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Susceptibility to infections in children with selective IgA- and IgA-IgG subclass deficiency*

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Abstract. This study included 36 children with IgA-deficiency, increased susceptibility to infections and/or other disorders. Recurrent, usually bacterial infections were noticed in 23 out of 26 patients (88%) with complete and in 7 out of 10 patients (70%) with partial IgA-deficiency. All patients with severe infections had complete IgA-deficiency. Complete IgA-deficiency was also present in the six children who had autoimmune disorders associated with recurrent infections. In 22 out of the 36 patients studied the serum could be analysed for concomitant IgG subclass deficiencies: one patient had marked decrease of IgG2. In a second patient IgG4 was not detectable. Two patients had combined IgG2-IgG4-deficiency. In a girl with severe acute and chronic infections and relapsing idiopathic thrombocytopenic purpura, IgA-IgG2-IgG4-deficiency was found to be the prodromal stage of common variable immunodeficiency with panhypogammaglobulinaemia.

Key words: IgA-deficiency – IgG subclasses – Infections

Introduction

Selective IgA-deficiency represents the most common primary immunodeficiency and is defined as complete absence or marked reduction of IgA in serum and secretions [11]. A majority of IgA-deficient individuals shows no signs of illness [13]. Those who are sick, however, suffer from frequent infections, autoimmune and collagen vascular diseases, allergies or from combinations of these and other disorders [13]. Occasionally, IgA deficiency may be transient, particularly in paediatric patients, and spontaneous recovery has been reported [3, 7]. In addition, it is known that IgA deficiency may appear later in life and can be secondary to treatment with anticonvulsive drugs [1, 14] and antirheumatics [17]. In some IgA-deficient patients, a concomitant deficiency of IgG subclasses, particularly of IgG2 and IgG4, was noticed and it was assumed that these patients were even more prone to pyogenic infections [10]. To characterize further IgA- and IgA-IgG subclass deficiency states, a retrospective study was performed in 36 children treated at our hospital during the last 6 years. The severity of infections was found to be related to the extent of IgA-deficiency. IgG subclass determinations were done in 22 patients with serious infectious complications and revealed deficiency states in 4 of them. One patient demonstrating transition of IgA-IgG subclass deficiency into panhypogammaglobulinaemia is described in detail.

* Dedicated to E. Rossi, M.D., on behalf of his 70th birthday

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Abbreviation: URTI = upper respiratory tract infections

Patients and methods

Patients. This study included 36 children who were seen repeatedly at the University Children's Hospital in Berne for various disorders, mostly recurrent and chronic respiratory and intestinal infections. There were 15 girls and 21 boys with ages ranging from 1 1/12–15 years (median age 7 7/12 years). The observation time was between 1 month and 12 years (median observation time 3 3/12 years).

Immunoglobulin levels in serum and secretions. IgA, IgM and IgG concentrations in serum samples were determined by radial immunodiffusion using NOR-Partigen plates (Behring, Marburg, FRG). For analysis of IgG subclasses, serum samples were stored at −20°C until used. Subclass specific antisera were raised in sheep and used for estimation of IgG subclass concentration in radial immunodiffusion tests as previously reproted [16]. IgA in secretions (tears, saliva) was assayed on electro-immunodiffusion plates according to Laurell [8]. Calibrated colostral IgA was used for reference curves.

Definition of IgA-, and IgG-subclass-deficiencies. Partial IgA-deficiency was assumed when serum IgA concentrations were more than 2 SD below age-related normal mean values. It therefore describes significantly decreased levels rather than real deficiency states. The term "partial" has been adopted from the literature [4]. *Complete IgA-deficiency* was diagnosed when IgA could not be detected in serum and in secretions. The limit of sensitivity of radial and electroimmunodiffusion techniques was 0.01 g/l.

IgG subclass-deficiencies were diagnosed when IgG2 and/or IgG4 levels were markedly below the normal age-related range (Table 3). Furthermore levels were compared with published values, which were found to be compatible with our determinations [19]. IgG subclass levels that were more than 2 SD below age-related mean values [19] were classified as deficient.

Case report

M.E. was born in August 1969 in Spain. Pregnancy, delivery and early development were normal. Since the age of 2 years she has suffered from frequently relapsing purulent rhinitis, bronchitis and otitis media. At the age of 4 years, bronchiectasis and hepatosplenomegaly were noticed. She experienced two episodes of idiopathic thrombocytopenic purpura at the age of 7½ and 11 years with platelet counts below 30×10^9/l followed by spontaneous recovery. In January 1981 the child was admitted to our clinic. The girl presented with bilateral chronic sinusitis, otitis media, bronchiectasis, hepatosplenomegaly, diffuse lymphadenopathy and markedly retarded bone maturation. Her height and weight were below the third percentile. *Hemophilus influenzae* and *Proteus* species were isolated from sputum. No IgA was detectable in serum and secretions (Table 4), but the girl appeared to be "too sick for IgA-deficiency". Determination of IgG subclasses in serum revealed the virtual absence of IgG2 and IgG4. Infectious symptoms temporarily improved on antimicrobial therapy, but she had to be readmitted in July 1981 and in September 1982 because of severe pneumonia. On these occasions a progressive decrease of serum IgM and IgG levels was found (Table 4). The white blood cell count was 3.5×10^9/l with 11% lymphocytes. Marker determinations on blood lymphocytes showed a normal percentage of B lymphocytes (5%), rosette forming (74%) and OKT3-pos. cells (84%). The balance of the T-cell subsets was disturbed in favour of helper T lymphocytes (OKT4-pos. cells 80%; OKT8-pos. cells 6%). Lymphocyte mitogenic responses to PHA and ConA were below normal. At that time the diagnosis had to be changed to common variable immunodeficiency. Antibiotic therapies plus periodic intravenous immunoglobulin replacement were only moderately successful. In September 1983 her general condition was virtually unchaged, but in addition to respiratory infections she then suffered from recurrent diarrhoea. Stool cultures revealed *Campylobacter jejuni.* Lymphopenia was less marked (9% of 7.1×10^9/l), but the serum IgG two months after the last replacement had further decreased to 1.7 g/l.

Results

Increased susceptibility to infections, the principal hallmark of selective IgA-deficiency, was encountered in 30 of the 36 patients (83%). Only six children showed exclusively non-infectious disorders. IgA-deficiency was complete in 26 (72%) and partial in 10 (28%). Secretory IgA could be analysed in 23 patients with complete and in 6 patients with partial IgA-deficiency. It was not detectable in tears or saliva of the children with complete but present in all six patients with partial IgA-deficiency. Associations between clinical patterns and extent of IgA-deficiency are demonstrated in Table 1: in ten of the eleven children (91%) who had recurrent and chronic infections but no other disorders, complete IgA-deficiency was observed. Partial IgA-deficiency states characterized by significantly decreased IgA levels were more frequent in the patients who had repeated infections combined with other disturbances (6/19; 32%), and in patients who had no infections (3/6; 50%). Recurrent respiratory tract infections occurred in 27 of the 36 patients studied (75%), most commonly as upper respiratory tract infections (URTI), including sinusitis, rhinitis, otitis media, tonsillitis and bronchitis. Twelve of these 27 children suffered almost continuously from infections. Lower respiratory tract infections, such as severe or relapsing pneumonia were observed in six patients, whereas two children presented with meningitis due to *Streptococcos pneumoniae* and *H. influenzae,* respectively. Gastrointestinal infections were seen in seven cases and were due to *Salmonella* species in three, to *Giardia lamblia* in one, and to an unknown aetiology in three patients. As summarized in Table 1, URTI and gastrointestinal infections were observed in children with complete as well as in those with partial IgA-deficiency. However, severe respiratory infections and meningitis were exclusively associated with complete IgA-deficiency. After several years of observation, chronic URTI or diarrhoea improved in six patients. This spontaneous recovery was accompanied by normalization of serum and secretory IgA as documented in one child with chronic gastrointestinal disease who it was possible to follow for 7 years (Table 2). Autoimmune disorders were found in six patients with complete lack of IgA (Table 1). They all had recurrent respiratory tract infections in addi-

Table 1. Infections and other disorders in paediatric patients with complete and partial[a] IgA-deficiency

	IgA-deficiency	
	Complete	Partial
Infections and other disorders:		
– Patients with recurrent and chronic infections but no other disorders	10	1
– Patients with infections and one or more other disturbances	13	6
– Patients without infections but with other disorders	3	3
Type of infections[b]:		
– Upper respiratory tract infections, including sinusitis, rhinitis, otitis media, tonsillitis and bronchitis	19	7
– Lower respiratory tract infections, including pneumonia, bronchiectasis	6	0
– Meningitis	2	0
– Gastrointestinal tract infections	5	2
Non-infectious disorders[b]:		
– Autoimmune diseases	6	0
– Involvement of the central nervous system	5	2
– Atopic diseases	2	3
– Haematological disorders	3	2
– Other disturbances	8	3

[a] Significantly decreased serum concentrations of IgA
[b] More than one type of infection or more than one non-infectious disorder could occur in the same patient

Table 2. Spontaneous recovery from selective IgA-deficiency (patient S.R., male, born December 1969)

Date	Clinical symptoms	IgA (g/l)		
		Serum	Tears	Saliva
March 1975	Chronic enteritis, diarrhoea, dystrophia, retarded bone age	0	0	0
August 1976	Unchanged	0.15	Trace	0
August 1978	Improvement of diarrhoea, weight gain	0.11	0.10	Trace
August 1980	Further improvement	0.53	>0.10	Trace
June 1982	Normalization	0.85	>0.10	8

Table 3. IgG subclass deficiencies in IgA-deficient patients

Patients			IgG subclass concentrations (g/l)				Clinical symptoms
Name	Sex	Age	IgG1	IgG2	IgG3	IgG4	
S.B.	m	2½	9.40	3.00	0.40	<0.01	Relapsing URTI, otitis, pneumonia
B.A.	m	3½	6.80	0.20	0.50	<0.01	Relapsing URTI, pneumonia, otitis
M.C.	m	8½	19.00	0.20	1.00	0.20	Relapsing URTI, pneumonia, Down syndrome
M.E.	f	11½	11.80	0.10	0.20	<0.01	Relapsing URTI, pneumonia, cf case report
Normal range:							
2 years	(n = 14)		3.00– 9.10	0.90–2.50	0.30–0.70	0.10–0.50	
3– 5 years	(n = 9)		6.50– 9.30	1.10–2.30	0.30–0.60	0.10–0.60	
7– 9 years	(n = 5)		7.40–10.60	1.30–3.30	0.30–0.50	0.20–0.70	
10–12 years	(n = 5)		5.30– 9.80	1.40–4.10	0.20–0.50	0.10–1.10	

Table 4. Development of severe hypogammaglobulinaemia from selective IgA-IgG subclass deficiency (patient M.E., female, born August 1969)

Date	IgA	IgM	IgG	IgG1	IgG2	IgG3	IgG4
January 1981	0	0.69[a]	12.60	97[b]	1	2	<1
July 1981	0	0.25	9.35	97	1	2	<1
September 1982	0	Trace	3.75	96	0	4	0
September 1983	0	Trace	1.70				
Normal values	50–300	45–250	700–1600	70	20	6	4

For details see text
[a] Serum concentrations of IgA, IgG and IgM in g/l
[b] IgG subclasses in percentages of total IgG

tion to idiopathic thrombocytopenic purpura, juvenile rheumatoid arthritis, lupus-like collagenopathy, autoimmune thyroiditis and a variety of autoantibodies. The other non-infectious disorders listed in Table 1 were associated with either complete (64%) or with partial (36%) deficiency of IgA. In two patients with central nervous system disorder, anticonvulsive therapy might have been responsible for partial IgA-deficiency [1, 14].

IgG subclass determinations could be performed in serum samples from 22 patients with complete IgA-deficiency, including those who suffered from severe infections. Decreased levels of IgG2, IgG4 or both subclasses were found in four patients who all had frequently relapsing URTI and pneumonia (Table 3). In one child, marked compensatory elevation of IgG1 could be observed. However, there were also children with serious infections including pneumonia and meningitis who had normal serum concentrations of all IgG subclasses. In one patients, IgA-IgG subclass deficiency initially was diagnosed. During the following 3 years, severe panhypogammaglobulinaemia developed, as shown in Table 4. The case history of this girl is reported.

Discussion

Our study demonstrates associations between the extent of IgA-deficiency and clinical manifestations of disease: complete IgA-deficiency clearly predominated in the group of patients with recurrent infections but no other illness and in patients with severe infections such as pneumonia and meningitis. Complete absence of IgA was also noticed in the six patients who suffered from both autoimmune disorders and recurrent infections. IgA-deficiency in children may be transient and spontaneous recovery as observed in our study is known to occur [3, 7]. Thus, markedly decreased IgA levels, or partial IgA-deficiency, associated with less pronounced susceptibility to infections may represent a transitory stage. The percentage of patients in whom there is a spontaneous recovery remains to be determined.

The overall susceptibility to infections in our patients (83%) was somewhat higher than that reported by Burgio et al., who noticed recurrent infections in 77% of paediatric patients with complete and in 20% of those with partial IgA-deficiency [4]. However, the percentages of patients affected by

serious or chronic infections were comparable to those in the literature [2, 4]. Associated deficiency of IgG subclasses was first reported by Oxelius and co-workers in 1981 [10] who found decreased serum IgG2 concentrations in 7 of 37 IgA-deficient patients with recurrent respiratory infections. In six of these seven patients as well as in other IgA-deficient patients and healthy persons, low IgG4 serum levels also were detected. The frequency of associated IgG subclass deficiencies was somewhat higher in their series of patients than in ours. In addition to 22 children their study included 15 adult patients. Possibly, decrease of IgG subclass levels may be secondary in some IgA-deficient patients and thus more frequently encountered in adults than in children. However, in a study reported by Ugazio et al. [18], IgG subclass deficiencies were even more frequent: Ten out of 13 IgA-deficient children with severe recurrent infections had concomitant deficiency of either IgG2, IgG4 or of a combination of both. On the other hand, 22 children with IgA-deficiency and other than infectious complications had normal IgG subclass levels. In their study, subclass deficiency was defined as "low for age or undetectable". Unfortunately, exact subclass serum levels were not given. In spite of differences in frequencies, our observations and another recent report [5] are in accordance with these findings. All patients with concomitant IgG subclass deficiency in our study were seriously ill. Both Oxelius et al. [10] as well as Ugazio and co-workers [18] stress the importance of IgG subclass deficiency, particularly IgG2, in susceptibility to infections. However, our study and the report of Ugazio et al. strongly suggest that IgG subclass deficiency is not the only factor causing proneness to infections in IgA-deficient individuals, since severe infections were also noticed in children with normal IgG subclass levels.

Absence of IgA antibodies in secretions favour colonization of mucous membranes and adjacent tissues by potentially invasive microorganisms [2]. IgG2 containes the majority of antibodies against bacterial polysaccharide capsular antigen [6, 12, 15, 20]. Thus, concomitant lack of such antibodies probably explains the increased susceptibility of these patients to severe and systemic infections caused by pneumococci, *H. influenzae* and other encapsulated microorganisms. In vitro studies suggest that in some cases immunoregulatory mechanisms or inadequate cellular cooperation could be responsible for defective IgA production [9]. Similar mechanisms selectively acting on the synthesis of IgG subclasses are possible, although not proven yet. These patients might be unable to mount a humoral immune response to many or any carbohydrate antigens [20]. As a consequence, serum IgG2 consisting mainly of antipolysaccharide antibodies would be low or absent. In patients with severe infectious problems and normal serum concentrations of IgG subclasses, the deficiency may be more selective, affecting antibody production against some clinically relevant bacterial polysaccharides only. Protective antibody specificities typical for IgG4 are not known. Hence there can be no speculation upon the significance of IgG4-deficiency in this context.

The history of M.E. has been reported in detail, since this girl might represent the protagonist of a new group of immunodeficient patients. In 1981, when she was seen with severe infectious disease, her case history and laboratory data were thought to be typical of IgA-IgG subclass deficiency newly described at that time [10]. Over the next years, however, panhypogammaglobulinaemia developed gradually, suggesting that the initial IgA-IgG subclass deficiency might have represented a prodromal stage of common variable immunodeficiency. So far, this transition is unique and the reasons for the progression of immunodeficiency are unclear. Immunoregulatory events could be responsible for it, although excess suppressor T-cells were not present. In addition, there was no evidence of concomitant viral infections or of protein losing enteropathy, which could have affected serum immunoglobulin levels. Follow-up examinations in such IgA-IgG subclass deficiencies will show whether these findings apply to a subset of the patients who ultimately present with common variable immunodeficiencies.

In conclusion, increased susceptibility to infections was observed in 30 of our 36 IgA-deficient children. Severe infections such as pneumonia and meningitis were seen exclusively in patients with complete IgG subclass deficiencies. In one girl, transition of IgA-IgG2, IgG4-deficiency to panhypogammaglobulinaemia was noticed.

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