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Selective IgA deficiency and COVID-19

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Clinical Implications

Subjects with selective IgA deficiency have significantly higher COVID-19 infection and reinfection rates.

Selective IgA deficiency (sIgAD) is the most common primary immunodeficiency disorder.[1] Selective IgA deficiency is defined as serum IgA levels below 0.07 g/L, with normal other immunoglobulin isotype levels and an otherwise normal immune system in an individual aged 4 years or older.[2] Only about 30% of sIgAD patients are symptomatic with recurrent upper respiratory tract infections and allergic or autoimmune disorders.[3] In one large series of 961 primary immunodeficiency patients infected with SARS-CoV-2, only seven sIgAD patients were infected with COVID-19, but there were no fatalities.[4] Another study found a strong positive correlation between the frequency of sIgAD and the COVID-19 infection rate per population in several countries.[5] We conducted a population-based study among members of Leumit Health Services (LHS), a large, nationwide health maintenance organization in Israel, which provides services to over 700,000 members. Leumit Health Services has a comprehensive computerized database that is continuously updated regarding subjects' demographics, medical diagnoses, medical encounters, hospitalizations, and laboratory tests. To identify patients with sIgAD, we searched the electronic database of LHS for individuals aged 4 years and older, with a chronic diagnosis of sIgAD (International Classification of Diseases, Ninth Revision code 279.01) or with serum IgA levels measured by Multiplex immunoassay (Bio-Rad, Hercules, CA) less than 7 mg/dL. Patients were excluded from the study if one or more of these chronic diagnoses were documented in the electronic health record: HIV/AIDS, common variable immunodeficiency, severe combined immunodeficiency, ataxia-telangiectasia primary immune deficiency, DiGeorge syndrome, agammaglobulinemia, or other immunodeficiency diagnoses. Ethnic group was defined according to the home address of the health maintenance organization member and was categorized into three groups: general population, Ultra-Orthodox Jews, and Arabs. The latter two groups are interesting because a large-scale epidemiology study showed that they had significantly higher rates of primary immunodeficiency and infections compared with the rest of the Israeli population. Baseline demographic and clinical data were extracted as of March 2020. Clinical outcomes were assessed by International Classification of Diseases, Ninth Revision codes documented between March 2020 and December 2022. We compared the number of subjects with a diagnosis of COVID-19 and the number of COVID-19 episodes during the study period. We adjusted for the main medical conditions expected to affect the risk for or severity of COVID-19 infection in the population: asthma, chronic heart failure, chronic obstructive pulmonary disease, chronic kidney disease, connective tissue diseases, diabetes mellitus, hypothyroidism, hypertension, inflammatory bowel disease, ischemic heart disease, and the presence of hematologic or solid malignancy, by matching conditional regression models adjusted for these conditions. The study was approved by the LHS Institutional Review Committee.

TABLE I. Demographic characteristics of subjects

Characteristics	Selective IgA deficiency	Control	*P*
n	772	3,860	
Sex, n (%)			
Female	386 (50.0%)	1,930 (50.0%)	>.999
Male	386 (50.0%)	1,930 (50.0%)	>.999
Age, y (mean [SD])	22.05 (17.53)	22.15 (17.66)	.881
4-9	200 (25.9%)	1,000 (25.9%)	>.999
10-18	258 (33.4%)	1,290 (33.4%)	>.999
19-29	126 (16.3%)	630 (16.3%)	>.999
30-39	62 (8.0%)	310 (8.0%)	>.999
40-49	42 (5.4%)	210 (5.4%)	>.999
50-59	46 (6.0%)	230 (6.0%)	>.999
60-69	21 (2.7%)	105 (2.7%)	
70-79	11 (1.4%)	55 (1.4%)	
≥80	6 (0.8%)	30 (0.8%)	>.999
Ethnicity, n (%)			
Arab	79 (10.2%)	395 (10.2%)	>.999
General	397 (51.4%)	1,985 (51.4%)	>.999
Jewish Ultra-Orthodox	296 (38.3%)	1,480 (38.3%)	>.999
Had at least one COVID-19 episode	374 (48.4%)	1,643 (42.6%)	.003
Pfizer-BioNTech mRNA vaccination doses received when first infected			
<2	27 (3.5%)	89 (2.3%)	.058
2	145 (18.8%)	711 (18.4%)	.800
3	84 (10.9%)	409 (10.6%)	.798
4	8 (1.0%)	45 (1.2%)	.855

Differences in demographic and clinical characteristics between groups were analyzed using independent sample *t* tests for continuous variables. The rates of infection, hospitalization, and mortality were compared by matching conditional logistic regression models on the matched cohort, with and without adjusting for comorbidity factors. All statistical analyses were conducted using R software (version 4.0.4, R Foundation, Vienna, Austria).

We identified 879 individuals with sIgAD among members of LHS at March 2020, 786 of whom were older than age 4 years. The sIgAD subjects were matched after excluding concomitant immunodeficiency diagnoses with 3,860 control subjects of the same age, sex, socioeconomic category, and ethnic groups. Demographic characteristics of individuals included in the cohort are presented in Table I.

TABLE II. Clinical characteristics of subjects

Comorbidity	Selective IgA deficiency	Control	*P*	Univariable model (odds ratio [95% CI])*	Multivariable logistic regression model (odds ratio [95% CI])†
n	772	3,860			
Chronic diseases					
Asthma, n (%)	72 (9.3%)	322 (8.3%)	.359	1.13 (0.85-1.48)	1.05 (0.79-1.38)
Chronic heart failure, n (%)	3 (0.4%)	9 (0.2%)	.434	1.67 (0.29-6.71)	0.87 (0.21-3.65)
Chronic kidney disease, n (%)	6 (0.8%)	17 (0.4%)	.256	1.77 (0.57-4.73)	1.34 (0.48-3.69)
Chronic obstructive pulmonary disease, n (%)	11 (1.4%)	35 (0.9%)	.229	1.58 (0.72-3.20)	0.98 (0.45-2.15)
Connective tissue disease, n (%)	20 (2.6%)	34 (0.9%)	<.001	2.99 (1.62-5.38)	2.26 (1.23-4.12)
Diabetes mellitus, n (%)	32 (4.1%)	112 (2.9%)	.087	1.46 (0.95-2.20)	1.45 (0.92-2.27)
Hypothyroidism, n (%)	39 (5.1%)	70 (1.8%)	<.001	2.88 (1.88-4.36)	2.67 (1.75-4.08)
Hypertension, n (%)	42 (5.4%)	206 (5.3%)	.930	1.02 (0.71-1.44)	0.61 (0.38-0.99)
Inflammatory bowel disease, n (%)	21 (2.7%)	12 (0.3%)	<.001	8.96 (4.19-20.1)	8.79 (4.25-18.2)
Ischemic heart disease, n (%)	12 (1.6%)	29 (0.8%)	.036	2.09 (0.96-4.24)	2.02 (0.91-4.47)
Hematologic malignancies, n (%)	14 (1.8%)	13 (0.3%)	.001	5.46 (2.37-12.7)	4.76 (2.07-10.9)
Solid tumors, n (%)	15 (1.9%)	38 (1.0%)	.039	1.99 (1.01-3.73)	1.45 (0.74-2.86)
COVID-19 infected, n (%)	374 (48%)	1643 (43%)	.020	1.26 (1.08-1.48)	1.27 (1.08-1.48)
COVID-19 episodes, n (%)					
1	312 (40%)	1472 (38%)	.240	1.09 (0.93-1.29)	1.10 (0.94-1.30)
2	61 (7.9%)	168 (4.4%)	<.001	1.90 (1.38-2.59)	1.85 (1.36-2.53)
3	1 (0.1%)	3 (0.1%)	.518	1.67 (0.03-20.8)	1.10 (0.10-12.2)
COVID-19 hospitalization, n (%)	5 (0.65%)	18 (0.47%)	.571	1.39 (0.40-3.90)	1.61 (0.59-4.40)
COVID-19 mortality, n (%)	1 (0.13%)	1 (0.026%)	.306	5.00 (0.06-392)	7.52 (0.43-132)
Reported long COVID-19, n (%)	2 (0.3%)	5 (0.1%)	.330	2.00 (0.19-12.3)	2.11 (0.40-11.1)
Other acute infectious diseases					
Upper respiratory tract infections, n (%)	198 (26%)	756 (20%)	<.001	1.83 (1.48-2.28)	1.80 (1.46-2.23)
Acute sinusitis, n (%)	47 (6.1%)	139 (3.6%)	<.001	2.18 (1.66-2.85)	1.93 (1.47-2.53)
Acute otitis media, n (%)	41 (5.3%)	117 (3.0%)	.014	1.42 (1.06-1.87)	1.45 (1.10-1.92)
Influenza, n (%)	7 (0.9%)	22 (0.6%)	<.001	1.65 (1.27-2.13)	1.53 (1.18-1.99)
Acute bronchitis, n (%)	24 (3.1%)	81 (2.1%)	<.001	1.55 (1.30-1.83)	1.50 (1.26-1.78)
Bacterial pneumonia, n (%)	24 (3.1%)	54 (1.4%)	<.001	1.77 (1.24-2.50)	1.77 (1.26-2.49)
Laryngitis or tracheitis, n (%)	29 (3.8%)	74 (1.9%)	<.001	1.59 (1.25-2.03)	1.52 (1.19-1.93)
Gastroenteritis, n (%)	44 (5.7%)	198 (5.1%)	<.001	1.69 (1.44-1.98)	1.70 (1.45-1.99)

*Univariable Fisher test contingency comparison.
†Multiple conditional logistic regression model adjusted for comorbidities (asthma, chronic heart failure, chronic kidney disease, chronic obstructive pulmonary disease, connective tissue disease, diabetes mellitus, hypothyroidism, hypertension, inflammatory bowel disease, ischemic heart disease, hematologic malignancies, and solid tumors).

Patients with sIgAD had higher rates of concomitant connective tissue disease, hypothyroidism, inflammatory bowel disease, ischemic heart disease, hematologic malignancies, and solid tumors, conditions known to be associated with sIgAD (Table II). Rates of COVID-19 infections were higher among sIgAD patients (374 [48%]) than in the control group (1,643 [43%]; odds ratio [OR] = 1.3; $P = .02$), and repeat COVID-19 infection were also more frequent in the sIgAD group (62 [8.0%]) compared with the sIgAD group (171 [4.5%]; OR = 1.9; $P < .001$). Other acute viral and bacterial infections were likewise significantly more frequent among sIgAD patients throughout the study period. These associations remained significant after adjustment for comorbidity factors. Hospitalization and mortality rates for COVID-19 were higher in the sIgAD group (0.65% and 0.13%, respectively) than in the control group (0.47% and 0.026%, respectively), but these differences did not reach statistical significance (Table II).

Secretory IgA dominates on mucosal surfaces in the early neutralizing antibody response to COVID-19.[6] Respiratory tract infections are the most common infections observed in sIgAD; therefore, it is thought that sIgAD can increase COVID-19 susceptibility and lead to a worse prognosis.[7]

In this large-scale cohort, we found that subjects with sIgAD had higher rates of COVID-19 disease and reinfection, which demonstrated a likely role of mucosal immunity in protecting against SARS-CoV-2.

Because of its retrospective nature, our study had several limitations. First, many patients with sIgAD are asymptomatic, and there is a risk for ascertainment bias. Second, undiagnosed or unreported COVID-19 infectious could not be excluded. Third, the study may have had information bias because of inaccurate clinical records, incomplete follow-up, or missing data.

A complementary approach would be to measure IgA levels in patients hospitalized with COVID-19. Such an approach was undertaken by Çölkesen et al,[8] who found that among 424 hospitalized patients with COVID-19, 11 (2.6 %) had sIgAD, which reflected a risk for severe COVID-19 that was approximately fourfold higher than in other patients with COVID-19. Another study performed on hospitalized patients found that serum IgA

levels were significantly associated with the severity of COVID-19 infection.[9] In the current cohort, we also observed higher rates for COVID-19 hospitalization and mortality among sIgAD patients, but these differences did not reach statistical significance.

In a matched cohort of 772 patients with sIgAD with matched controls who were observed for 34 months, sIgAD was associated with higher rates of COVID-19 infection and reinfection.

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