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ORIGINAL ARTICLE

Follow-up and outcome of symptomatic partial or absolute IgA deficiency in children

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Abstract

Selective IgA deficiency is defined as absolute or partial when serum IgA level is < 7 mg/dl or 2 SD below normal for age, respectively. Few data are available on partial selective IgA deficiency, as probably most children with low serum IgA are seldom referred to a specialist clinic in common pediatric practice. The aim of our study was to better define the profile of both symptomatic forms and their clinical outcome in a pediatric immunology setting. Thus, clinical and immunological data from 103 symptomatic patients with selective IgA deficiency (53 absolute and 50 partial), 4–18 years of age, were collected at diagnosis and 80 patients (44 absolute and 36 partial) were monitored for a mean period of 5 years. Also, the prevalence of *TNFRSF13B* mutations has been assessed in 56 patients. The most common clinical features were infections (86/103; 83%), allergy (39/103; 38%), and autoimmunity (13/103; 13%). No significative differences were observed between absolute and partial selective IgA deficiency patients. However, a significative difference in the rate of IgA normalization between partial and absolute selective IgA deficiency patients (33 vs 9%, $p = 0.01$) was detected. Furthermore, a lower incidence of infections was associated to a normalization reversal compared to a final absolute or partial defect status (12 vs 53 and 64% respectively, $p < 0.01$).

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Conclusions: Regardless of a diagnosis of absolute or partial defect, monitoring of symptomatic patients with selective IgA deficiency is recommended overtime for prompt identification and treatment of associated diseases. Further, diagnostic workup protocols should be revisited in children with IgA deficiency.

What is Known:
- *Selective IgA Deficiency is the most common primary immunodeficiency and is usually asymptomatic.*
- *Symptomatic pediatric patients with selective IgA deficiency mostly suffer with respiratory and gastrointestinal infections.*

What is New:
- *Symptomatic children with partial IgA defect may have similar clinical, immunological, and genetic features than symptomatic children with absolute IgA deficiency.*
- *Symptomatic children with partial IgA deficiency deserve accurate monitoring for associated diseases as per children with absolute IgA deficiency.*

Keywords TNFRSF13B · Antibody deficiency · Primary immunodeficiency · Recurrent respiratory infections

Abbreviations

SIGAD	Selective IgA deficiency
PID	Primary immunodeficiency disease
TACI	Transmembrane activator and calcium modulator and cyclophilin ligand interactor
CVID	Common variable immunodeficiency
aSIGAD	Absolute selective IgA deficiency
pSIGAD	Partial selective IgA deficiency

Introduction

Selective IgA deficiency (SIGAD) is the most common primary immunodeficiency disease (PID) that occurs in 1:300–1:700 individuals [5, 7, 42, 44]. This antibody defect is characterized by decreased or absent serum IgA level with normal IgG and IgM values in patients older than 4 years of age [48]. SIGAD is usually defined "absolute" when serum IgA level is less than 7 mg/dl and "partial" when IgA level is 2 SD below normal for age [48].

The pathogenesis of SIGAD is still unknown, but a defect in class switch recombination and mutation of some genes have been related to the disease. Particularly, polymorphisms of the HLA system, variants of genes known to regulate IgA production and mutations in the gene encoding transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), the *TNFRSF13B* gene, have been observed [1, 8–10, 42, 46]. The identification of *TNFRSF13B* gene mutations in other primary immunodeficiencies, such as common variable immunodeficiency (CVID) [35, 48] and transient hypogammaglobulinemia of infancy [6], supports the idea of a common relationship [48].

SIGAD is often asymptomatic and the diagnosis is sometimes incidental [48]. Symptomatic patients represent approximately 10–15% of all PID [30, 42] and 10–35% of all SIGAD [47, 48] with a higher prevalence in males [7]. In children, recurrent infections are the major manifestations that can lead to an immunological investigation [11, 46]. Infections, which usually involve the respiratory, urinary, and gastrointestinal tracts, are commonly caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Giardia lamblia*, *Helicobacter pylori*, *Salmonella*, or *Campylobacter* [2, 11, 13, 21, 33, 37, 48]. Rarely, disseminated infections have been reported [7].

Allergic diseases are also frequent [2, 43, 46] and may be the first and/or the sole feature. Several studies have reported a high incidence of allergy presumably due to the loss of the capacity to block the allergen absorption with further sensitization and development of allergic disease in these patients [43, 47].

A variety of autoimmune diseases including hematologic disorders, i.e., neutropenia and thrombocytopenia; gastrointestinal disorders, i.e., coeliac disease, Crohn disease, ulcerative colitis, and primary biliary cirrhosis; lupus-like illnesses; arthritis; autoimmune thyroiditis; and type 1 diabetes [5, 7, 22, 44, 45] have been observed in SIGAD patients, predominantly in adult women [11, 13, 20, 48]. Several mechanisms have been postulated to be involved in the autoimmune pathogenesis such as the absence of secretory IgA, which could enable the transition of environmental antigens and the formation of autoantibodies by molecular mimicry with self-antigens, and the presence of abnormal Treg cell levels, which could lead to the breakdown of immune tolerance [46].

Furthermore, during the natural course of the disease, malignancies, i.e., gastric carcinoma and lymphoproliferative syndrome, may occur with age [47, 48].

Most SIGAD patients have a good prognosis and sometimes IgA levels may normalize over time. Conversely, 5% of these patients may represent part of a phenotype of a more severe disease and likely progress to CVID disease [4, 7, 22, 44, 45, 48]. Symptomatic children with partial IgA deficiency are commonly considered with a mild variant of SIGAD that rarely deserves referral to a specialist clinic. Thus, there is a general attitude to focus both scientific papers and PID registries on the absolute form and scarce data on symptomatic patients with partial IgA deficiency are

available. This study was undertaken to draw the profile and clinical outcome of both forms in patients evaluated in three pediatric immunology settings.

Methods

Patients with absolute and partial IgA deficiency were identified during routine assessment for recurrent infections and/or allergy and/or autoimmunity and enrolled at the Pediatric Immunopathology and Allergology Unit of Policlinico of Tor Vergata in Rome, at the Department of Pediatrics of Malpighi Hospital in Bologna, and at the Pediatric Immunology Center of Federico II University in Naples. Clinical and immunological features of 103 SIGAD patients (57 males and 46 females), 53 (31 males and 22 females) with absolute IgA deficiency (aSIGAD), and 50 (26 males and 24 females) with partial IgA deficiency (pSIGAD) were analyzed. According to the diagnostic criteria of the Italian Primary Immunodeficiency Network, symptomatic patients with an absolute defect matched the following criteria: (a) age ≥ 4 years, (b) serum IgA levels <7 mg/dl, (c) normal serum IgG and IgM levels. On the other hand, we classified symptomatic patients with a partial defect when the following criteria were matched: (a) age ≥ 4 years, (b) IgA levels 2 SD below normal for age, (c) normal serum IgG and IgM levels. All symptomatic SIGAD patients had normal values of T and B lymphocyte subsets as detected by FACS and compared to age-appropriate values [12, 39], specific IgG antibody response to *Haemophilus influenzae*, tetanus, and/or *Streptococcus pneumoniae* as analyzed by ELISA (Binding Site, Birmingham, England) and IgG subclasses assay by radial immunodiffusion. Also, secondary causes of hypogammaglobulinemia were excluded.

Clinical and immunological data were collected at enrollment and every 6–12 months according to common clinical practice for a total mean follow-up period of 5 years. Immunological data included Ig quantification by nephelometry and antinuclear antibody (ANA).

Genetic analysis for *TNFRSF13B* mutation was performed in 56 patients (32 aSIGAD and 24 pSIGAD).

The institutional review board approved the study and informed consent was obtained at diagnosis from all individual participants included in the study.

Statistical analysis

Clinical and immunological data of patients with absolute vs partial IgA deficiency were compared using Fisher's exact test and chi-square test. A P value < 0.05 was considered as significant.

Results

Clinical and immunological features of 103 patients at diagnosis

Our cohort of 103 SIGAD patients was composed of 53 aSIGAD and 50 pSIGAD. Mean age was of 7 years (age range 4–18 years). As reported in Table 1, a positive family history for PID was present in the family of 20 (19%) patients with a higher incidence of SIGAD (90%), and of unclassified primary immunodeficiency and common variable immunodeficiency in 15 and 10%, respectively. Allergy and autoimmunity characterized the family history of 47 (46%) and 31 (30%) patients, respectively. Autoimmune thyroiditis and coeliac disease were the major autoimmune diseases and were observed in the family of 10 (32%) and 8 (26%) patients, respectively. A comparison of family history between aSIGAD and pSIGAD groups showed no significative difference.

As reported in Table 2, clinical features could be grouped into four categories: infections, allergy, autoimmunity, and other conditions. Infections were observed in 86/103 (83%) patients, mainly involving the respiratory tract (82/86, 95%). Upper respiratory tract infections affected 56/82 (68%) patients, lower respiratory tract infections involved only 5/82 (6%) patients, and the simultaneous occurrence of upper and lower respiratory tract infections was found in 21/82 (26%) patients. Gastrointestinal infections represented the second most frequent infections occurring in 16/86 (19%) patients. The main gastrointestinal pathogen was represented by *Giardia lamblia*, found in 6/16 (38%) patients. Allergic diseases were reported in 39/103 (38%) patients with rhinitis in 19/39 (49%), atopic dermatitis in 13/39 (33%), asthma in 11/39 (28%), and conjunctivitis in 10/39 (26%). Autoimmunity was observed in 13/103 (13%) SIGAD patients with a higher incidence of coeliac disease in 8/13 (62%) whereas autoimmune thyroiditis and idiopathic juvenile arthritis were found in 3/13 (23%) and in 2/13 (15%) patients, respectively. Among the other conditions, in 9/103 patients (9%), recurrent abdominal pain (56%) and oral aphthosis (22%) were reported. At diagnosis, malignancy was never observed in any group. As detailed in Table 2, no significative differences emerged in the clinical picture of aSIGAD vs pSIGAD. Of note, when in both cohorts we evaluated the impact of age (< 10 years vs > 10 years) on all described clinical categories, no significative differences were found (data not shown).

When antinuclear antibodies (ANA) were analyzed in all SIGAD patients, among those 16/103 (16%) who tested positive, only one ANA+ pSIGAD patient suffered from idiopathic juvenile arthritis (data not shown).

The analysis for *TNFRSF13B* gene was performed in 56 patients (32 aSIGAD and 24 pSIGAD), and 11/56 (20%), 4 aSIGAD (13%) and 7 pSIGAD (29%), carried a variant

Table 1 Family history for primary immunodeficiency, allergy, and/or autoimmunity of 103 patients with selective IgA deficiency (SIGAD)

	SIGAD	aSIGAD	pSIGAD	*p* value
Primary immunodeficiency (PID)	20/103 (19%)	10/103 (10%)	10/103 (10%)	1.0
Selective IgA deficiency (SIGAD)	18/20 (90%)	9/10 (90%)	9/10 (90%)	
Unclassified PID	3/20 (15%)	2/10 (20%)	1/10 (10%)	
Common variable immunodeficiency (CVID)	2/20 (10%)	0/10 (0%)	2/10 (20%)	
Allergy	47/103 (46%)	20/103 (19%)	27/103 (26%)	0.11
Rhinitis	33/47 (70%)	15/20 (75%)	18/27 (66%)	
Conjunctivitis	19/47 (40%)	14/20 (70%)	5/27 (19%)	
Asthma	12/47 (26%)	5/20 (25%)	7/27 (26%)	
Not defined respiratory allergy	4/47 (9%)	2/20 (10%)	2/27 (7%)	
Other	8/47 (17%)	3/20 (15%)	5/27 (19%)	
Autoimmunity	31/103 (30%)	16/103 (16%)	15/103 (15%)	1.0
Autoimmune thyroiditis	10/31 (32%)	5/16 (31%)	5/15 (33%)	
Coeliac disease (CD)	8/31 (26%)	5/16 (31%)	3/15 (20%)	
Type I diabetes mellitus (DM)	7/31 (23%)	2/16 (12%)	5/15 (33%)	
Autoimmune cytopenias	4/31 (13%)	1/16 (6%)	3/15 (20%)	
Arthritis	2/31 (6%)	1/16 (6%)	1/15 (7%)	
Other	7/31 (23%)	3/16 (19%)	4/15 (27%)	

The percentages total more than 100% because some patients had more than one disease in family history

(Table 3). The heterozygous C104R mutation was identified in four patients and three of them had a partial SIGAD. Among TACI-mutated patients, a positive family history for autoimmune diseases was observed in 2/4 (50%) aSIGAD and in 5/7 (71%) pSIGAD. Autoimmune manifestations were present in two patients at diagnosis and maintained at follow-up. Both had a partial defect, were heterozygous for C104R, and suffering with coeliac disease, associated to autoimmune thyroiditis in one of them. Antinuclear antibodies were detected in 1/11 (9%) TACI-mutated patients; no autoimmune disease was ever observed in this pSIGAD patient. Again, no significative differences appeared in the group of aSIGAD vs pSIGAD patients.

Clinical and immunological features of 80 patients at follow-up

In our study, we monitored 80 patients (44 aSIGAD and 36 pSIGAD, mean age 12 years) for a mean period of 5 years. As reported in Fig. 1, IgA values changed overtime. Particularly, 29/44 (66%) patients with initial diagnosis of aSIGAD retained the absolute defect, conversely 11/44 (25%) shifted to a partial SIGAD defect, and 4/44 (9%) spontaneously reached normal IgA values. In patients with an initial diagnosis of pSIGAD, we observed a persistence of partial IgA deficiency in 17/36 (47%), whereas 7/36 (19%) patients evolved to an absolute defect and 12/36 (33%) to IgA normalization. Our data showed that the chance for IgA normalization was higher for pSIGAD than that for aSIGAD patients (33 vs 9%, $p = 0.01$) (Fig. 1). Mean age of normalization was 9 years for both groups.

At final follow-up, absolute and partial defects were observed in 36/80 (45%) and 28/80 (35%) patients, respectively, whereas 16/80 (20%) patients had reversed to normal IgA values. Clinical data of patients with aSIGAD, pSIGAD, and normalization reversal at follow-up are reported in Fig. 2. Particularly, infections of the respiratory and gastrointestinal tract remained the most common clinical features in aSIGAD (19/36; 53%) and in pSIGAD (18/28; 64%), whereas normalization of IgA values was associated to a significative lower rate of infections (2/16; 12%) compared to aSIGAD ($p = 0.007$) and pSIGAD ($p = 0.001$).

Allergy represented the second most frequent clinical condition with an irrelevant distribution from 25 to 38% in the different groups of aSIGAD, pSIGAD, and patients with normalization of IgA values. In all groups, rhinitis was predominant, followed by conjunctivitis and asthma.

Autoimmune diseases, such as coeliac disease, autoimmune thyroiditis, and diabetes, were observed in 3/36 (8%) aSIGAD and in 5/28 (18%) pSIGAD patients. Two of them from each group developed autoimmunity with time. Conversely, no autoimmune disease was ever observed in patients who normalized IgA levels. Furthermore, other gastrointestinal conditions, such as recurrent abdominal pain and aphthosis, were observed in 2/36 (5%) aSIGAD, 4/28 (14%) pSIGAD, and 3/16 (18%) patients with normalization of IgA values. The incidence of autoimmunity and other gastrointestinal conditions was not significant among all groups; also, no malignancies were observed at follow-up. Again, when both cohorts were stratified according to age (< 10 years vs > 10 years) for all described clinical categories, no significative differences were found (data not shown).

Table 2 Clinical manifestations of 103 patients with selective IgA deficiency (SIGAD) at diagnosis

Clinical manifestations	SIGAD	aSIGAD	pSIGAD	*p* value
Infections	86/103 (83%)	44/53 (83%)	42/50 (84%)	1.0
Respiratory tract infections	82/86 (95%)	41/44 (93%)	41/42 (98%)	
URTI	56/82 (68%)	25/41 (61%)	31/41 (76%)	
LRTI	5/82 (6%)	3/41 (7%)	2/41 (5%)	
URTI+LRTI	21/82 (26%)	13/41 (32%)	8/41 (20%)	
Gastrointestinal infections	16/86 (19%)	6/44 (14%)	10/42 (24%)	
Giardia infections	6/16 (38%)	2/6 (33%)	4/10 (40%)	
Urinary tract infections (UTI)	5/86 (6%)	1/44 (2%)	4/42 (10%)	
Fever	1/86 (1%)	1/44 (2%)	0/42 (0%)	
HSV and VZV infections	3/86 (3%)	1/44 (2%)	2/42 (5%)	
Candidiasis	2/86 (2%)	0/44 (0%)	2/42 (5%)	
Allergy	39/103 (38%)	19/53 (36%)	20/50 (40%)	0.68
Rhinitis	19/39 (49%)	8/19 (42%)	11/20 (55%)	
Atopic dermatitis	13/39 (33%)	3/19 (16%)	10/20 (50%)	
Asthma	11/39 (28%)	5/19 (26%)	6/20 (30%)	
Conjunctivitis	10/39 (26%)	7/19 (37%)	3/20 (15%)	
Other	10/39 (26%)	6/19 (32%)	4/20 (20%)	
Autoimmunity	13/103 (13%)	4/53 (8%)	9/50 (18%)	0.14
Coeliac disease (CD)	8/13 (62%)	3/4 (75%)	5/9 (56%)	
Autoimmune thyroiditis	3/13 (23%)	1/4 (25%)	2/9 (22%)	
Idiopathic juvenile arthritis (IJA)	2/13 (15%)	0/4 (0%)	2/9 (22%)	
Type I diabetes mellitus (DM)	1/13 (8%)	1/4 (25%)	0/9 (0%)	
Other	1/13 (8%)	0/4 (0%)	1/9 (11%)	
Other conditions	9/103 (9%)	4/53 (8%)	5/50 (10%)	0.73
Recurrent abdominal pain	5/9 (56%)	2/4 (50%)	3/5 (60%)	
Aphthosis	2/9 (22%)	1/4 (25%)	1/5 (20%)	
Other	3/9 (33%)	1/4 (25%)	2/5 (40%)	
Malignancy	0/103 (0%)	0/53 (0%)	0/50 (0%)	1.0

The percentages total more than 100% because some patients had more than one type of clinical manifestation

URTI upper respiratory tract infections, *LRTI* lower respiratory tract infections

Table 3 Autoimmunity in 11 SIGAD patients with TNFRSF13B gene mutation at

Patient	Sex	Age	Mutation	Family history for autoimmunity	Autoimmunity at diagnosis	Autoimmunity at follow-up	ANA
aSIGAD							
Pt.1	M	12	C104	Yes	No	No	Neg
Pt.2	F	14	C66X	No	No	No	Neg
Pt.3	F	6	C193X	Yes	No	No	Neg
Pt.4	M	8	G190A	No	No	No	Neg
pSIGAD							
Pt.1	M	17	fsX80	Yes	No	No	Neg
Pt.2	M	7	C104R	Yes	CD	CD	Neg
Pt.3	F	17	C104R	Yes	CD, AT	CD, AT	Neg
Pt.4	F	4	R202H	No	No	No	Neg
Pt.5	M	12	C104R	No	No	No	Neg
Pt.6	F	12	I87N	Yes	No	No	Pos
Pt.7	F	10	fs220X	Yes	No	No	Neg

CD coeliac disease, *AT* autoimmune thyroiditis, *Neg* negative, *Pos* positive

aSIGAD vs pSIGAD $p = 0.17$

Discussion

Selective IgA deficiency (SIGAD) is the most common primary immunodeficiency disorder, with a worldwide incidence ranging from 1:300 to 1:600 individuals. The incidence is higher in Caucasians; however, community settings and definition criteria for IgA deficiency account for the different rates reported so far. To limit the variables that affect epidemiologic data, we focused on symptomatic > 4-year old children referred to our specialty clinics who followed an established routine protocol that led to the identification of low IgA values with the exclusion of other immunological abnormalities and secondary causes.

Several studies have provided a clinical and immunological characterization of patients with an absolute defect (aSIGAD) as defined when serum IgA level is < 7 mg/dl, but few data are available on partial IgA deficiency (pSIGAD) as defined when serum IgA level is 2 SD below normal for age. In fact, pSIGAD commonly goes unnoticed or it is considered as a mild variant of SIGAD with a better clinical outcome. In our study, clinical, immunological, and genetic features of aSIGAD versus pSIGAD patients indicate that both conditions deserve a proper evaluation and regular monitoring.

A positive family history is the most significant warning sign to identify an immunodeficiency [36]. It has been estimated that about 20–25% of SIGAD patients have a family history of PID [7]. We observed PID in the family members of 19% of SIGAD patients with equal distribution between aSIGAD and pSIGAD cohorts. Conversely, scarce data are available on the family history for allergy and/or autoimmunity in children with SIGAD. In our SIGAD patients, 46% of them had a family history for allergy disorders and 30% for autoimmunity. Although no significant differences were found in the frequency and type of allergy or autoimmune disorders in the family of our aSIGAD vs pSIGAD cohorts, the proportion of SIGAD family members with autoimmunity is relevant. Therefore, considering their lower frequency in the general population, awareness among healthcare physicians should be raised in the presence of parents/family members who suffer of a variety of immune dysregulations for early counseling.

Patients with SIGAD show a heterogeneous clinical phenotype, from an asymptomatic state to a range of associated manifestations that can be categorized into infections, allergy, autoimmunity, and malignancy. In our study, at diagnosis, symptomatic children with aSIGAD shared the same clinical profile of symptomatic pSIGAD patients. Indeed, infectious diseases, predominantly respiratory and gastrointestinal tract infections, are the most common clinical manifestations of symptomatic SIGAD children in 40–90% of cases [3, 5]. Conversely, a lower incidence of infections is observed in adult cohorts of SIGAD individuals [27, 32]. Our results demonstrate that not only aSIGAD but also pSIGAD children show a high frequency of infections as previously reported [3, 6] since we detected a frequency of 93–98% for respiratory infections and of 14–24% for gastrointestinal infections. Thus, the function and the quantity of IgA in mucosal immunity, especially in the defense against pathogens harboring the respiratory and the gastrointestinal tract, seem critical in the pediatric age.

Allergies and autoimmune disorders may characterize the clinical picture of SIGAD patients and may be the first and/or sole clinical manifestation, too. The prevalence of allergy and autoimmune diseases in SIGAD patients mostly ranges from 25 to 50% and from 5 to 30%, respectively [13, 14, 21, 34, 37, 42, 43, 47]. In our SIGAD cohorts, the prevalence of allergic disorders was of 38% which fits previous estimates on similar cohorts and the notion that allergy and autoimmunity may be overexpressed in SIGAD patients than in the general population [6]. In fact, the frequency of autoimmune disorders in our aSIGAD and pSIGAD patients, 8 and 18% respectively, was higher than the 3–5% reported in Western general population. Further, the high prevalence of IgA deficiency among patients initially diagnosed with autoimmune disorders is also true, pointing to the protective role of IgA against autoimmunity with a strong genetic and environmental influence. The incidence of autoimmunity has been demonstrated to be higher in the adult SIGAD population [32] compared to the pediatric SIGAD cohort supporting the assertion that the occurrence of autoimmune diseases comes with age [46, 47].

Several studies have suggested that SIGAD patients have an increased risk of neoplasia, such as lymphoma and gastric cancer, especially at older ages [28, 42, 46]. Other neoplasia identified in SIGAD patients are carcinoma of the colon, ovarian cancer, lymphosarcoma, melanoma, and thymoma [4, 46]. Ludvigssonn et al. found a 31% increased relative risk of cancer in a cohort of absolute IgA-deficient adults. In our study, no malignancy emerged in both SIGAD variants, in accordance with previous reports that showed the low prevalence of malignancy in children with SIGAD [46, 48].

Although sera from SIGAD patients may contain antinuclear antibodies, the relevance of autoantibody production in the absence of clinical autoimmunity needs to be elucidated with a rigorous long-term follow-up.

The pathogenesis of IgA deficiency is still unknown but a failure of B cell differentiation with abnormal cytokine release and/or cellular signaling unbalance as well as increased apoptosis are reported as major causative mechanisms as per CVID. Both CVID and SIGAD share clinical manifestations and are identified in family members. Progression to CVID may occur in SIGAD patients. The hypothesis of a shared genetics that might include several genes is intriguing. Several susceptibility loci have been described for IgA deficiency [1, 15, 16, 19, 23, 29, 31, 46]. A recent genome-wide

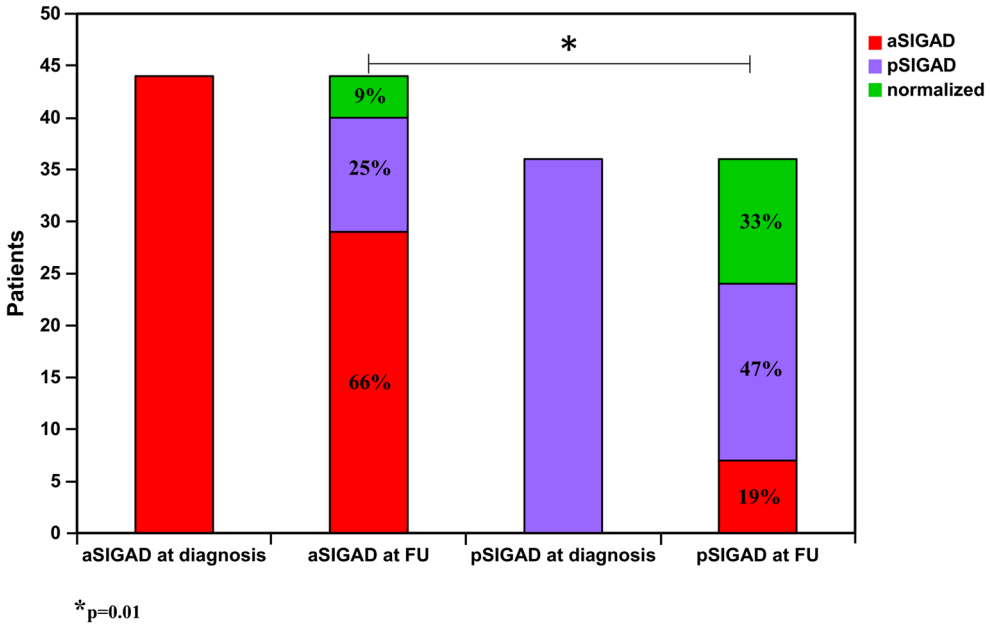

Fig. 1 The progress of patients with selective IgA deficiency (SIGAD) over a 5-year period. Red bars refer to patients with an absolute defect, lilac bars to patients with partial IgA defect, and green bars to normalized patients. The asterisk indicates a significant difference ($p < 0.05$) between the two analyzed groups

association study meta-analysis identified common variants of PVT1, ATG13-AMBRA1, AHI1, and CLEC16A associated with SIGAD [8].

The role of TACI in B cell proliferation, isotype switching, antibody responses, and central tolerance has been previously demonstrated [17]. *TNFRSF13B* gene mutation has been reported in approximately 10% of CVID patients and heterozygous variants found to be associated with autoimmune and lymphoproliferative disorders. Conversely, in IgA-deficient patients, although *TNFRSF13B* mutations have been variably detected according to the different cohorts [17, 26], as well as in about 2% of healthy subjects, they do not seem to play a primary role but do act as modifiers and co-participants of the disease [18]. In accordance with the study by Pulvirenti et al. [35], we found a relative higher frequency of *TNFRSF13B* mutations (13%) in our cohort of symptomatic aSIGAD patients and even more in those with partial defect (29%). In our TACI-mutated cohort, eight different genetic alterations were

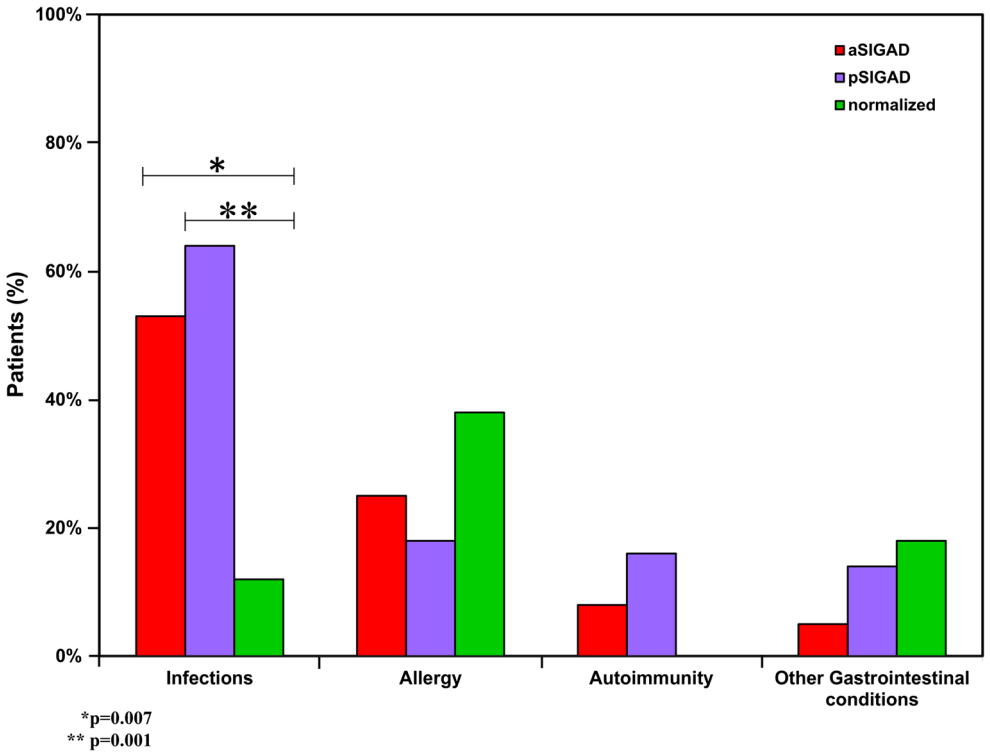

Fig. 2 Distribution of patients with selective IgA deficiency (SIGAD) in relation to clinical features at follow-up. Red bars refer to patients with an absolute defect, lilac bars to patients with partial IgA defect, and green bars to normalized patients. The asterisk indicates a significant difference ($p < 0.05$) between the two analyzed groups

observed, but monoallelic C104R was identified more frequently than non-C104R mutations. However, the clinical significance of *TNFRSF13B* variants in SIGAD patients is controversial and the occurrence of autoimmunity may vary according to a combination of several demographic, genetic, and environmental components [6]. Also, careful monitoring of family members might add valuable information on the breakdown of human immune system [18, 26, 38].

Currently, few studies with a long-term follow-up of SIGAD patients are available. Several studies reported that pediatric SIGAD patients may reach normal IgA values over time [21, 41] and sometimes shift to a partial defect [21]. Normalization and evolution to a partial defect were both observed in 28% of patients [25]. Also, in our 5-year follow-up of 80 patients, IgA values may change over time. In detail, the persistence of an absolute defect was observed in 66% of aSIGAD, the shift to a partial defect in 25% of cases, and normalization of IgA values occurred in 9% of patients.

Few studies have characterized pSIGAD patients over time [24, 40]. In our cohort, the partial defect was maintained in 47% of patients and shifted to absolute in 19%. Normalization of IgA levels was significantly more frequent in pSIGAD than in aSIGAD (33 vs 9%, $p = 0.01$), and it occurred at a mean age of 9 years for both forms of SIGAD.

Interestingly, patients who retained an absolute or partial IgA defect continued to present symptoms, regardless of their initial absolute or partial IgA deficiency. Conversely, normalization of IgA levels led to a significant reduction of infectious manifestations. Since autoimmunity comes with age in both PID and non-PID patients, extensive studies on partial and absolute SIGAD adults could aid to clarify the natural history of the disease and might envisage the revision of diagnostic criteria to improve preventive and therapeutic management of these patients. Yet, the strong association of SIGAD with other immune-mediated diseases and the high prevalence of family members with different immune pathologies would imply that SIGAD is often a warning sign of a more complex disorder.

The lack of homogeneous cohorts renders critical any data comparisons from the different sources; however, the notion that pediatric IgA deficiency may be a reversible or progressive disorder is clear. Our data suggest that a negative family history for PID, absence of autoimmune diseases, and fewer infections seem to predict a benign condition. Although we might provide only a partial view of an evolving process in which several environmental and genetic factors are involved, the role of the different actors of the disease, including *TNFRSF13B*, needs to be further elucidated.

In conclusion, a regular long-term follow-up of patients with IgA deficiency is required for early diagnosis of associated diseases and to implement workup protocols. Further, the impact of partial IgA deficiency should be monitored in clinical practice for a more comprehensive examination of the complex interplay that regulates the specialized role of IgA.

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Authors' contributions VM designed the study, analyzed and interpreted the data, wrote and critically reviewed the manuscript. LC and SG contributed to data interpretation and writing of the manuscript. CP, AP, FS critically reviewed and approved the final manuscript. MS, VG, EC contributed to the acquisition of data. SF, GDM, SDC performed all genetic and immunological analysis. VM designed the study, analyzed and interpreted the data, wrote and critically reviewed the manuscript. LC contributed to data interpretation and writing the manuscript. SG contributed to data interpretation and writing the manuscript. CP critically reviewed and approved the final manuscript. AP critically reviewed and approved the final manuscript. FS critically reviewed and approved the final manuscript. MS contributed to the acquisition of data. VG contributed to the acquisition of data. EC contributed to the acquisition of data. SF performed all genetic and immunological data. GDM performed all genetic and immunological data. SDC performed all genetic and immunological data.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained at diagnosis from all individual participants included in the study.

Ethical standards The approval for the study was obtained from the institutional review board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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