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ORIGINAL ARTICLE

Clinical and Laboratory Features of 184 Italian Pediatric Patients Affected with Selective IgA Deficiency (SIgAD): a Longitudinal Single-Center Study

Vassilios Lougaris[1] · Annamaria Sorlini[1] · Chiara Monfredini[1] · Giulia Ingrasciotta[1] · Andrea Caravaggio[1] · Tiziana Lorenzini[1] · Manuela Baronio[1] · Marco Cattalini[1] · Antonella Meini[2] · Laura Ruggeri[2] · Annamaria Salpietro[2] · Alba Pilotta[2] · Livia Grazzani[2] · Elena Prandi[2] · Barbara Felappi[2] · Giulio Gualdi[3] · Antonella Fabiano[3] · Maurizio Fuoti[2] · Alberto Ravelli[2] · Vincenzo Villanacci[4] · Annarosa Soresina[2] · Raffaele Badolato[1] · Alessandro Plebani[1]

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Abstract

Purpose Selective IgA deficiency (SIgAD) is the most common humoral primary immunodeficiency. Long-term follow-up data in large cohort of pediatric patients are scarce.

Methods We report on a single-center cohort of 184 pediatric patients affected with selective IgA deficiency and describe the characteristics at diagnosis and during follow-up.

Results Respiratory infections were the most common clinical finding leading to the initial diagnosis (62%). Positive family history for antibody deficiencies (selective IgA deficiency, common variable immunodeficiency) led to SIgAD diagnosis in 16% of cases. During follow-up, while the incidence of respiratory infections was not particularly high, gastrointestinal symptoms were reported in 27% of patients. Allergic manifestations were found in 23% at diagnosis and an additional 16% of patients during follow-up, leading to a prevalence of atopy of 39% among SIgAD patients. Autoimmune manifestations, excluding celiac disease, were found in 9% of affected patients during follow-up. Celiac disease was found in a high prevalence (14%). Increase of serum IgA levels to partial deficiency (9%) and normal serum levels for age (4%) was observed during follow-up. A small percentage of patients (2%) progressed to common variable immunodeficiency (CVID).

Conclusions In conclusion, this is the first study to describe a large single-center pediatric cohort of patients affected with SIgAD, revealing that overall most patients do well with regard to infections. Many develop CD, at a rate much higher than the general population. A few normalize their IgA levels. A few progress to CVID. Thus, careful follow-up is suggested to diagnose and treat potential complications earlier for avoiding potential morbidities.

Keywords Selective IgA deficiency · pediatric · allergic manifestations · celiac disease · common variable immunodeficiency

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✉ Vassilios Lougaris
vlougaris@yahoo.co.uk

[1] Pediatrics Clinic and Institute for Molecular Medicine A. Nocivelli, Department of Clinical and Experimental Sciences, University of Brescia and ASST-Spedali Civili of Brescia, Brescia, Italy

[2] Pediatrics Clinic, ASST-Spedali Civili of Brescia, Brescia, Italy

[3] Department of Dermatology, ASST Spedali Civili di Brescia, University of Brescia, Brescia, Italy

[4] Institute of Pathology, ASST-Spedali Civili of Brescia, Brescia, Italy

Introduction

Selective IgA deficiency (SIgAD) is the most common primary immunodeficiency with an incidence of ~ 1:600 [1]. SIgAD is diagnosed when serum IgA levels are equal to or below 7 mg/dL with normal IgG and IgM levels in patients older than 4 years of age with otherwise normal immune system [2]. Laboratory findings in SIgAD may include mild alterations in T and B cells of not clear significance [3–5].

Immunoglobulin A, is the principal antibody class present in the secretions that bathes the mucosal surfaces of the respiratory, gastrointestinal, and genitourinary tracts, and acts as an important first line of defense [6]. Although SIgAD is rather

frequent, little is known on the underlying pathogenetic mechanism [7–13]. Because of the familial occurrence of SIgAD and CVID and the possible progression from SIgAD to CVID, a common genetic basis for the two disorders has been proposed [14].

Affected individuals may be asymptomatic and may be diagnosed during routing screening for blood donations. The most common finding in symptomatic SIgAD is recurrent respiratory infections [9, 10, 15]. Patients with SIgAD may also present with susceptibility to gastrointestinal disorders, such as giardiasis, gastroenteritis, celiac disease, and lactose intolerance. Allergies, including asthma, atopic dermatitis, allergic rhinitis or conjunctivitis, and urticaria, have been reported to affect more than 30% of patients [9]. Finally, autoimmune diseases are associated to SIgAD in approximately 21% of the subjects [9]. The prognosis of these patients is good and depends mainly on associated symptoms, although published data frequently refer to small numbers of patients or limited follow-up periods.

Available clinical data on exclusive pediatric patients affected with SIgAD are limited. There are basically three recent reports: the one by Shkalim et al. (9 10) that studied 63 pediatric patients, the one by Aytakin et al. [11] that studied 118 patients, and the one by Moschese et al. [12] that studied 53 patients. These studies were either single-center studies [10, 11] or tri-center study [12] over a limited period of follow-up [10–12].

In the present study, 184 pediatric patients affected with SIgAD were followed from 1989 to 2011 in a single center; this is the most representative and comprehensive SIgAD pediatric cohort described to date.

We investigated the clinical and laboratory features at diagnosis and during follow-up with annual monitoring of serum immunoglobulin levels, clinical manifestations, associated diseases, and outcome. With a long cumulative follow-up of 812 patient-years, we aimed to provide a better clinical description of the natural history of the condition, including possible complications and possible evolution in more severe forms of primary immunodeficiencies such as CVID.

Patients and Methods

Patients

The patients' cohort consisted of 184 patients affected by SIgAD, 80 females (44%) and 104 males (56%), followed during a 22-year period (from 1989 to 2011) for a total of 812 patient-years. Mean follow-up time per child was 8.9 years. The mean age at diagnosis was 7.7 years (range 4–17 years). Three patients declared parental blood relationship.

Patient's diagnosis was made according to the ESID criteria (serum IgA level < 7 mg/dL; age > 4 years; normal IgG and IgM serum levels). All patients were regularly followed at the Pediatrics Clinic, University of Brescia and ASST-Spedali Civili of Brescia, Brescia, Italy. Children with a single blood immunoglobulin test or with partial IgA deficiency defined as detectable but decreased IgA levels that are more than 2 standard deviations below normal age-adjusted values were excluded from our study. The patients' records were reviewed for gender, age at diagnosis, parental blood relationships, familiarities, clinical manifestations at diagnosis and during follow-up, associated diseases, laboratory findings, and outcomes.

Methods

IgA, IgG, and IgM levels were measured by nephelometry "RATE (Beckman)", while IgE levels were determined by radioimmunoassay. All results were compared with age-related reference values.

Anti-nuclear antibodies were evaluated by indirect immunofluorescence assay. For celiac disease screening, IgG antibodies anti-transglutaminase (IgG tTG) and anti-gliadin were used. Anti-transglutaminase were tested by enzyme-linked immunosorbent assay (ELISA), while anti-gliadin antibodies were tested by indirect immunofluorescense assay. IgG tTG were considered positive if superior to 9.0 UI/ml, while IgG anti gliadin antibodies were considered positive if superior to 30.0 U. Duodenal biopsy was performed for the diagnosis of celiac disease, which was based on the ESPGHAN criteria.

Results

Patients' Clinical Characteristics at Diagnosis

Recurrent infections of the upper respiratory tract (URTI: rhinitis, pharyngitis, otitis media, sinusitis) were the most common clinical manifestations leading to SIgAD diagnosis in 114/184 patients (62%), while infections of the lower respiratory tract (pneumonia) were only associated with diagnosis in 3/184 patients (2%). Growth delay/celiac disease (CD) suspicion and articular pain were the main causes for immunoglobulin serum levels testing in 16/184 patients (9%) and 7/184 patients (4%), respectively (Table 1). SIgAD diagnosis was achieved in 24/184 (13%) and 5/184 (3%) due to positive family history for SIgAD and common variable immunodeficiency (CVID), respectively. Finally, due to positive family history for CD (prevalence in the general population of ~ 1%), screening for CD was performed in 6/184 patients (3%) leading to SIgAD diagnosis, due to the lack of detection of IgA (Table 1).

Detailed evaluation of patients' family characteristics revealed that SIgAD patients had a positive family history for allergies in 106/184 cases (58%), psoriasis in 13/184 cases

Table 1 Clinical and familial features of 184 patients affected with SIgAD at diagnosis

Patients' features	Numbers (percentages)
Sex (M:F)	104:80 (56% vs 44%)
Recurrent URTI	114/184 (62)
Pneumonia	3/184 (2)
Growth delay/Celiac disease suspicion	16/184 (9)
Articular pain	7/184 (4)
Allergies	42/184 (23)
Positive family history	
SIgAD	24/184 (13)
CVID	5/184 (3)
Celiac disease	10/184 (5)
Allergies	106/184 (58)
Psoriasis	13/184 (7)
Vitiligo	4/184 (2)
Thyroid disease	14/184 (8)

(7%), vitiligo in 4/184 cases (2%), and thyroid disease in 14/184 cases (7%) (Table 1).

Patients' Clinical Characteristics at Follow-Up

During follow-up, incidence of URTI per year among SIgAD was 3.1 events/year, while the incidence of pneumonia per year was < 1/year. Adenotonsillectomy was performed in 37/184 patients (20%) of which 18/37 patients were allergic. During the study period, 50/184 patients (27%) presented at least one episode of gastrointestinal symptoms. Allergies were initially diagnosed in 42/184 patients (23%). An additional 30 patients (16%) were diagnosed with allergic disease during the study period, leading to the total presence of allergies in 72/184 patients (39%) (Table 2). The most common allergic sensitivities in our cohort of patients were grass and dust mites both at diagnosis and during follow-up, followed by birch, olive, cat, and dog (Table 3). Of note, almost two-thirds of the patients were positive for more than one allergen (Table 3). Allergies were diagnosed by symptoms in 19% of cases, by skin prick tests in 49%, by RAST in 32% of cases, while skin prick test and RAST were positive in 32% of cases. Among the allergic patients, 86% had a positive family history for allergies (Table 3). Celiac disease (CD) was present at diagnosis in 6 patients (3%). During follow-up, another 20 (11%) pediatric SIgAD patients were diagnosed with CD, leading to an overall prevalence of CD among this cohort of patients of 14% (Table 4). The second most frequent autoimmune manifestation during follow-up was thyroid disease diagnosed in 6/184 patients (3%). Minor frequencies were registered for vitiligo, psoriasis, diabetes mellitus, and alopecia (Table 4).

Table 2 Patients' clinical features during follow-up

Infections during follow-up	
Incidence of URTI/year	3.1 episodes (mean)
Incidence of pneumonia/year	0.4 episodes (mean)
Gastrointestinal infections	50/184 patients (27%)
Diagnosis during follow-up	Numbers (percentages)
Celiac disease	20/184 (11%)
Autoimmune manifestations	12/184 (7%)
Allergies	30/184 (16%)
Adenotonsillectomy	37/184 (20%)

Evolution of SIgAD During Follow-Up

During follow-up, IgA serum levels reached normal levels for age in 7/184 patients (4%), while SIgAD progressed to partial IgA deficiency in 17/184 patients (9%). Normalization of serum IgA levels occurred at a mean age of 12.7 years (range 6–17 years). Progressive reduction of serum IgG and IgM during follow-up was observed in 3/184 patients (2%). All three patients were in their adolescence when CVID diagnosis was made (mean age at CVID diagnosis: 15 years; range 14–16 years). Further immunological evaluation in these patients showed defective antibody response upon vaccine boost and loss of memory B cells, leading to diagnosis of CVID. Genetic analysis for *TNFRSF13B* mutations was performed in these patients, but only yielded the presence of the already reported synonymous variants rs8072293, rs35062843, and rs11078355.

Discussion

SIgAD is the most frequent primary immunodeficiency, with an incidence of 1:600 in the Caucasian population [1]. Despite the high prevalence of the disease, available data at onset and clinical outcome are limited and usually refer to small cohorts and/or short follow-up.

Over a 22-year period, 184 pediatric SIgAD patients were regularly followed in our center (male:female = 104:80). Mean follow-up time per child was 8.9 years. The mean age at diagnosis was 7.7 years (range 4–17.1 years). Of interest, 16% of patients presented a positive family history for primary humoral immunodeficiency.

In our study, infectious episodes of the upper respiratory tract were the most common clinical manifestations at the time of diagnosis, in agreement with previous studies [4, 9, 10, 12–14], but over the study period occurred at < 1% per year, indicating that upper respiratory tract infections are not an ongoing problem in patients with SIgAD. Gastrointestinal tract symptoms resulted the second more frequent manifestation in our cohort, a finding that has not been reported before in pediatric SIgAD.

Table 3 Detailed allergen positivity in SIgAD pediatric patients at diagnosis ($n = 42$) and during follow-up ($n = 42 + 30$)

Allergen positivity in pediatric SIgAD patients		
Allergen	At diagnosis (%)	At last follow-up (%)
Grass	79	72
Dust mites	76	68
Alternaria	10	10
Cypress	7	7
Birch	23	21
Hazelnut	12	8
Alder	7	4
Hornbeam	2	3
Pellitory	10	14
Olive	21	24
Cat	12	15
Dog	10	15
Composite	12	10
Aspergillus	10	6
More than 1 allergen	64	60
Positive family history for allergies	86%	

This study confirms the high incidence of allergic manifestations in SIgAD patients similar to what was reported previously [4, 10–12, 15]. Our data also underline how the development of allergic manifestations is a continuum during follow-up: at diagnosis, 23% of patients were allergic, and during follow-up, another 16% developed allergic manifestations, suggesting that periodic allergic assessment in SIgAD patients is warranted, especially when a positive family history for allergies is present. Of note, the general prevalence of autoimmune manifestations in our cohort was not particularly high. Finally, no malignancies were found during follow-up in our cohort.

We then compared our cohort with previously reported pediatric cohorts (Table 5) [10–12]. While URTI was common in all cohorts, LRTI (lower respiratory tract infection) was not frequent in our cohort and in the one described by Moschese et al. [12], in contrast with what observed in the other two ones [10, 11] (Table 5). The incidence of celiac disease (CD) was higher in our index cohort when compared with the other studies [10–12] (Table 5) and it was greater than that observed in the healthy pediatric population (1%) [16]. Interestingly, gastrointestinal symptoms were particularly frequent among our cohort, while they were uncommon in two cohorts [11, 12] and absent in one [10] (Table 5). The prevalence of allergic manifestations and autoimmune diseases was rather similar among the four cohorts (Table 5). While malignancies (3 cases in male patients) have been reported previously in a pediatric cohort of SIgAD [11], no malignancies were registered during follow-up in our cohort of patients. More than 15% of the pediatric patients of the index cohort showed a positive family history for primary humoral immunodeficiencies, slightly higher from what was reported by Moschese et al. [12]; unfortunately, similar data are not available for the other two cohorts [10, 11].

Table 4 Autoimmune features at diagnosis and during follow-up in 184 pediatric SIgAD patients

	At diagnosis		Follow-up		Total	
	N	%	*N*	%	*N*	%
Celiac disease	6	3	20	11	26	14
Vitiligo	2	1	1	0.5	3	2
Psoriasis	1	0.5	2	1	3	2
Alopecia	1	0.5	1	0.5	2	1
Diabetes mellitus	0	0	1	0.5	1	0.5
Thyroid disease	0	0	6	3	6	3
Psoriatic arthritis	0	0	1	0.5	1	0.5

A further aim of our study was to determine the outcome of SIgAD in affected patients.

We observed a progression to partial IgA deficiency in 17/184 patients (9%) and a complete normalization of IgA levels in 7/184 patients (4%). Mean age at time of normalization was 12.7 years (range 6–17 years). Normalization of IgA serum levels in SIgAD has been previously reported although with different percentages and different lengths of follow-up. In the study by Plebani et al. [14], 80 children, 40 affected by SIgAD and 40 by partial IgA deficiency, were followed for 8 years:

Table 5 Comparison of clinical features in reported pediatric cohorts of patients with selective IgA deficiency

	Index study	Shkalim et al. [9]	Aytakin et al. [10]	Moschese et al. [11]
Number of patients	184	63	118	53
Country	Italy	Israel	Turkey	Italy
Recurrent URTI	Yes	Yes	Yes	Yes
Recurrent LRTI	No	Yes	Yes	No
Celiac disease	Yes (14%)*	Yes (3%)	Yes (6%)	Yes (6%)
Gastrointestinal symptoms	Yes (27%)	NA	Yes (7%)	Yes (11%)
Allergies	Yes (39%)	Yes (32%)	Yes (43%)	Yes (36%)
Autoimmune diseases	Yes (8%)	Yes (21%)	Yes (17%)	Yes (8%)
Progression to CVID	Yes (2%)	No	No	NA
Malignancy	No	Yes (5%)	No	No
Positive family history for humoral immunodeficiency	Yes (16%)	NA	NA	Yes (10%)

NA, not available

Percentages in parentheses indicate the percentage of patients presenting the indicated complication

while IgA levels normalized in 50% of patients with partial defect, none of the SIgAD patients presented a normalization of the IgA serum levels during follow-up. Roberton et al. [17] studied for a 10-year period 67 children, 18 affected by SIgAD and 49 by partial IgA deficiency, and observed that IgA serum levels normalized in 22% of SIgAD patients (22%) and in 78% of partial IgA deficient patients. On the other hand, only one patient in the Israeli cohort [10] was reported to have normalization of the IgA serum levels, while normalization of the IgA serum levels was not observed in the Turkish cohort during the 5-year follow-up [11]. It appears evident that the trend regarding IgA serum levels during follow-up in selective IgA deficiency is variable and cannot be defined a priori based on available data in literature.

Finally, three patients (2%), 2 males and one female, showed a progressive reduction of both IgG and IgM during follow-up with concomitant lack of antibody response to recall vaccinations and reduction of memory B cells, both switched and non-switched (Supplementary Table 1), thus leading to the diagnosis of CVID in their adolescence. Of note, while previously described SIgAD patients progressing to CVID have been reported to present complicated clinical follow-up [18–21], the three patients from our cohort are currently in good health under immunoglobulin replacement treatment without any major clinical complications.

In conclusion, this study describes for the first time long-term follow-up in the most numerous cohort of pediatric SIgAD patients reported to date. Our data confirm the association of SIgAD with autoimmune diseases, with allergic manifestations at diagnosis and even more during follow-up, underlines the increased prevalence of celiac disease in this disorder and the possible evolution towards a more severe form of primary immunodeficiency, i.e., common variable immunodeficiency (CVID). These findings underline the importance of a regular follow-up for SIgAD patients with periodic clinical and laboratory evaluations.

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Authors' Contribution V.L. and A.P. designed the study and wrote the manuscript; V.L., A.S., C.M., G.I., A.C., and M.B. analyzed patients' data; V.L., T.L., M.C., A.M., L.R., A.S., A.P., L.V., E.P., B.F., G.G., A.F., M.F., A.R., V.V., A.S, and R.B. followed the patients; all authors reviewed the manuscript before publication.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflicts of interest.

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