LOW INCIDENCE OF SELECTIVE IgA DEFICIENCY IN NORMAL MALAYSIANS

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INTRODUCTION

IN populations residing in the temperate regions selective IgA deficiency is the most common of the primary immunodeficiency diseases occurring in about 1:500 to 1:700 individuals (Bachmann, 1965; Hanson, 1968; Hobbs, 1968; Johansson *et al.*, 1968; Koistinen, 1975). The condition is characterized by serum IgA levels less than 5 mg/100 ml with normal serum levels of the other class of immunoglobulins and absence of T cell deficiency. In many of the individuals with selective IgA deficiency, thymus defects of varying severity are present and therefore some degree of T-cell hypofunction is expected (Horowitz & Hong, 1975; Buckley, 1975).

The deficient serum IgA is usually associated with absence of secretory IgA from the body secretions but occasional individuals possess the capacity for normal production of secretory IgA (Bellanti *et al.*, 1966). Also, individuals with secretory IgA deficiency in the presence of normal serum IgA have been recorded (Krakaeur *et al.*, 1975).

Ammann & Hong (1971) reviewed the clinical features of 205 patients with IgA deficiency and found that autoimmune disorder were present with greates frequency and also, many patients experienced recurrent sinopulmonary infections and gastrointestinal disorders. A surprising observation was that about 10 per cent of the individuals with selective IgA dificiency were clinically normal. Similar observations had also been made by other investigators (Hanson, 1968; Koistinen, 1975).

The exact mechanism by which IgA deficiency occurs remains unclear but at least two separate mechanisms have been shown to occur. In one, there is insufficient helper T cell activity for IgA antibodies because of the defect in thymus development, and in the second, B lymphocytes destined to produce IgA are arrested at an early stage of development. The selective IgA dificiency can occur sporadically but autosomal dominant, autosomal recessive, intermediate polygenic modes of inheritance and chromosome abnormality have been reported (Nell *et al.*, 1972; Koistinen, 1976; Horowitz & Hong, 1977). Environmental factors, too, can be important in its development. Lewkonia *et al.* (1976) noted the presence of IgA deficiency in one of the monozygotic twins. In some individuals IgA deficiency develops following penicillamine or phenytoin therapy (Hjalmarson *et al.*, 1977; Stanworth *et al.*, 1977).

There is very little information on selective IgA deficiency in Malaysians, or for that matter for populations normally resident in the tropics (Yadav, 1977). Some individuals with selective IgA deficiency have the potential of forming anti-IgA antibodies with the resultant and sometimes fatal anaphylactoid reactions on transfusion with IgA containing plasma (Vyas *et al.*, 1969), and therefore it is important to konw the incidence of IgA deficiency in normal Malaysians.

The aims of this study was to determine the normal range of serum IgA level in Malaysians from the urban (Chinese, Malay & Indian) and rural (Malay and Orang Asli) areas with special reference to low or absent levels of serum IgA. The observations show that selective IgA deficiency is uncommon in healthy Malaysian blood donors.

MATERIALS AND METHODS

Blood Samples: Sera from 2,025 healthy donors were obtained from the Blood Bank, University Hospital, University of Malaya; the Gombak Orang Asli Hospital, Selangor; through the cooperation of secondary schools in Petaling Jaya, Selangor and through the cooperation of

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the Filaria Unit, Sungei Patani, Kedah. The sera were kept frozen at -20°C until required.

Quantitative Determination of Immunoglobulin: The sera was assayed for immunoglobulin A by the single radial immuno-diffusion method (Mancini *et al.*, 1965) as previously described (Yadav, 1977; Yadav & Shah, 1978). The agar diffusion plates incorporating H-chain specific rabbit antisera were either prepared in our laboratory or the immunodiffusion plates were purchased from a commercial source (Behringwerke, Germany). Standards from the World Health Organisation or commercial sources were used.

RESULTS

Selective IgA deficiency was not observed in 2,025 sera analysed for IgA from urban and rural Malaysians. (Table I). The serum IgA level ranged from 57 to 846 mg/100 ml in rural and 45 to 430 mg/100 ml in urban folks. The frequency histogram of serum IgA was skewed to the right for the samples from the rural population. The mode was between 121-200 mg/100 ml for urban Malaysians, 161-240 mg/100 ml for rural Malays and 321-360 mg/100 ml in the Orang Asli. For the total sample the mode fell between 161-200 mg/100 ml. The mean serum IgA level for urban sample was 200 mg/100 ml which was significantly lower than the mean value of 267 mg/100 ml for the rural sample.

DISCUSSION

Selective IgA deficiency occurs in 1:700 healthy individuals in Sweden (Bachmann, 1965; Hanson, 1968; Johansson *et al.*, 1968), 1:310 in school children 5-19 years old and 1:454 in hospital patients 0-19 years old in Canada (Collins-William *et al.*, 1972), 1:398 in rheumatoid arthritis patients and 1:1255 in blood donors in Norway (Natvig *et al.* 1971), 1:2190 in blood donors in France (Frommel *et al.*, 1973) and 1:396 in blood donors in Finland (Koistinen, 1975). It is believed that the marked difference in the frequency of selective IgA deficiency may be caused by genetic factors in different ethnic groups (Koistinen, 1975). However, it is also possible that the low incidence in some groups is because IgA deficient individuals would not survive through early life in a pathogenically hostile environment. In Malaysia the analysis of 2,025 sera from healthy blood donors has not revealed a single case of IgA deficiency. Previously, we have reported that in a 10 years old girl with bronchiectasis, chronic diarrhoea and recurrent episodes of otitis media, the serum IgA level was low (31 mg/100 ml) and the other classes of immunoglobulins were markedly elevated (Yadav *et al.*, 1977). Since IgA is the first line of defense of the secretory system which primarily protects the respiratory and gastrointestinal tracts, uncontrolled antigenic assault in those areas in individuals with low or absent protective IgA would result in development of clinical disease. In the tropics relatively more opportunities are prevalent for assault from a variety of viral, bacterial, fungal, helminthic and other agents. In view of the above it is questionable whether asymptomatic selective IgA deficiency can be present in the tropics. Thus, in the temperate regions the significant number of individuals with asymptomatic selective IgA deficiency (Koistinen & Sarna, 1976; Horowitz & Hong, 1975) do not develop clinical disease presumably because environmental infective agents are relatively uncommon and secondly, the compensatory mechanisms including secretion of IgM (Thompson, 1970) on the mucosal surface are adequate under the conditions, to exclude the entry of pathogenic antigens.

In an analysis of 606 sera from adult out- and in-patients seeking treatment for a variety of disorders e.g. bronchitis, tuberculosis, asthma, gastritis, gastroenteritis, appendicitis, cholecystitis, typhoid, malaria, aches & pains, coughs & colds, and others, serum IgA levels were never less than 35 mg/100 ml (Yadav, unpublished). This observation leads us to believe that patients with selective IgA deficiency may get life threatening infections in early life.

In the newborn IgA in serum ($<$0.8 mg/ml) was present in 36.4, 40.5, 31.6, and 62.5 per cent of full term Chinese, Indian, Malay and Orang Asli, respectively (Shah & Yadav, 1977). It is not known how soon after birth the infants attain protective levels of serum IgA and more significantly when the secretory IgA on mucosal surfaces reaches optimal levels. However, in a preliminary analysis of the serum immunoglobulins in 497 infants aged 1 month to 4 years admitted to the University Hospital for various

Fequency Distribution of Serum IgA Concentration of Malaysians aged 11 to 60 years

Table I

Race	Serum IgA Concentration mg/100 ml*													
	Total Samples	5	5-40	41-80	81-120	121-160	161-200	201-240	241-280	281-320	321-360	361-400	401-440	441-900
URBAN														
Chinese	466	0	0	3[a]	73	112	123	54	36	39	21	4	1	0
Indians	390	0	0	4	38	54	78	62	47	50	47	7	3	0
Malays	326	0	0	3	32	92	89	46	27	22	8	6	2	0
RURAL														
Malays	605	0	0	5	15	78	129	111	85	74	35	33	21	19
Orang Asli (Aborigines)	238	0	0	0	6	12	4	10	23	30	36	32	22	63
Total	2,025	0	0	15	164	348	423	282	218	215	147	82	49	82
Per cent		0	0	0.7	8.1	17.2	21.0	13.9	10.8	10.6	7.3	4.0	2.4	4.0

* Multiply by 0.5952 to convert to IU/ml.

[a]Number of individuals.

gastrointestinal disorders it was noted that 33 infants (6.6 per cent) had less than 5 mg/100 ml IgA in serum (Yadav & Iyngkaran, unpublished). The majority of the infants presented with acute infective gastroenteritis, cow's milk protein-sensitive enteropathy or malabsorption as their primary clinical feature. Transient IgA deficiency is present in many infants and in some is thought to predispose to atopy, possible by allowing penetration of antigens through mucosal membrane barriers (Soothil, 1974). However, the atopy has also been observed in infants with normal serum IgA. Thus, other factors including genetic constitution and pathogenicity of infective agents may be important in the development of the gastrointestinal defects. However, we have no information on the incidence of transient IgA deficiency in normal Malaysian infants and children, and therefore are unable to comment on the overall significance of the deficiency on the development of atopy in children.

SUMMARY

Immunoglobulin A level were assayed according to the Mancini's method in 2,025 sera from clinically healthy donors of four racial origins (Malay, Indian, Chinese, Orang Asli) residing in urban (1,182 individuals) and rural (843 individuals) parts of Malaysia. The serum IgA level ranged from 45 to 430 mg/100 ml for urban and 57 to 846 mg/100 ml for rural folks. The frequency distribution of the serum IgA concentration for the rural population was skewed to the right. No case of selective IgA deficiency was noted in the samples. It is suggested that the incidence of asymptomatic IgA deficiency is low in the tropics compared to its incidence in the temperate regions, because the prevalence of pathogens in the tropics would eventually result in an uncontrolled antigenic assault on the mucosal surface resulting in the development of disease which may be fatal.

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