

Prevalence of dermatologic diseases among patients with selective immunoglobulin A deficiency

Eli Magen, M.D.,¹⁻³ Atheer Masalha, M.D.,^{3,4} Dan Andrei Waitman, M.D.,¹ Natan Kahan, Ph.D.,^{1,5} Igor Viner, M.D.,^{3,6} Leonora Klassov, M.D.,^{3,6} and Daniel Vardy, M.D., M.Sc.^{3,4}

ABSTRACT

Background: There are no published large-scale epidemiologic studies regarding the prevalence of skin diseases in patients with selective immunoglobulin A (IgA) deficiency (sIgAD). The purpose of this study was to investigate the prevalence of dermatological diseases in patients with sIgAD.

Methods: This retrospective matched case-control study was based on data from the Leumit Healthcare Services data base (approximately 725,000 residents of Israel), which was searched for all subjects aged ≥ 12 years who had undergone serum total IgA measurements during 2004–14 for any reason. The case group included subjects with sIgAD. The control A group was randomly sampled from those subjects in whom an IgA was drawn ($n \approx 725,000$), with a ratio of 10 controls for every case (1:10). The control A group was randomly sampled from those subjects in whom an IgA was drawn ($n = 104,729$) and the control B group was randomly sampled from the full study population ($n \approx 725,000$), with a ratio of 10 controls for every case (1:10). Comorbidity was compared between the study groups.

Results: The sIgAD group was characterized: 1) By a higher prevalence of atopic dermatitis (AD) (16 [4.6 %]) than the control A group (76 [2.1 %]; $p = 0.004$ and the control B group (64 [1.9 %]; $p = 0.002$). 2) By higher prevalence of acne (69 [19.9 %]) than the control A group (516 [13.8 %]; $p = 0.013$) and control B group (494 [14.2 %]; $p < 0.001$). 3) By higher rate of chronic spontaneous urticaria (CSU) (17 [4.9 %]) than in the control A group (31 [0.9 %], with odds ratio 5.54 [3.04–10.13]; $p < 0.001$) and the control B group (28 [0.8 %]; $p < 0.001$).

Conclusions: sIgAD is characterized by a higher prevalence of AD, CSU and acne.

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Immunoglobulin A (IgA) is the most abundant antibody isotype in the body and plays a specialized role in mucosal immunity, immunologic tolerance, and protection against infection.^{1,2} The worldwide prevalence of selective IgA deficiency (sIgAD) varies, depending on ethnic background, with a prevalence that ranges from 1:142 to 1:965 in white populations.^{3,4} Among Israeli blood donors, the frequency of sIgAD was found to be markedly lower among Sephardi Jews (0.053% [1:1883]) than among those of Ashkenazi origin (0.130% [3:2192]).⁵ Some patients with sIgAD have a tendency to develop recurrent sinopulmonary infections, gastrointestinal infections and disorders, allergies, autoimmune diseases, and malignancies.^{6,7} Autoimmune diseases are some of the most important

clinical manifestations in sIgAD.⁸ The prevalence of systemic and organ-specific autoimmune diseases was found to vary from 20 to 30%, based on the age range of the studied populations.^{9,10} Allergic disorders also seem to be common in patients with sIgAD.^{11–14} To our knowledge, there are no published large-scale epidemiologic studies regarding the prevalence of skin diseases in patients with sIgAD. The purpose of this population-based case-control study was to investigate the prevalence of dermatologic diseases in patients with sIgAD.

METHODS

Data Source

This was a retrospective, matched, case-control study based on data from the Leumit Health Care Services (LHS) data base in Israel. LHS is a health maintenance organization that covers $\sim 725,000$ residents of Israel, and its electronic data base includes comprehensive information on the insured population: demographic data, records of clinical visits, laboratory tests (performed at a single centralized laboratory), and diagnostic codes that use the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM, <http://www.cdc.gov/nchs/icd/icd9cm.htm>). This data base was used to obtain information on di-

From the ¹Leumit Health Services, Medical Division, Tel Aviv, Israel, ²Medicine B Department, Allergy and Clinical Immunology Unit, Barzilai University Medical Center, Ashkelon, Israel, ³Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel, ⁴Dermatology Department, Soroka University Medical Center, Beer Sheva, Israel, ⁵Sackler Faculty of Medicine, School of Public Health, Tel-Aviv University, Tel-Aviv, Israel, and ⁶Department of Emergency Medicine, Barzilai University Medical Center, Ashkelon, Israel

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Address correspondence to Eli Magen, M.D., Barzilai University Medical Center, 7830604, Hahistadrout St 2, Ashkelon, Israel

E-mail address: allergologycom@gmail.com

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agnoses and laboratory results by means of cross-linkage by using a unique patient identifier. The LHS data base fully represents all population groups in Israel and is used by national health care authorities to compare the quality-monitoring systems in Israeli health plans and managed care organizations. The LHS data base was searched for all subjects ages ≥ 12 years who had undergone serum total IgA measurements during 2004–2014 for any reason. The study was approved by LHS Institutional Review Committee.

METHODS

Inclusion Criteria

The case group samples were drawn from the full study population ($\sim 725,000$) and included all subjects with a serum IgA of ≤ 7 mg/dL (≤ 0.07 g/L) but normal serum IgG and IgM levels in whom other causes of hypogammaglobulinemia had been excluded (ICD-9-CM diagnostic code 708.1). The control A group was randomly sampled from those subjects in whom an IgA was drawn ($n = 104,729$) and the control B group was randomly sampled from the full study population ($\sim 725,000$), with a ratio of 10 controls for every case (1:10). The randomization was performed by using the Epi Info 6 software (Centers for Disease Control and Prevention, Division of Health Informatics & Surveillance, Atlanta, GA). The matching was performed according to the exact year of age and for the exact age at IgA diagnosis.

The comorbid diseases, diagnosed by the corresponding board-certificated physicians ≤ 5 years before serum total IgA testing, were identified and retrieved from the LHS electronic data base by using the relevant ICD-9-CM diagnostic codes, which included patients who had at least two separate visits in which the chief concern was related to one of these comorbid allergic (691.(0–8) atopic dermatitis (AD) and related conditions, 692.(0–90) contact dermatitis and other eczema), systemic autoimmune (714.(0–9) rheumatoid arthritis, 710.3 dermatomyositis, 710.1 systemic sclerosis, 710.0 systemic lupus erythematosus), organ-specific autoimmune (idiopathic urticaria; 279.01 696 psoriasis and similar disorders), 694.0 dermatitis herpetiformis (DH), 704.01 alopecia areata, 709.01 vitiligo, 697.0 lichen planus, 695.2 erythema nodosum, 694.(0–9) bullous dermatoses, 245.2 chronic lymphocytic thyroiditis, 242.0 toxic diffuse goiter, 281.0 pernicious anemia, 579.0 celiac disease, 556.(0–9) ulcerative colitis, 555.(0–9) regional enteritis, 357.(0–9) inflammatory and toxic neuropathy, 287.31 immune thrombocytopenic purpura, 250.(0–9) diabetes mellitus 1 type), and other dermatologic diseases (acne, seborrheic dermatitis, chronic spontaneous urticaria, scabies, herpes simplex, herpes zoster, molluscum contagiosum, cellulitis). The presence of allergic, autoimmune, and

dermatologic diseases confirmed in the medical records data base by using the relevant ICD-9-CM diagnostic codes was registered for each subject. From these collected data, the comorbidities were measured by the total number of comorbidities.

Exclusion Criteria

The exclusion criteria were the following: the presence of any selective IgG or IgM deficiency, common variable immunodeficiency, ataxia telangiectasia, human immunodeficiency virus or acquired immunodeficiency syndrome, on chronic systemic corticosteroid therapy, or on any other form of immunosuppressive therapy. Chronic corticosteroid therapy has been defined as systemic corticosteroid treatment over a period that lasts at least 3 months (irrespective of the daily dosage of cortisone administered).

Immunoglobulin Measurements

Serum immunoglobulin levels (IgM, IgA, IgG, IgG1, IgG2, IgG3, IgG4) were measured in the LHS central laboratory. Immunoglobulin levels were measured by using nephelometry (BN II System; Dade Behring, Deerfield, IL). Serum samples were analyzed for total IgE levels by using the immunometric assay with the Immulite 2000 system (Diagnostic Products Corporation, Erlangen, Germany). All the case subjects had to have laboratory data available for these immunoglobulins to be included in this study.

Clinical Evaluation of Chronic Spontaneous Urticaria

All patients with an electronically documented diagnosis of chronic spontaneous urticaria (CSU) from the sIgAD group were identified and retrieved from the LHS electronic data base by using the relevant ICD-9-CM diagnostic codes registered by the attending board-certificated physicians. Patient characteristic; medical histories; and details of diagnostic workup, medical treatment, and follow-up were retrieved from the electronic patient record data base of LHS. Only the subjects who met the criteria for diagnosis of chronic spontaneous urticaria according to The European Academy of Allergology and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA2LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO) guidelines¹⁵ were included in the study, and the patients with other types of chronic urticaria were excluded. In the CSU control group, consecutive patients with CSU (ages ≥ 12 years) referred to our outpatient allergy clinic from the Ashdod region (Ashdod, Israel) between April 2015 and December 2015 were included and prospectively studied. Informed consent to partic-

ipate in the study was obtained from the subjects from the CSU control group.

All the patients with CSU underwent a physical examination, complete blood cell count, erythrocyte sedimentation rate, thyroid function tests, antinuclear antibodies tests, antithyroglobulin and antiperoxidase antibodies tests, and IgE evaluation. To exclude physical types of urticaria, the following were performed: a test for dermatographism, cold provocation and threshold test by using ice cubes, heat provocation and threshold test by using warm water, and pressure test by using pressure of 0.2–1.5 kg/cm² for 10 and 20 minutes. An autologous serum skin test (ASST) was performed by injecting 0.05 mL of the patient's own serum intradermally into the left flexor forearm 5 cm below the antecubital crease and a saline solution control into the right forearm. A reading of the wheal was taken after 30 minutes. A wheal and flare of >1.5 mm in diameter than that of the control was considered a positive result.

Statistical Analyses

Differences in demographic and clinical characteristics between the groups were analyzed by using the Wilcoxon signed rank test for nonparametric variables. The mean and standard deviation were calculated for continuous variables. Statistical significance for categorical variables was calculated by using the χ^2 test. The multiple regression analyses adjusted for sex and age (odds ratio with 95% confidence intervals) were performed separately for each group of comorbidities. All statistical analyses were conducted by using the statistical package SPSS version 16.0 (IBM, Chicago, IL).

RESULTS

Demographic and Laboratory Characteristics of Cases and Controls

A total of 104,729 subjects, ages 12–76 years, were identified as having received a serum total IgA test between January 1, 2004, and December 31, 2014. Among these, 347 subjects, ages 12–74 years, were identified as having sIgAD. The corresponding control A and control B groups, therefore, consisted of 3470 subjects each; there were no differences between the subjects in cases and control groups with regard to demographic characteristics (Table 1). The 347 subjects with sIgAD were in the LHS data base for mean $\pm$ standard deviation 21.3 $\pm$ 14.1 months and 3470 subjects without sIgAD for 20.2 $\pm$ 16.4 months ($p = 0.23$). The frequency of allergic and autoimmune comorbidities according to one diagnosis of allergic condition and one diagnosis of autoimmune disease was similar to that according to two diagnoses in at least two separate visits.

Clinical Manifestations

Allergic Skin Diseases. The sIgAD group was characterized by a higher prevalence of AD (16 [4.6%]) than the control A group (76 [2.1%]; $p = 0.005$) and the control B group (64 [1.9%]; $p < 0.001$). No differences in the prevalence of contact dermatitis were found between the sIgAD and control groups (Table 1).

Skin Infectious Diseases. There was no statistically significant difference in the prevalence of particular nosologic forms of skin infections between the sIgAD and control groups (Table 1).

Skin Autoimmune Diseases. No statistically significant difference was observed in the prevalence of skin autoimmune diseases between the sIgAD and control groups (Table 1).

Acne. The sIgAD group was characterized by a higher prevalence of acne (69 [19.9%]) than the control A group (516 [13.8%]; $p = 0.013$) and the control B group (494 [14.2%]; $p < 0.001$) (Table 1).

CSU. In the sIgAD group, a significantly higher rate of CSU (17 [4.9%]) was observed than in the control A group (31 [0.9%]), with odds ratio 5.54 [95% confidence interval, 3.04–10.13]; $p < 0.001$) and the control B group (28 [0.8%]; $p < 0.001$) (Table 1).

Comparison of Subjects with CSU with and without sIgAD. The 17 subjects with sIgAD and CSU were compared with 142 consecutive patients (ages ≥ 12 years) with CSU who were referred to our outpatient allergy clinic from the Ashdod region (Ashdod, Israel) between April 2015 and December 2015. The 17 subjects with CSU and sIgAD had a higher overall prevalence of systemic autoimmune (4 [23.5%]) and non-skin organ specific autoimmune diseases (7 [41.2%]) than the 142 consecutive patients with CSU (7 [4.9%], $p = 0.004$; and 24 [16.9%], $p = 0.002$) (Table 2). There was no difference in skin allergy comorbidity, prevalence of a positive ASST result, and antihistamine treatment resistance between the subjects with CSU did and those who did not have concomitant sIgAD (Table 2).

Comparison of sIgAD Subjects with and without CSU. The subjects with sIgAD with concomitant CSU were characterized by a higher prevalence of both systemic and organ-specific autoimmune diseases (13 [76.5%]) than the subjects with sIgAD and without CSU (99 [30%], $p < 0.001$; with odds ratio 7.58 [95% confidence interval, 2.41–23.83]) (Table 2). Among 17 patients with CSU and sIgAD (sIgA group), we identified 8 patients (47.1%) with concomitant autoimmune diseases and 9 patients (52.9%) without concomitant autoimmune dis-

Table 1 Skin infectious, allergic, and autoimmune diseases in the patients with sIgAD and in matched controls

	Subjects with sIgAD, Control A Subjects, Control B Subjects, no. (%) (n = 347)			p*	p#	p§	Multiple Logistic Regression Model	
							OR (95% CI)	p
Female subjects	159 (45.9)	1594 (45.9)	1594 (45.9)	0.99	0.99	0.99		
Age, mean ± SD, y¶	24.1 ± 15.7	24.9 ± 16.4	25.3 ± 16.1	0.35	0.69	0.87		
Serum IgA, mean ± SD, mg/dL¶¶	0.4 ± 0.2	118.5 ± 69.4		<0.001				
Skin infectious diseases								
Scabies	3 (0.9)	11 (0.3)	9 (0.3)	0.11	0.08	0.61	2.74 (0.76–9.87)	0.12
Herpes simplex	4 (1.1)	17 (0.5)	14 (0.4)	0.14	0.06	0.54	2.36 (0.79–7.08)	0.13
Herpes zoster	1 (0.3)	8 (0.2)	5 (0.1)	0.52	0.39	0.37	1.25 (0.15–10.03)	0.83
Molluscum contagiosum	2 (0.6)	5 (0.1)	3 (0.08)	0.11	0.06	0.45	4.01 (0.78–20.79)	0.09
Cellulitis	5 (1.4)	29 (0.8)	18 (0.5)	0.21	0.08	0.09	1.73 (0.67–4.51)	0.26
Skin allergic diseases								
Atopic dermatitis	16 (4.6)	76 (2.1)	64 (1.9)	0.005	<0.001	0.28	2.21 (1.28–3.85)	0.006
Allergic contact dermatitis	11 (3.2)	94 (2.8)	87 (2.6)	0.71	0.43	0.51	1.21 (0.64–2.29)	0.62
Acne	69 (19.9)	516 (13.8)	494 (14.2)	0.013	<0.001	0.69	1.49 (1.13–1.99)	0.052
Seborrheic dermatitis	4 (1.2)	42 (1.3)	37 (1.1)	0.99	0.74	0.52	0.92 (0.32–2.59)	0.93
CSU	17 (4.9)	31 (0.9)	29 (0.8)	<0.001	<0.001	0.75	5.54 (3.04–10.13)	<0.001
Skin autoimmune diseases								
Psoriasis	7 (2)	68 (1.9)	61 (1.7)	0.82	0.63	0.48	1.03 (0.47–2.26)	0.94
Dermatitis herpetiformis	0	0	1 (0.03)	0.99	0.99	0.99	9.98 (0.19–504.13)	0.25
Alopecia areata	2 (0.6)	25 (0.7)	29 (0.8)	0.72	0.99	0.58	0.79 (0.19–3.87)	0.76
Vitiligo	2 (0.6)	17 (0.5)	13 (0.4)	0.81	0.62	0.54	1.17 (0.27–5.11)	0.73
Lichen planus	0	14 (0.4)	19 (0.5)	0.62	0.39	0.47	0.34 (0.02–5.76)	0.46
Erythema nodosum	0	5 (0.1)	2 (0.05)	0.42	0.63	0.39	0.91 (0.05–16.43)	0.95
Pemphigus vulgaris	0	2 (0.06)	1 (0.03)	0.64	0.73	0.34	1.99 (0.096–41.65)	0.64
Pemphigus foliaceus	0	0	0	0.99	0.99	0.99	9.98 (0.19–504.13)	0.25
Bullous pemphigoid	0	0	0	0.99	0.99	0.99	9.98 (0.19–504.13)	0.25

sIgAD = Selective immunoglobulin A deficiency; OR = odds ratio; CI confidence interval; SD = standard deviation; CSU = chronic spontaneous urticaria.

^{*}Between subjects with sIgAD and control A subjects.[#]Between subjects with sIgAD and control B subjects.[§]Between control A subjects and control B subjects.[¶]Values are presented as mean (SD).

Table 2 Concomitant allergic and autoimmune diseases in Patients with CSU with and Patients without sIgAD

	Patients with sIgAD with CSU, no. (%) (n = 17)	Patients with sIgAD without CSU, no. (%) (n = 330)	CSU Controls, no. (%) (n = 142)	p*	p#	Multiple Logistic Regression Model between Patients with CSU with and without sIgAD	
						OR (95% CI)	p
Female subjects	9 (52.9)	150 (45.5)	97 (68.3)	0.15	0.15		
Age, mean ± SD, y§	27.6 ± 14.1	23.9 ± 15.8	41.5 ± 17.3	0.002	0.31		
Autologous serum skin test performed	11 (64.7)		63 (47.9)	0.11			
Autologous serum skin test positive result	5/11 (45.5)		24/63 (38.1)	0.72			
Antihistamine resistant CSU¶	3 (17.6)		12 (8.5)	0.17			
Antinuclear antibodies positive result	3 (17.6)		7 (4.9)	0.09			
Skin allergic diseases							
Atopic dermatitis	1 (5.8)	15 (4.5)	3 (2.1)	0.35	0.51	1.31 (0.16–10.57)	0.79
Allergic contact dermatitis	0	11 (3.2)	5 (3.5)	0.99	0.99	0.79 (0.04–14.03)	0.87
Systemic autoimmune diseases	4 (23.5)	17 (5.1)	7 (4.9)	0.004	0.002	5.67 (1.67–19.23)	0.005
Sjogren's disease	1 (5.8)	2 (0.6)	2 (1.4)	0.21	0.11	10.25 (0.88–119.06)	0.06
Rheumatoid arthritis	2 (11.8)	9 (2.7)	3 (2.1)	0.08	0.07	4.79 (0.96–24.82)	0.06
Dermatomyositis	0	1 (0.3)	0	0.99	0.99	4.75 (0.94–23.96)	0.059
Systemic sclerosis	0	2 (0.6)	0	0.99	0.99	3.75 (0.17–81.21)	0.39
Systemic lupus erythematosus	1 (5.8)	3 (0.9)	2 (1.4)	0.24	0.15	6.81 (0.67–69.19)	0.11
Organ-specific autoimmune diseases	7 (41.2)	72 (21.8)	24 (16.9)	0.017	0.06	2.51 (0.92–6.82)	0.07
Hashimoto thyroiditis	3 (17.6)	12 (3.6)	12 (8.5)	0.14	0.021	5.67 (1.43–22.43)	0.013
Graves disease	0	5 (1.5)	3 (2.1)	0.99	0.99	1.69 (0.09–31.82)	0.72
Pernicious anemia	1 (5.8)	3 (0.9)	2 (1.4)	0.27	0.15	6.81 (0.68–69.19)	0.11
Celiac disease	2 (11.8)	22 (6.7)	3 (2.1)	0.15	0.39	1.92 (0.41–8.96)	0.40
Ulcerative colitis	0	7 (20.1)	0	0.99	0.99	1.23 (0.068–22.46)	0.89
Crohn's disease	0	5 (1.5)	1 (0.7)	0.99	0.99	1.69 (0.09–31.82)	0.72
Fibromyalgia	0	4 (1.2)	1 (0.7)	0.99	0.99	2.07 (0.11–40.05)	0.63
Immune-mediated neuropathy	0	2 (0.6)	1 (0.7)	0.99	0.99	3.75 (0.17–81.21)	0.39
Immune thrombocytopenic purpura	0	1 (0.3)	0	0.99	0.99	4.75 (0.94–23.96)	0.059
Type I diabetes mellitus	1 (5.8)	8 (2.4)	2 (1.4)	0.26	0.34	2.51 (0.29–21.35)	0.39

Table 2 Continued

	Patients with sIgAD with CSU, no. (%) (n = 17)	Patients with sIgAD without CSU, no. (%) (n = 330)	CSU Controls, no. (%) (n = 142)	p*	p#	Multiple Logistic Regression Model between Patients with CSU with and without sIgAD
						OR (95% CI)
Skin autoimmune diseases	1 (5.8)	10 (3.1)	9 (6.3)	0.31	0.39	2 (0.24–16.59)
Psoriasis	0	7 (2.1)	3 (2.1)	0.99	0.99	1.25 (0.07–22.94)
Dermatitis herpetiformis	0	0	0	0.99	0.99	18.89 (0.36–980.22)
Alopecia areata	0	2 (0.6)	0	0.99	0.99	3.75 (0.17–81.21)
Vitiligo	1 (5.9)	1 (0.6)	1 (0.7)	0.17	0.08	20.56 (1.23–343.91)
Lichen planus	0	0	0	0.99	0.99	18.89 (0.36–980.22)
Erythema nodosum	0	0	1 (0.7)	0.99	0.99	18.89 (0.36–980.22)
Pemphigus vulgaris	0	0	0	0.99	0.99	18.89 (0.36–980.22)
Pemphigus foliaceus	0	0	0	0.99	0.99	18.89 (0.36–980.22)
Bullous pemphigoid	0	0	0	0.99	0.99	18.89 (0.36–980.22)

CSU = Chronic spontaneous urticaria; sIgAD = selective immunoglobulin A deficiency; OR = odds ratio; CI = confidence interval; SD = standard deviation.
The data in bold represent the sum of all cases of skin autoimmune diseases.

*Between subjects with sIgAD and with CSU and the CSU control group.

#Between subjects with sIgAD with and without concomitant CSU.

\$Values are presented as mean (SD).

¶The patients with CSU who had to increase antihistamine medications to the fourfold dose to suppress their urticaria symptoms were considered to be antihistamine resistant.

eases. Among 31 patients with CSU and without sIgAD (control A group), 11 patients (35.5%) had at least one concomitant autoimmune disease, whereas 20 (64.5%) had none. The sIgAD prevalence was not different between patients with CSU and patients without associated autoimmune disorders ($p = 0.73$).

DISCUSSION

The results of this study showed a higher prevalence of acne, AD and CSU in subjects with sIgAD, whereas there was a similar prevalence of skin infectious and autoimmune diseases in subjects with and subjects without sIgAD. The frequency of subjects with sIgAD among the individuals who sought medical attention in our study was ~1:302, markedly above the expected frequency in the general Israeli population.⁵ Actually, most individuals with sIgAD are asymptomatic (in 85–90% of the cases), and there is no established routine screening program for IgA deficiency, consequently, sIgAD prevalence may be significantly higher. Probably our study revealed the prevalence of sIgAD among a population with frequent infections, allergy, or autoimmune diseases, and did not reflect a real prevalence of sIgAD in the whole population.

The higher rate of AD in our patients with sIgAD, likewise, has been observed previously.^{9,16,17} Although a protective role of IgA has been seen in experimental models of asthma,¹⁸ a possible role for IgA in AD pathogenesis has not yet been studied. Although the recent cohort study showed that levels of secretory IgA in breast milk were inversely associated with the development of AD up to 2 and 4 years of age among infants who were breast-fed,¹⁹ other studies, conversely, did not find IgA levels in breast milk to be associated with AD.²⁰ The reasons for this particularly high incidence of AD in patients with sIgAD have to be investigated in further studies. Acne occurs in ~15% of healthy persons, with the highest prevalence in adolescence.²¹ Most of our patients with sIgAD mean $\pm$ standard deviation (age, 24.1 ± 15.7 years) had passed adolescence; nevertheless, we observed a higher prevalence of acne in the subjects with sIgAD than in sex- and age-matched controls. A role of IgA in the pathophysiology of acne is largely unknown. It is possible that some degree of the immune dysregulation that characterizes sIgAD may explain these results.

Several case reports showed an association between sIgAD and vitiligo,^{9,22–24} lichen planus,²² alopecia areata,^{16,25} and psoriasis¹⁶; nevertheless, we failed to detect a positive association between sIgAD and skin autoimmune diseases. Interestingly, although sIgAD was shown to be associated with celiac disease, with a reported overall prevalence of 1:39 among both children and adults,^{26,27} there is no reported association of sIgAD with DH. Immunofluorescence findings in di-

rect immunofluorescence studies from skin biopsy specimens of patients with DH cover a much wider spectrum than previously known (deposits of IgG, IgA, IgM, complement component 3, the first subcomponent of the C1 complex, and fibrinogen); granular IgA deposits, however, are the key diagnostic features of DH that differentiate this blistering disease from all other dermatologic disorders.^{28,29} It is probable that the absence of IgA and subsequent inability to produce granular IgA deposits in sIgAD could explain the non-existence of DH in subjects with sIgAD.

Another finding of our study was the high prevalence of CSU observed in patients with sIgAD. An association of sIgAD with CSU was described previously in two case reports.^{30,31} Recently, Frossi *et al.*³² reported on four patients with CSU and sIgAD. ASST was positive in all four patients, and their sera were found to induce CD63 upregulation on basophils, which indicates an autoimmune nature of chronic urticaria.³² We identified 17 subjects with CSU within our cohort of patients with sIgAD. Although these subjects were characterized by higher rates of concomitant systemic and non-skin organ specific autoimmune disorders than 142 consecutive patients with CSU (but not sIgAD), there was no difference in the prevalence of any positive ASST results between 11 subjects with CSU and sIgAD and 63 patients with CSU. Notably, there was no difference in the rates of concomitant skin autoimmune diseases between the CSU and sIgAD group and the CSU group.

CONCLUSION

The clinical and immunologic features of sIgAD in our relatively large cohort of adult subjects are similar to those reported previously. The novelty of our report was that we specifically checked for the prevalence of dermatologic diseases among patients with sIgAD and did not find a positive correlation between sIgAD and skin autoimmune diseases. For us, it was an unexpected finding, especially when taking into consideration that previous literature indicates that sIgAD is associated with a variety of systemic and non-skin organ specific autoimmune diseases.^{33,34} At the same time, the study has several limitations due to the retrospective design implemented. First, the prevalence of some diseases in sIgAD and control A groups may be biased, because only patients with symptoms were screened for IgA levels. Second, although clinical evaluation and classification of chronic urticaria in our patients was performed according to an The European Academy of Allergology and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA2LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO) guide-

lines¹⁵ and only those who met the criteria for a diagnosis of CSU were included, the role of some triggers of chronic urticaria have not been investigated in the current study. Therefore, to assess whether sIgAD predisposes to the development of CSU, a general population of patients with chronic urticaria without any associated disease should be prospectively studied for sIgAD. Additional research is needed to determine possible pathophysiologic mechanisms that link sIgAD with acne and CSU.

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