

Clinical Symptoms in Adults with Selective IgA Deficiency: A Case-Control Study

G. H. Jorgensen · A. Gardulf · M. I. Sigurdsson ·
S. Th. Sigurdardottir · I. Thorsteinsdottir · S. Gudmundsson ·
L. Hammarström · B. R. Ludviksson

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Abstract Selective IgA deficiency (SIgAD) is the most common primary immunodeficiency in Caucasians with a prevalence of 1/600 and is generally considered a mild disorder. In this study, the clinical status of 32 adults with SIgAD was investigated and compared to 63 age- and gender matched controls, randomly selected from a population database. The SIgAD individuals reported significantly more often contracting various upper and lower respiratory infections, with 8 (25.0 %) having been diagnosed with ≥ 1 pneumonia in the preceding two years, compared to one (1.6 %) control ($p < 0.001$). Furthermore, the SIgAD individuals were found to have increased proneness to infections and increased prevalence of allergic diseases and autoimmunity, with a total of 84.4 % being affected by any of these diseases, compared to 47.6 % of the controls ($p < 0.01$). This study challenges the common statement of SIgAD being a mild form of immunodeficiency. It also highlights the importance of using matched

controls in PID clinical research to better detect clinically important manifestations.

Keywords Primary immunodeficiency · IgA deficiency · infections · autoimmunity · allergy

Introduction

Selective IgA deficiency (SIgAD), defined as serum IgA levels < 0.07 g/L, with normal levels of serum IgG and IgM, is the most common primary immunodeficiency [1]. While the majority of SIgAD individuals discovered by screening blood donors are asymptomatic at the time of diagnosis, some individuals develop recurrent infections, autoimmunity manifestation and allergic diseases [2–4]. SIgAD is commonly considered a mild disorder, with approximately 65–70 % of the affected being reported as asymptomatic [2, 5].

Previous studies on the clinical significance of SIgAD have been affected by selection bias towards ‘disease’ or ‘healthy’ SIgAD individuals and/or lacking control groups from randomly selected population cohorts and/or longitudinal follow-ups. To our knowledge, this is the first clinical SIgAD study using age- and gender-matched population controls.

Subjects and Methods

Thirty-two adults (13 women, 19 men; mean age 48 [26–75] years), fulfilling the criteria for SIgAD [1] were investigated. Five individuals were identified by screening of serum from blood donors at the Icelandic blood bank (samples collected 1999–2001), 11 were identified by re-evaluating serum from SIgAD individuals from a previous screening of blood donors (1974–1979) [6] and 16 were identified by evaluating

G. H. Jorgensen and A. Gardulf have contributed equally

G. H. Jorgensen · M. I. Sigurdsson · B. R. Ludviksson
Department of Medicine, University of Iceland, Reykjavík, Iceland

G. H. Jorgensen (✉) · S. T. Sigurdardottir · B. R. Ludviksson
Department of Immunology, Landspítali University Hospital,
Eiríksgata 5,
Reykjavík 101, Iceland
e-mail: gudmhj@landspitali.is

A. Gardulf · L. Hammarström
Division of Clinical Immunology at the Department of Laboratory
Medicine, Karolinska Institutet at Karolinska University Hospital
Huddinge, Stockholm, Sweden

I. Thorsteinsdottir
Department of Biochemistry, Landspítali University Hospital,
Reykjavík, Iceland

S. Gudmundsson
Icelandic Blood Bank, Reykjavík, Iceland

individuals found to have low serum IgA levels when analysed at the Departments of Clinical Chemistry and Immunology, Landspítali University Hospital, Iceland during 1992–2006. No SIgAD individual was excluded from participation during the process of recruitment. The clinical status of the 32 SIgAD individuals was unknown to the investigators prior to the study. Serum samples from the 32 individuals were re-analysed before entering the study and shown to have IgA levels <0.07 g/L and normal, or in a few cases, mildly elevated levels of IgG and IgM and no IgG subclass deficiency.

Ninety-six age- and gender-matched individuals were randomly selected from the Icelandic National Registry. No exclusion criteria for the individuals in the control group were set up; thus the controls might suffer from other chronic diseases/conditions and thereby better reflect the ordinary population. 88/96 individuals could be found at given addresses and 63 (71.6 %) participated (29 women, 34 men; mean age 50 [27–76] years). The controls had normal serum IgG, IgA and IgM levels.

The SIgAD and controls did not differ significantly for any demographic variables (gender, age, education, marital status).

Methods used for the totally 95 participants:

- a study specific and self-administered questionnaire comprising 122 items. The items focused on demographic and socioeconomic status, diagnoses and incidence of various infections, asthma, allergic and autoimmune diseases, together with symptoms from skin and the musculoskeletal, respiratory and gastrointestinal systems. The questionnaire was answered before the individuals underwent any clinical examination.
- standardized interview always performed by the same study physician. All current and previous disease diagnoses reported by participants were noted and also their use of any medication.
- extensive physical examination was performed in a standardized manner by the same study physician.
- skin prick tests (GREER, Lenoir, NC 28645, USA); 20 common air- and food allergen extracts. A wheal formation of ≥ 3 mm was regarded as positive.
- lung function tests using spirometry (Medikro Spiro 2000, version 1.6.); individuals with FEV1 <80 % of predicted value for age, sex and size, along with a FEV1/FVC ratio of <0.7 , were considered having bronchial obstruction (obstructive spirometry).
- laboratory assessments, including evaluation of serum immunoglobulins.

The National Bioethics Committee of Iceland and the Data Protection Committee of Iceland approved the study. Informed consent was obtained from all participants in the study.

Results

Infections

SIgAD individuals reported significantly more often having various upper and lower respiratory infections (Table I). The infections shown in Table I are self-reported but for pneumonias and sinusitis all the diagnoses had to be confirmed by a physician as bacterial pneumonia/sinusitis necessitating antibiotic treatment. Moreover, in ≥ 85 % of reported pneumonias the diagnose was also confirmed by lung X-ray. Hence, thirteen (40.6 %) of the SIgAD had been diagnosed with pneumonia ≥ 1 times in the preceding 5 years, of which 8 (25 %) in the preceding 2 years, as compared with 1 (1.6 %) control ($p<0.001$) (Table I).

When comparing the overall predisposition for infections using a study-specific classification system based on frequency and severity of different types of infections, with class 1=least prone to infections to class 3=most prone to infections, SIgAD individuals demonstrated significantly higher proneness towards infections; 28.1 %, 15.6 % and 56.3 % for classes 1, 2 and 3; compared with 69.8 %, 14.3 %; and 15.9 % in controls ($p<0.001$ comparing distribution between SIgAD and controls).

When comparing the 16 SIgAD individuals recruited via the Departments of Clinical Chemistry and Immunology with the 16 SIgAD individuals recruited through screening of blood donors, no significant differences were found regarding the proportion of individuals diagnosed having pneumonia (≥ 1 pneumonia the last 2 years, 25 % vs. 25 %) or general proneness to infections (class 3; 68.8 % vs. 43.8 %, n.s.)

Asthma and Allergy

No difference between the groups was observed regarding having been diagnosed with asthma (18.8 % vs. 12.7 %, $p=0.54$), while prevalence of allergic-rhinoconjunctivitis tended to be increased in the SIgAD group (37.5 % vs. 19.0 %, $p=0.08$) (Table II). SIgAD individuals with either asthma and/or allergic-rhinoconjunctivitis, were classified as having a more severe disease ($p<0.05$) (Table II) using a classification system class 1=low symptom severity, class 4=highest symptom severity.

When comparing the number of individuals diagnosed with ≥ 1 form of allergic disease, the overall prevalence was significantly higher in the SIgAD group (46.9 % vs. 25.4 %, $p<0.05$) (Table II).

Eighteen SIgAD individuals (56.3 %) showed positive skin prick tests results (sensitized) to ≥ 1 allergen vs. 14/63 (22.2 %) controls ($p<0.01$) (Table II). A positive prick test against ≥ 1 airborne allergen was noted in 15 SIgAD individuals (46.9 %) vs. 12 controls (19.0 %), and a positive

Table 1 Comparison of self-reported data regarding infections in 32 individuals with selective IgA deficiency (SIgAD) and 63 age- and gender-matched controls

	5 years ^b	2 years ^a			<i>p</i> -value
	Never (%)	Never (%)	1–4 times (%) ^c	≥5 times (%) ^d	
Respiratory infections					
Upper respiratory tract infections					
Infectious conjunctivitis					
SIgAD	20 (62.5)	22 (68.8)	9 (28.1)	1 (3.1)	5 y <0.05
Controls	52 (82.5)	59 (93.7)	3 (4.8)	1 (1.6)	2 y <0.01
Common viral cold (1 year)					
SIgAD		1 (3.1)	23 (71.9)	8 (25.0)	1 y <0.001
Controls		10 (15.9)	48 (76.2)	5 (7.9)	
Pharyngitis ^e					
SIgAD	1 (3.1)	5 (15.6)	19 (59.4)	8 (25.0)	5 y <0.001
Controls	17 (27.0)	24 (38.1)	36 (57.1)	3 (4.8)	2 y <0.01
Laryngitis					
SIgAD	23 (71.9)	26 (81.3)	5 (15.6)	1 (3.1)	5 y <0.05
Controls	57 (90.5)	59 (93.7)	4 (6.3)	0	2 y n.s.
Sinusitis ^f					
SIgAD	20 (62.5)	20 (62.5)	10 (31.3)	2 (6.3)	5 y n.s.
Controls	47 (74.6)	50 (79.4)	10 (15.9)	3 (4.8)	2 y n.s.
Acute otitis media (5 years and 1 year)					
SIgAD	31 (96.9)	32 (100)	0	0	5 y n.s.
Controls	61 (96.8)	62 (98.4)	1 (1.6)	0	1 y n.s.
Lower respiratory tract infections					
Bronchitis					
SIgAD	17 (53.1)	20 (62.5)	11 (34.4)	1 (3.1)	5 y <0.01
Controls	50 (79.4)	53 (84.1)	8 (12.7)	2 (3.2)	2 y <0.05
Pneumonia ^f					
SIgAD	19 (59.4)	24 (75.0)	8 (25.0)	0	5 y <0.001
Controls	62 (98.4)	62 (98.4)	1 (1.6)	0	2 y <0.001
Gastrointestinal infections					
Campylobacter/salmonella					
SIgAD	32 (100)	32 (100)	0	0	5 y n.s.
Controls	62 (98.4)	62 (98.4)	1 (1.6)	0	2 y n.s.
Infectious gastroenteritis nos					
SIgAD	30 (93.8)	31 (96.9)	1 (3.1)	0	5 y n.s.
Controls	60 (95.2)	60 (95.2)	3 (4.8)	0	2 y n.s.
Protozoal- or worm infections					
SIgAD	32 (100)	32 (100)	0	0	5 y n.s.
Controls	63 (100)	63(100)	0	0	2 y n.s.
Urogenital infections					
Cystitis (1 year)					
SIgAD		28 (87.5)	4 (12.5)	0	1 y n.s.
Controls		59 (93.7)	3 (4.8)	1 (1.6)	
Pyelonephritis					
SIgAD	30 (93.8)	30 (93.8)	2 (6.3)	0	5 y n.s.
Controls	61 (96.8)	61 (96.8)	1 (1.6)	1 (1.6)	2 y n.s.
Prostatitis (5 years) ^g					
SIgAD (19 men)	18 (94.7)		0	1 (5.3)	5 y n.s.
Controls (34 men)	32 (94.1)		2 (5.9)	0	

Table 1 (continued)

	5 years ^b	2 years ^a			<i>p</i> -value
	Never (%)	Never (%)	1–4 times (%) ^c	≥5 times (%) ^d	
Skin infections					
External otitis					
SIgAD	27 (84.4)	30 (93.8)	2 (6.3)	0	5 y n.s.
Controls	58 (92.1)	61 (96.8)	2 (3.2)	0	2 y n.s.
Bacterial skin infections					
SIgAD	24 (75.0)	26 (81.3)	6 (18.8)	0	5 y n.s.
Controls	51 (81.0)	54 (85.7)	9 (14.3)	0	2 y n.s.

^a The time interval is 2 years unless specifically noted after each infection (i.e. 1 year, 5 years).

^b For simplification, 5-years (5 y) incidence is only represented in the table with “never in 5 years” unless specifically noted. Consequently, as for 2 years (2 y) *p*-values, all the 5 y *p*-values represent a comparison of the complete frequency of every infection the preceding 5 years.

^c The incidence rate “1–4”, represents the combined incidence scales of 1–2 and 3–4 asked for in the questionnaire.

^d The incidence rate “≥5 times” represents combined incidence scales of 5–6 and ≥7.

^e Data on incidence of pharyngitis have been published (ref. [8]) but are shown here to provide complete information.

^f All reported pneumonias and sinusitis needed to be diagnosed by a physician as bacterial pneumonia/sinusitis, necessitating antibiotic treatment.

^g Only information on 5-years incidence for prostatitis was asked for and is shown in the table.

Antibiotic usage in both groups has been published earlier (ref. [8]), with 71.8 % of the SIgAD individuals having received ≥1 antibiotic treatment the preceding 12 months, compared to 33.3 % of the controls (*p*<0.0001).

prick test against ≥1 foodborne allergen was noted in 3 SIgAD individuals (9.4 %) vs. 4 controls (6.3 %).

Lung auscultation revealed a pronounced expiratory phase and/or rhonchi in 8 of the SIgAD (25 %) and 7 of the controls (11.1 %) (n.s.), but none of the SIgAD or controls fulfilled the predefined criteria for bronchial obstruction on spirometry.

Autoimmune Diseases

In a previous report, 8 (25 %) of the 32 SIgAD individuals were found to be suffering from various types of autoimmunity, evenly distributed between systemic (RA, polymyalgia rheumatica, sarcoidosis and psoriasis) and organ-specific (autoimmune thyroid diseases, pernicious anemia, pemphigus, interstitial cystitis and ITP) diseases, with four individuals having two different autoimmune diseases [7]. For comparison 3 (4.8 %) of the matched controls suffered from autoimmune diseases (*p*<0.05) [8], diagnosed with autoimmune thyroid disease, Addison’s disease, RA and Sjögren’s syndrome respectively.

Other Diseases

None of the SIgAD individuals or the controls had been diagnosed with coeliac disease or gastrointestinal cancer. No significant differences were reported in the prevalence of gastritis and/or gastric ulcer (SIgAD 21.9 % vs. controls 15.9 % during the 5 preceding years), nor for musculoskeletal-, cardiovascular-, neurological-, or psychiatric diseases.

Cutaneous Abnormalities

A high prevalence of cutaneous abnormalities was observed at skin examination; 84.4 % SIgAD individuals vs. 42.9 % controls (*p*<0.05). Signs of fungal infection in the skin and/or nails were more common in the SIgAD group: 56.3 % vs. 20.6 % (*p*<0.001). A higher prevalence of warts was also noted among SIgAD individuals: 18.8 % vs. 4.8 % albeit not statistically significant (*p*=0.06). Other skin disorders were not significantly more often observed within the SIgAD group when compared to controls, such as eczema (28.1 % vs. 14.3 %), psoriasis (6.3 % vs. 0), acne (6.3 % vs. 4.8 %) and rosacea (3.1 % vs. 4.8 %), respectively.

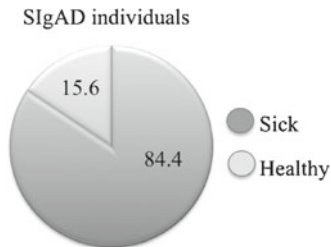
Sick Leave

Three SIgAD individuals (9.4 %) had for several years been receiving long-term sickness benefits, versus none among the controls (*p*<0.05). All three SIgAD individuals suffered from repeated infections (pneumonias and/or sinusitis and/or urinary tract infections) and allergic rhinoconjunctivitis; two had asthma and two had been diagnosed with autoimmune diseases severely affecting their health (one with RA and polymyalgia rheumatica; one with interstitial cystitis and pernicious anaemia).

SIgAD Individuals More Affected than Previously Reported?

When combining SIgAD individuals that fulfilled infection-proneness class 3 and/or were diagnosed with any allergic

Table II Comparisons of individuals with selective IgA deficiency to controls regarding diagnosed allergic diseases, and a comparison of how many in each group are affected by infections, allergic diseases and/or autoimmunity

	SIgAD (n=32)		Controls (n=63)		p-value ^a	Sick vs. Healthy (%)
	n (%)	Positive prick test n (%)	n (%)	Positive prick test n (%)		
1. Asthma	6 (18.8)	4 (66.7)	8 (12.7)	2 (25.0)	n.s.	
Disease severity ^b					<0.05	
class 1	0 (0)	0	1 (1.6)	0		
class 2	0 (0)	0	5 (7.9)	1		
class 3	1 (3.1)	1	1 (1.6)	1		
class 4	5 (15.6)	3	1 (1.6)	0		
2. Allergic rhinoconjunctivitis	12 (37.5)	8 (66.7)	12 (19.0)	6 (50.0)	n.s.	
Disease severity ^b					<0.05	
class 1	3 (9.4)	2	5 (7.9)	3		
class 2	3 (9.4)	3	0 (0)	0		
class 3	2 (6.3)	1	0 (0)	0		
class 4	4 (12.5)	2	7 (11.1)	3		
3. Allergic urticaria	2 (6.3)	1	1 (1.6)	1	n.s.	
4. Food allergy	2 (6.3)	2	1 (1.6)	1	n.s.	
5. Allergic anaphylaxis	1 (3.1)	1	0 (0)	0	n.s.	
Number of individuals with ≥ 1 of above (1-5) mentioned allergic diseases	15 (46.9)	10 (66.7)	16 (25.4)	6 (37.5)	<0.05	
6. General eczema	8 (25.0)	5	16 (25.4)	3	n.s.	
7. Contact dermatitis	6 (18.8)	4	0 (0)	0	<0.01	
- either 6 or 7	13 (40.6)	8	16 (25.4)	3	n.s.	
Allergic diseases (1-5) and history of eczema (6 or 7)	21 (65.6)	14 (66.7)	27 (42.9)	8 (29.6)	0.05	
Eczema alone ("no other" allergic disease)	6 (18.8)	3	11 (17.5)	2	n.s.	
Total number of individuals with positive skin prick test	18 (56.3)		14 (22.2)		<0.01	

The table demonstrates the prevalence of allergic diseases and eczema, diagnosed by a doctor and reported by the participants, together with results from skin prick testing found at clinical evaluation.

^a P-values in the table show the results from statistical comparison of allergic diseases 1–7 and not the prevalence of positive prick test.

^b Individuals diagnosed with asthma or allergic rhinoconjunctivitis were classified after disease severity into 4 classes, with class 1 representing individuals with the mildest form of the disease and class 4 those having the most severe form.

The right side of the table compares the overall prevalence of sick vs. healthy in both groups. Individuals were considered sick if being classifying in infection-proneness class 3 and/or diagnosed with any allergic disease (asthma, allergic rhinoconjunctivitis, food allergy, allergic urticaria, allergic anaphylaxis and/or eczema) and/or diagnosed with an autoimmune disorder. Those not fulfilling this criteria were, for this comparison, considered healthy, although possibly affected by other diseases.

disease (asthma, allergic-rhinoconjunctivitis, food allergy, allergic urticaria, allergic anaphylaxis and/or eczema) and/or diagnosed with an autoimmune disorder, 27 (84.4 %) of the SIgAD individuals vs. 30 (47.6 %) of the controls fell into this classification ($p<0.01$) (Table II).

Discussion

SIgAD individuals showed a markedly higher infection proneness (3.5 times that of the controls), mostly due to upper- and lower respiratory infections. They were also more often diagnosed with autoimmune- and allergic diseases, and those

diagnosed with asthma and/or allergic-rhinoconjunctivitis had a worse disease severity compared to controls. The physical examination demonstrated an unexpected frequent occurrence of skin- and nail-fungal infections among SIgAD individuals. Moreover, we also investigated the health-related quality of life (HRQL) in the same two groups as in this article and found that the SIgAD individuals reported a significantly worse infection-related HRQL with increased fear of getting infections and perceived increased susceptibility to infections correlating with poorer HRQL (Jorgensen et al., submitted).

The high prevalence of different autoimmunity, infections and allergic diseases compared to controls, cannot be explained by the SIgAD individuals investigated being more

related internally and thereby representing a unrepresentative subgroup of SIgAD individuals sharing common high risk genes for different diseases. This was proven when analysing the SIgAD group at the Icelandic genealogy database (“The Book of Icelanders”), demonstrating that the SIgAD group was no more related than the general population.

Although a comparison of the SIgAD individuals recruited from screening of blood donors (16 cases) and those recruited from the departments of clinical chemistry and immunology (16 cases) was not the aim of the study, it is important to notice that no significant difference could be observed between the groups when comparing the overall infection proneness and frequency of pneumonias. Hence, this uniform mixture of SIgAD individuals presented in this study minimises a possible selection bias toward either “healthy SIgAD individuals” or “sick SIgAD individuals”.

The significantly increased number of respiratory tract infections in SIgAD individuals (infectious conjunctivitis, pharyngitis, laryngitis, viral colds, bronchitis, pneumonia) confirms previous findings by others [3, 4, 9]. The low number of acute otitis media in the SIgAD group (Table I) is interesting, especially in the light of the otherwise increased overall frequency of upper and lower respiratory infections. Similarly, no significant difference was noted in the incidence of sinusitis (Table I), although in the case of sinusitis, the lack of significance is most likely due to the relatively small study groups, given the expected prevalence for that disease. Moreover, the current study did not indicate that the individuals with SIgAD suffered from major problems of infections in the gastrointestinal- and urogenital system. These findings are in accordance with current literature, demonstrating only minimal predisposition to bacterial gastrointestinal- and urinary tract infections [3, 4, 9–12].

In the current study a significantly higher prevalence of allergic diseases was observed within the SIgAD individuals (Table II) indicating a predisposition to allergic diseases. An increased prevalence of allergic manifestation in SIgAD individuals has previously been reported. Interestingly, more recent studies have not been consistent as to whether allergic diseases are more common within SIgAD individuals; while some report high prevalence of allergic diseases (32–84 %) [3, 10, 13], others have not found higher prevalence than in controls or than expected within the population [4, 9, 14].

The high prevalence of autoimmune diseases (8/32) within the SIgAD individuals investigated has been reported earlier [7]. The prevalence of autoimmune diseases in SIgAD individuals has been shown to vary from 7 to 36 % [15]. Although, several different hypotheses exist to explain the association between SIgAD and autoimmunity (discussed in [15]) the currently most favoured theory is that autoimmune diseases and SIgAD share a common genetic denominator.

The results of this study, the first using a randomly selected age- and gender-matched population control group, challenge the common view of SIgAD as a mild or symptom

free immunodeficiency. More clinical notice needs to be given to patient with SIgAD and a large, prospective, population-based study is warranted to better answer questions regarding the clinical status of individuals with SIgAD.

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Conflict of Interest No conflict of interest is reported for any of the authors.

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