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Decreased serum immunoglobulin A level in a patient with bronchiectasis

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IN RECENT YEARS immunoglobulin A (IgA) has assumed great biological significance. Although a relatively minor constituent of serum, it is the predominant immunoglobulin in external secretions, particularly of the gastrointestinal and upper respiratory tract, and appears to play an important protective role in local defence mechanisms (Tomasi & Bienenstock, 1968).

The incidence of IgA deficiency in Caucasians ranges from 2 to 7 per 1000. (Ammann & Hong, 1973; Rosen, 1975); the incidence in Malaysians is not known. Although recurrent mild and moderately severe respiratory and intestinal tract infections have been observed in many cases of isolated IgA deficiency (Hobbs, 1968), there are many IgA – deficient individuals who remain healthy throughout life (Rockey et al., 1964; Hereman & Crabb, 1968). Thus it is not entirely clear why some IgA-deficient individuals are asymptomatic whereas others suffer recurrent infections.

The present study is an outcome of observations over several years on a patient with bronchiectasis, chronic diarrhoea and recurrent episodes of otitis media.

Immunological studies recently performed suggest that the clinical manifestations are probably a consequence of decreased IgA levels and markedly elevated IgE levels observed in the patient.

Case Report

The patient, N.K. a Punjabi female now aged 10 years (Dec, 1975) and the youngest in a family of 6 girls and 1 boy, has a normal birth history and a history of having received full immunisation in the first 2 years of life. She has had no immunising diseases. The parents and other relatives are healthy. There is no consanguinity.

N.K. was first seen at age 2½ years for heavy *trichuris* infection. From age 2½ years she had a chronic cough and by 4 years she had been admitted once for bronchopneumonia and otitis media, and three times for chronic diarrhoea. Rectal biopsy revealed a non-specific colitis. The chronic diarrhoea resolved spontaneously after age 4 years. At age 5, a left lobectomy was performed for poorly controlled bronchiectasis. The patient required several further admissions for inguinal lymphadenitis, maxillary sinusitis, chronic suppurative otitis media and exacerbations of bronchiectasis. (Table 1).

Cultures of sputum and ear swabs yielded *H. influenza,* Diphtheroids, *Klebsiella, Staphlococcus, serratia marcescens* (ear swab) or *proteus.* Several antibiotics including Gentamycin, Bactrim, Ampicillin, Penicillin, Tetracycline and Erythromycin were used singly and in combination to control the infections.

Other data obtained on 22/12/75: height 125 cm; weight 22 kg. Blood group: A positive; Haemoglobin: 11.7 gm%, MCHC 30; WBC 10,600 cells/mm (Polymorphs 63%, Lymphocytes 23%, Monocytes 5%, Eosinophils 9%): ESR 45 mm/hr; Platelets 102×10^3; Mantoux test negative; α_2 fraction of serum proteins increased.

Table 1
Summary of Clinical History of Patient NK

Admission number	Year	Age in years	Clinical History
1	1968	2½	Trichuriasis.
2	1968	2½	Bronchopneumonia, trichuriasis, and (¾) amoebiasis, diarrhoea.
3	1969	3	Non-specific diarrhoea and chronic otitis media.
4	1969	3	Chronic diarrhoea and chronic otitis media.
5	1971	5	Bronchiectasis and recurrent pneumonia, L. lobectomy for bronchiectasis.
6	1972	6	Bronchiectasis and bronchopneumonia.
7	1975	9	Inguinal lymphadenitis, chronic maxillary sinusitis, adenitis, bilateral chronic suppurative otitis media and exacerbation.
8	1975	9	Bronchiectasis, chronic otitis media.
9	1975	10	Bronchiectasis, (L) otitis media, IgA deficiency.

Immunological Studies:

The recurrent episodes of infection suggested an underlying immunological disorder and tests of cellular and humoral immunity were carried out.

The patient's polymorphs gave a normal (65 percent) Nitroblue tetrazolium (NBT) reduction test. The Mantoux test was negative. The stimulation index of Phytohemagglutinin (1% PHA) transformed peripheral blood lymphocytes separated by Ficoll-Hypaque centrifugation and cultured in medium RPMI 1640 at a concentration of 1×10^6 cell/ml was of the order of 10 and comparable in magnitude to those observed in controls.

Serum immunoglobulins A, G, M and D levels were assayed by the single radial immunodiffusion method (Mancini et al., 1965) using plates obtained from a commercial source (Behringwerke AG, Germany). Serum IgE was determined by a radio immunoassay procedure using a kit from Pharmacia AB Diagnostics, Sweden.

Table 2 summarises the serum immunoglobulin A, G, M, D and E levels in the patient, her mother and three elder sisters. Sera from other members of her family were not available at the time the work was carried out.

Table 2

Serum Immunoglobulin Levels in Family Members

Family**	Birth year	Age in years	Relationship to patient	SERUM IMMUNOGLOBULINS* IgG	IgA	IgM	IgD	IgE
1. –	–	55	Father	ND	ND	ND	ND	ND
2. G.K.	–	40	Mother	243	139	138	0	9000
3. –	1953	23	Sister	ND	ND	ND	ND	ND
4. P.K.	1955	21	Sister	243	156	273	0	3300
5. –	1958	18	Brother	ND	ND	ND	ND	ND
6. M.K.	1961	15	Sister	278	136	306	0	2200
7. B.K. (Twin I)	1963	13	Sister	213	139	153	0	6500
8. B.K. (Twin 2)	1963	13	Sister	178	69	138	0	2200
9. N.K.	1969	10	Patient	337	31	356	475	2600
Control mean value ± standard deviation for Malaysian Indians				154 ± 38	146 ± 51	217 ± 79	29 ± 42	1300 ± 2000

* Values in International/ml. (Blood samples obtained on 26–29/12/75). To convert to mg percent, multiply values by 8.33 for IgG, 1.51 for IgA, and 0.89 for IgM; Data from Shah & Yadav (unpublished).

** All members of the family alive and well.

ND = Tests not performed as donors not available.

Discussion:

The patient had reduced IgA levels whereas the other immunoglobulins were raised. The markedly elevated IgD level is of interest as this is the first instance such a high value has been recorded in our laboratory. Serum immunoglobulin levels of other members of the family fall within the normal range for the Indian population in Malaysia. The serum IgE levels in all members of the family are elevated (pathologic range >800 IU/ml) and these are probably related to intestinal and other parasitism.

In selective IgA deficiency serum IgA levels are often less than 5 mg percent; there is no deficiency of other immunoglobulins and a normal antibody-mediated and cell-mediated immunity is present (Ammann & Hong, 1971). The patient N.K. has decreased serum IgA level (47 mg%) and not isolated IgA deficiency. Here the defect may be a failure of maturation of the B cell on antigenic stimulation or possibility the presence of suppressor T cells that inhibit the maturation. The description of suppressor T cells in a number of patients with immunodeficiency states represents an important recent development (Waldmann et al., 1974). The nature of the block in B cells is unknown.

IgA plays a major role in the first line defence against microbial, parasitic and viral infections at the local level (Per Brandtzaeg, 1973) especially in the respiratory and gastrointestinal tract. In the presence of decreased levels of secretory IgA antibodies, synthesis of the other immunoglobulins may be elevated as seen in our patient. Lack of secretory IgA can impair antigen exclusion by the mucosal lining resulting in antigenic challenge with elevation of IgE (Taylor et al., 1973).

11 individuals with combined IgA and IgE deficiency studied by Polmer et al (1972) were free of any respiratory disease. But 10 of 14 IgA-deficient patients, with normal IgE levels had significant disease. These observations suggest that elevated IgE levels may play an important role in the occurrence of respiratory disease in IgA deficient patients.

The markedly elevated IgD serum levels observed in our patient is of interest. It is well established that the main immunoglobulin receptors on lymphocytes are IgM and IgD. The lymphocyte surface IgD receptors are present in all age groups including newborn. The precise biological function of *serum* IgD remains unknown. An analysis of large number of normal sera obtained from various sources in Malaysia (Yadav, unpublished) shows the patient N.K. to have the highest level of record. Luster and co-workers (1976) have reported elevated serum IgD levels in patients with allergic bronchopulmonary aspergillosis.

The present report draws attention to the paucity of immunological studies and other data on patients with immunological disorders in Malaysia.

Summary:

The patient, a 10-year old Punjabi girl, was first seen at age 2 years for heavy trichuris infection. From age 2 years to 4 years, she had a chronic cough and was admitted once for bronchopneumonia and otitis media and three times for chronic diarrhoea. Rectal biopsy at this time showed a non-specific colitis. The chronic diarrhoea resolved spontaneously after age 4 years. At age 5 years, a left lobectomy was performed for bronchiectasis and recurrent pneumonia. The patient required several further admissions for lymphadenitis, sinusitis, otitis media and bronchiectasis.

Immunological investigations revealed a normal NBT-dye reduction by her leukocytes and a normal *in-vitro* response by her lymphocytes to PHA. The serum IgA was reduced while other immunoglobulins (IgG, IgM, IgD and IgE) were markedly elevated. Since IgA is the primary immonoglobulin of secretory surfaces, its decrease or absence may be associated with infections in the respiratory and gastrointestinal tracts.

It is suggested that high IgE levels in IgA-deficient patients are primarily responsible for the clinical manifestations of respiratory and gastrointestinal infections.

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