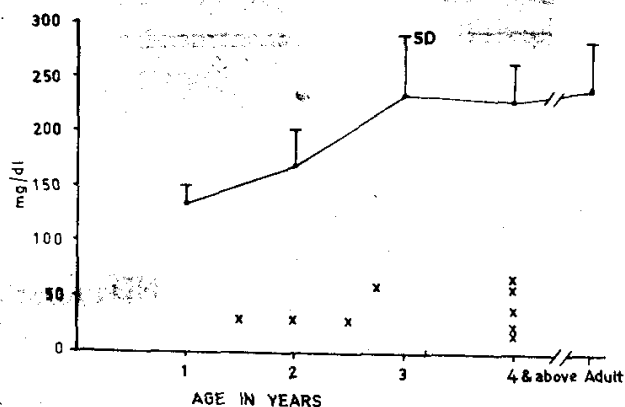


Fig. 2. Selective IgA deficient with age matched control (each dot represents mean and SD of four children).

with similar symptoms. The family history suggested a sex linked dominant inheritance. Certain features like severe infection, presence of 7% B cells and normal IgM suggests a common variable immunodeficiency. The child survived on intravenous gammaglobulins for 3 years and died of infection when therapy was withdrawn.

Fourteen patients showed selective immunoglobulin deficiency (Table II). Eleven patients had complete serum and secretory IgA deficiency; 9 were children; 2 adults aged 27 and 40. Secretory IgA deficiency was observed in 2 and IgM was low in one. The dominant clinical features were related failure to thrive, gastrointestinal tract infections like recurrent giardiasis, malabsorption and bacterial diarrhea and bronchopneumonia. Of the two adults, diarrhea was present off and on since childhood. Nodular lymphoid hyperplasia in jejunal biopsy was seen in both the patients.

In two other patients, serum immunoglobulins were normal but secretory IgA was absent in jejunal fluid as well as saliva.

On histology, mild atrophy of villi with nodular lymphoid hyperplasia was seen. Immunoperoxidase staining for IgA producing plasma cells was negative. One patient had very low blood levels of IgM. Tests for cell mediated immunity were normal.

Discussion

Depending on the deficiency of serum immunoglobulins, the WHO characterized 13 types of B cell defects(4). The defect may be intrinsic in the lymphoid cell, in the microenvironment for maturation or in the regulatory cells which control the humoral or cell mediated immunity(6,7). Recurrent infections like giardiasis and bronchopneumonia continue to pester the patient despite immunoglobulin therapy. This is in contrast to the Western studies where giardiasis has been eliminated and gastrointestinal infections are less common whereas viral infections are more prevalent in children with replacement therapy(8).

Transient hypogammaglobulinemia is a well, recognized entity(1). The development of ability to produce immunoglobulins varies in different individuals. According to the Western literature, the levels of IgM, reach normal at 1 yr, IgG at 5 to 7 yrs and IgA at 10 to 14 yrs(1). We have observed that IgA levels were much higher in our controls (Fig. 2) and reach adult level early. This may be due to repeated exposure to pathogens.

Boys with X-linked agammaglobulinemia are usually normal at birth and begin to have infection when they have catabolized substantial amount of maternal antibodies by 6 months. The immunoglobulin production is controlled by a gene on the X-chromosome, the product of which is essential for the maturation of B cells and production of immunoglobulins(2). Al-

TABLE II—Profile of Patients with Specific IgA/M Deficiency

Case No.	Age/ Sex (yrs)	Symptoms	Immunoglobulins			Salivary IgA
			A	G	M	
1.	8 M	Growth failure	65	110	158	Absent
2.	2.5 M	Growth failure, Rec. diarr- hea, bronchopneumonia	30	1000	110	Absent
3.	1.5 M	Rec. giardiasis	30	720	45	ND
4.	4.5 M	Rec. bronchopneumonia	60	1450	210	ND
5.	5 M	Malabsorption	25	1240	115	Absent
6.	3 M	Rec. giardiasis	60	740	105	Absent
7.	4 M	Rec bronchopneumonia	21	765	126	Absent
8.	6 M	Necrotizing pyogenic abscess	45	1328	55	Absent
9.	1.5 M	Septic arthritis	40	1802	94	ND
10.	27 M	Rec. diarrhea	58	958	83	Absent
11.	40 M	-do-	42	1450	155	Absent
12.	13 M	Malabsorption syndrome	137	1112	177	Absent
13.	43 M	-do-	119	2125	88	Absent
14.	1.5 M	Repeated viral infection	149	958	20	ND

ND = Not done; Rec. = Recurrent.

though CMI and neutrophil functions are normal, metabolic defects in T cells have been shown(7). These patients rarely show complete absence of B cells and small amount of immunoglobulins are always present, suggesting that immature B cells are present(9). Using monoclonal antibodies, Golay and Webster have shown an early block in B cell ontogeny.

Common variable immunodeficiency (CVID) also identified as idiopathic late onset agammaglobulinemia(4) is a heterogeneous group of disorders. The clinical presentation and laboratory findings are similar to X-linked agammaglobulinemia; the principal difference being that it pres-

ents at a much later age and the infections are slightly less severe. Subtle T cell defects are noted in both. A recent study on CVID(10) has shown that the B cells from peripheral blood of CVID patients respond well to the cytokines and suggest a defect at the differentiation stage rather than in the growth phase. Subtle defects in T cell function may also be due to deficiency of T cell activating cytokines(11).

The association of nodular lymphoid hyperplasia in the ileum with immunodeficiency has been well described(8). However, a study from Vellore(12) has shown that this is a relatively common finding in patients with diarrhea. The

paucity of immunoglobulin staining (G, M and A) cells on histology sections confirm the diagnosis of hypogammaglobulinemia.

Selective IgA deficiency in healthy individuals is reported to be 1 in 700 to 1 in 328 in the West(1). No such mass scale studies are available from this country. Age matched children with other infections who were controls in this study show maturation of IgA much earlier. By the age of 3 years, adult values are seen. The exposure of the children to the multiple antigens in our environment may be a stimulus for early maturation. The exact cause of this deficiency is not clear, but any one of the causes in the differentiation and secretion of IgA producing B cells may be there(4). Deficiency of secretory IgA has been shown to be the result of deficiency in the production of secretory component(1). In an extension of this study, we have observed selective IgA deficiency in 58.8% of 22 patients of ataxia telangiectasia(13).

Patients of agammaglobulinemia are known to do fairly well with regular doses of intravenous immunoglobulins(14). Regular therapy with gammaglobulins is a very expensive affair in this country and most of the patients cannot afford treatment. However, this should not discourage us from trying to help such patients.

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NOTES AND NEWS

ATAXIA-TELANGIECTASIA Call for Cases

We have established a diagnostic test for this disorder which can be used for prenatal diagnosis. It is based on the sensitivity of the cells to radiation and other mutagenic agents. We have successfully carried out prenatal diagnosis in two cases. We would be willing to accept cases for diagnosis, including prenatal diagnosis, and would appreciate if you refer the cases to us, at the following address:

Dr. I.C. Verma,
Professor of Pediatrics and
Officer-in-charge,
Department of Pediatrics,
Genetic Unit,
Old Operation Theatre Building,
All India Institute of Medical Sciences,
New Delhi 110 029.

or **Miss Madhumita Roy Choudhury,**
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