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Clinical and immunological features of transient IgA deficiency in children

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SUMMARY

Of eighteen children, in whom no IgA was detected in serum or whole saliva, twelve remained IgA-deficient, but six developed normal IgA levels between the age of 5 and 13 years. In the former, allergic asthma, elevated serum IgM and IgE levels, a high number of IgE-bearing and -containing peripheral lymphocytes, and rather low numbers of circulating T cells and PHA responses were common. Conversely, most of the latter suffered from respiratory tract infections, had normal T and B cell assays, serum IgM and IgE and no asthma. When serum and saliva IgA increased, their recurrent respiratory tract infections ceased.

INTRODUCTION

Some children with IgA deficiency have frequent bronchopulmonary infections (Buckley, 1975), bronchial asthma (Buckley, 1975; Østergaard, 1976) and gastrointestinal allergy (Buckley, 1975; Østergaard, 1977a), but others are well (Bachmann, 1965; Collins-Williams *et al.*, 1972). Selective IgA deficiency may be transient, particularly in children below the age of 2 years (Buser, Pflugshaupt & Schertz, 1974; Østergaard, 1977a). The present paper reports transient IgA deficiency in older children; the increase in serum and saliva may be followed by the disappearance of their tendency to recurrent respiratory infections.

MATERIALS AND METHODS

Eighteen children, aged from 4 to 15 years (median 8 4/12 years), who presented with recurrent and chronic respiratory infections and various allergic diseases—mainly bronchial asthma—in whom no IgA was detected in serum or saliva, but with normal IgG levels, were studied. None received corticosteroids or hyposensitization therapy. None had *Giardia lamblia*, cystic fibrosis or α_1-antitrypsin deficiency. Finally, none of the patients received phenytoin, penicillamine or other drugs known to cause secondary IgA deficiency.

In twelve patients, IgA remained undetected (sustained IgA-deficiency group), and in six patients, IgA levels rose to normal (transient IgA-deficiency group). The two groups had median ages of 8 9/12 and 10 years, respectively.

Nineteen healthy children from the same area as the patients were selected with regard to age to match the patients. None of the controls had experienced recurrent respiratory infections or atopy,

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and none had close relatives with allergic diseases. The age of the controls ranged from 5 to 14 years with a median age of 8 5/12 years.

Serum and whole saliva IgG, IgA and IgM were assayed by an electroimmuno technique (Østergaard, 1976). The lower limits of detection of IgG, IgA and IgM in serum were 0·1, 0·01 and 0·02 g/l, respectively, and of detection of IgA and IgM in saliva 0·007 and 0·001 g/l, respectively. Serum IgE was measured with a paper-radioimmunosorbent test (PRIST, Pharmacia, Copenhagen); the lower limit of detection was 5 iu/ml.

Assays for E rosette test (E-RFC) and IgG-, IgA-, IgM- and IgE-bearing and -containing lymphocytes have been reported elsewhere (Østergaard & Eriksen, 1979; Østergaard 1977); briefly, lymphocytes were isolated on a Ficoll–Isopaque preparation, and E-RFC were detected by the method of Jondal, Holm & Wigzell (1972). Lymphocytes with three or more sheep red blood cells attached to their surface were counted as E-RFC.

For Ig-bearing cells, the procedure was essentially that of Winchester & Fu (1976). The FITC-conjugated antisera were preincubated at 37°C in order to avoid capping of the Fc fragments of IgG (Lobo, Vestervelt & Horwitz, 1975). Incubation with antisera was carried out at 4°C. Cells with a bright fluorescing semicircular ring were counted under a fluorescence microscope.

Intracellular Ig synthesis was studied by the method of Broom *et al.* (1976). The lymphocytes were cultured with RPMI (BIOCULT, Glasgow) supplemented with 10% autologous serum for 7 days in moistened 5% CO_2 with or without 10 μl pokeweed mitogen (PWM, MEDA, Copenhagen). Incubation of 0·0025 ml of the cell pellet was performed with 0·0025 ml of the conjugated antisera, and the percentage of proliferating blasts with bright fluorescence of the cytoplasm were counted under the fluorescence microscope.

Cultures of 3×10^5 cells per ml were performed in round-bottomed microculture plates with or without 0·2, 1·0 and 5·0 μg phytohaemagglutinin (PHA, Wellcome) per culture and incubated at 37°C in humidified air with 5% CO_2 for 72 hr. Eighteen hours before stopping culture, 0·12 μCi ^{14}C-thymidine was added to each well. The cultures were harvested on glass fibre filtres and counted in a liquid scintillation counter (Packard).

Statistical analysis of the results was by the Mann–Whitney test.

RESULTS

Symptoms of the two groups of patients studied appear in Table 1. In the sustained IgA-deficiency group, asthma and eczema were common, and two of them had previously suffered from glomerulonephritis; recurrent respiratory tract infections were rare. Asthma and eczema were rare in the transient IgA-deficiency group, but recurrent and chronic bronchopulmonary infections with pneumococci and *Haemophilus influenzae* were common. Gastrointestinal allergy to milk and egg was found in one of the latter patients.

The sustained IgA-deficiency group had higher levels of serum and salivary IgM and serum IgE than did the controls (Table 2). In the transient IgA-deficiency group, the increase of serum IgE levels was not significant, and serum and saliva IgM levels were normal. In the sustained IgA-deficiency group, the number of E-RFC and the PHA responses were lower than the controls but not

Table 1. Clinical features of patients with IgA deficiency

Subjects	Recurrent respiratory infections	Asthma	Eczema	Gastrointestinal allergy	Glomerulonephritis
Sustained IgA deficiency (12)	2	10	6	1	2
Transient IgA deficiency (6)	6	1	0	1	0

significantly so (Table 3). Normal numbers of E-RFC and normal PHA-stimulated lymphocytic cultures were found in all the transient IgA-deficient patients. Ig-bearing and -containing peripheral lymphocytes in both groups were normal except for a significant increase of IgE-bearing and -containing cells in the sustained IgA-deficiency group (Table 3).

When first seen, the median age of the six children with transient IgA-deficiency was 5 6/12 years (range: 1 6/12 to 8 1/12 years). When IgA was first detected in small amounts in their serum and

Table 2. Ranges and medians of serum and saliva Ig levels in the patients with IgA when first seen

		Serum Ig levels			Saliva Ig levels (g/l)	
Subjects	IgG (g/l)	IgA (g/l)	IgM (g/l)	IgE (iu/ml)	IgA	IgM
Sustained IgA deficiency (12)						
Range	8·4–12·2	0	0·81–42	64–4,040	0	0–0·084
Median	10·4	0	1·92	610	0	0·021
Controls (11)						
Range	7·8–14·8	0·51–2·4	0·4–2·4	10–210	0·48–0·152	0
Median	10·1	1·1	0·84	40	0·058	0
P	>0·1	<0·01	<0·01	<0·01	<0·01	<0·02
Transient IgA deficiency (6)						
Range	7·1–13·2	0	0·38–2·10	21–900	0	0
Median	9·8	0	0·88	94	0	0
Controls (8)						
Range	6·7–15·1	0·65–1·9	0·5–2·6	15–140	0·51–0·168	0
Median	10·8	0·98	0·94	68	0·62	0
P	>0·1	<0·05	>0·1	>0·05	<0·01	

Table 3. The *in vitro* lymphocyte population studies in patients with IgA deficiency and their controls

	Ig-bearing cells (%)				Ig-containing cells (%)					
Subjects	IgG	IgA	IgM	IgE	IgG	IgA	IgM	IgE	E-RFC (%)	PHA-stimulation (c.p.m. × 10^3)
Sustained IgA deficiency (12)										
Range	0·5–3	1–4	7–18	1–7	1–4	0–4	6–12	2–8	42–82	0·42–52·5
Median	2·0	2·0	9·5	3·0	2·5	2·0	7·5	3·5	56·5	16·8
Controls (11)										
Range	0–4	0·5–4	6–19	0–1	1–3	1–3	4–11	0–3	63–78	18–48·4
Median	2·5	1·5	8·5	0·5	2·5	1·0	6·5	0·5	69·5	23·5
P	>0·1	>0·1	>0·1	<0·01	>0·1	>0·1	>0·1	<0·01	>0·05	>0·05
Transient IgA deficiency (6)										
Range	0–2	0–4	9–18	0–1	2–4	0–3	3–10	0	62–74	6·8–60·2
Median	1·5	1·5	10·5	0	2·0	1·0	6·0	0	70·5	24·2
Controls (8)										
Range	1–3	0–3	8–17	0–2	1–3	1–4	5–11	0–2	59–79	9·6–44·6
Median	1·5	1·0	9·5	0·5	1·5	1·5	7·0	0·5	72·5	21·1
P	>0·1	>0·1	>0·1	>0·1	>0·1	>0·1	>0·1	>0·1	>0·1	>0·1

Table 4. The rise in serum and saliva IgA in patients with transient IgA deficiency

Patient no.	Sex	Age and IgA levels (g/l) when first seen			Age and IgA levels (g/l) when IgA first detected			Age and IgA levels (g/l) when obtaining normal IgA		
		Age	Serum IgA	Saliva IgA	Age	Serum IgA	Saliva IgA	Age	Serum IgA	Saliva IgA
1	F	1 6/12	<0·01	<0·007	3	0·04	0·009	5	0·82	0·041
2	F	2 1/12	<0·01	<0·007	4 6/12	0·12	n.d.	6	1·10	0·082
3	M	6 1/12	<0·01	<0·007	7 1/12	0·42	0·012	10	1·2	0·084
4	M	5 1/12	<0·01	<0·007	7 3/12	0·51	n.d.	10	0·98	0·064
5	M	7 1/12	<0·01	<0·007	9 1/12	0·38	0·009	13	0·58	0·028
6	F	8 1/12	<0·01	<0·007	9 6/12	0·46	0·011	13	1·42	0·162

n.d. = Not done.

saliva, their median age was 7 2/12 years (range: 3 to 9 6/12 years), and finally, when they obtained normal IgA levels, their median age was 10 years (range: 5 to 13 years). The IgA concentrations at these ages are given in Table 4.

DISCUSSION

In children with no detectable IgA, the deficiency may be transient or sustained; the latter is associated with asthma and eczema. By contrast, those with transient IgA deficiency had frequent respiratory tract infections, and normal IgA and IgE, T cells and PHA responses.

IgM may 'compensate' for IgA in healthy IgA-deficient individuals (Brandtzaeg, 1970; Savilahti, 1973), and increased IgM levels may have protected most of the patients with sustained IgA deficiency from respiratory tract infections, but not from the development of allergic asthma. However, Brandtzaeg *et al.* (1979) recently found an excess of IgM-making cells in IgA-deficient patients in gastrointestinal mucosa, but the lacrimal and parotid glands contained mainly IgD-producing cells. These findings are consistent with the report by Sewell *et al.* (1979) who demonstrated IgD in whole saliva and parotid saliva but not in jejunal juice, and Forsgren & Grub (1979) showed a high binding of IgD to *Neisseria catarrhalis* and *Haemophilus influenzae*, normal pathogens of the respiratory tract in humans. Hence, IgD may play a protective role in the defence against respiratory tract infections. We did not study IgD in our patients, so these interpretations are speculative.

Several experimental and clinical reports suggest that IgA production is influenced by T cells (Ammann *et al.*, 1970; Clough, Mims & Strober, 1971; Ebersole, Taubman & Smith, 1979), and T cells are low in allergic patients with or without low IgA levels (Strannegård, Lindholm & Strannegård, 1976; Østergaard, 1977b). IgA deficiency may therefore be due to a thymic dysfunction.

It has previously been shown that in children below the age of 2 years, transient IgA deficiency is rather common (Taylor *et al.*, 1973; Buser *et al.*, 1974). Conversely, in older children with severe IgA deficiency, transient IgA deficiency is presumably rare. Of seventy children with selective IgA deficiency, Buckley (1975) found two patients who developed normal IgA levels 5 years later, and five other children with low IgA levels who developed normal serum IgA concentrations. These observations indicate that low, but detectable, IgA levels may be transient. We show that even older children with serum and saliva IgA undetectable by a sensitive method may develop normal IgA levels.

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