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RESEARCH ARTICLE

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The epidemiology and clinical feature of selective immunoglobulin a deficiency of Zhejiang Province in China

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Abstract

Background: Selective immunoglobulin A deficiency (SIgAD) is the most common primary antibody deficiency disease and frequently reported in the Western countries. However, large-scale epidemiologic studies on SIgAD in China are still lacking.

Methods: The clinical information of 555 180 subjects (age >4 years) including the outpatient, inpatient, and healthy subjects who had ordered serum immunoglobulin A, G, M in 9 hospitals of Zhejiang Province in China was collected. The SIgAD individuals were defined as IgA level <0.07 g/L with normal levels of serum IgG and IgM, whose age should be over 4 years, and any other secondary diseases causing SIgAD were also excluded. Then, the geographical and prevalence distribution of SIgAD individuals in Zhejiang Province and patients' clinical characteristics at the time of diagnosis were also reviewed.

Zhang, Kong, and Ni contribute equally.

Result: Among these 555 180 subjects who had ordered the immunoglobulin evaluation, the prevalence of SIgAD was 109/555180 (0.02%). The ratio of male to female of these SIgAD individuals was 1:1.37, which also included 87 adults (≥18 years) and 22 children (18 > age >4 years). For adults, the common clinical features were infections (43/87, 49.43%), autoimmune disorders (31/87, 35.63%), allergic cases (5/87, 5.75%), and tumor cases (4/87, 4.60%). Additionally, infectious diseases (20/22, 90.91%), autoimmune disorders (4/22, 18.18%), and allergic cases (1/22, 4.55%) were found in 22 children.

Conclusion: We first describe a large cohort of SIgAD individuals of Zhejiang Province in China. The incidence was 0.020%. The common clinical features were infection, autoimmune disorders, tumor, and allergy, and the infection rate was higher in children than the adults.

KEYWORDS

allergic disease, autoimmune disease, infection, selective IgA deficiency, tumor

1 | INTRODUCTION

Selective IgA deficiency is the most common primary immunodeficiency.[1] It is defined as serum IgA levels <0.07 g/L with normal serum levels of IgM and IgG in individuals of 4 years old.[1,2] Affected individuals may be asymptomatic and screened out during physical examination.[3]

IgA is the most abundant immunoglobulin in human body.[4] In humans, IgA exists in two forms—IgA1 and IgA2, with the former more common in blood and the latter primarily in secretions.[5,6] It can inhibit the adhesion of microorganisms to the mucosal epithelium and slows the reproduction of the virus which has an important immune barrier, and antibody activity against certain viruses, bacteria, and antigens.[7] Therefore, serum IgA can be used as the second line of defense by eliminating pathogens which have destroyed the mucosal surface.[8] Therefore, the most common symptoms of SIgAD individuals are recurrent respiratory tract infections.[9,10] It is found at the highest ratio of 1/142 in Caucasians, and the prevalence of SIgAD is approximately 1:328 to 1:531 in North America, 1:408 in Finland. In contrast, the prevalence of Asian countries is significantly lower, from 1:18 550 to 1:22 500 in Japan.[4]

In China, the prevalence of SIgAD was 0.062% on Shanghai blood donors in 2001 and other two studies in Beijing showed that the incidence of SIgAD is 0.037% and 0.024% in 1987 and 1992.[11] However, the prevalence and clinical information of a large cohort of SIgAD individuals in China is still lacking. Thus, in this study, the immunological data and clinical information from 9 hospitals, which consist of 555,180 subjects who had received immunoglobulin assay at different areas in Zhejiang Province, were investigated on the database of laboratory and hospital information system.

2 | PATIENTS AND METHODS

2.1 | Patients

We investigated 555 180 (271 622 males and 283 558 females) residents who had received immunoglobulin assay for any reason from The Second Affiliated hospital of Zhejiang University School of Medicine (102 213 cases), Shaoxing Second Hospital (95 595 cases), the First Affiliated Hospital of Wenzhou Medical University (94 930 cases), the First Hospital of Jiaxing (80 347 cases), The 2nd Affiliated Hospital and Yuying Children's Hospital of WMU (52 431 cases), Lishui City People's Hospital (50 282 cases), Taizhou Hospital of Zhejiang Province (39 192 cases), Hwa Mei Hospital of University of Chinese Academy of Sciences (23 013 cases), Jinhua People's hospital (17 150 cases) (Table 1). Finally, 109 SIgAD individuals were screened out on the international criteria of <0.07 g/L with normal levels of serum IgG and IgM of age over 4 years. Additionally, other secondary diseases causing hypo-IgA had been excluded.[1,12] Patient information, clinical manifestations, and immunological results were obtained through the medical records on the laboratory and hospital information system.

2.2 | Immunoglobulin measurement

Measurement of IgA, IgG, and IgM by different nephelometries (Beckman Coulter Au5800, Beckman Coulter IMMAGE800, Olympus Au5811 and Au5821, Siemens BNII, Siemens XP and Biosystems A25) was used in different hospitals (Table 1). All results were compared with age-related and each hospital reference values.

TABLE 1 Prevalence of IgA in different regions and instrument

Hospital	No. of patients	Date	Instrument	Incidence
Shaoxing Second Hospital, Zhejiang Province	28/95595	January 1, 2016 to November 13, 2018	Beckman Coulter Au5800	0.029%
The 2nd Affiliated Hospital and Yuying Children's Hospital of WMU, Zhejiang Province	21/52431	January 4, 2012 to October 16, 2018	Beckman Coulter IMMAGE800 and Siemens BNII	0.040%
The First Hospital of Jiaxing, Zhejiang Province	17/80374	January 2, 2013 to September 28, 2018	Beckman Coulter IMMAGE800	0.021%
The First Affiliated Hospital of Wenzhou Medical University, Zhejiang Province	9/94930	January 3, 2012 to December 12, 2016	Beckman Coulter IMMAGE800	0.009%
Lishui City People's Hospital, Zhejiang Province	10/50282	November 1, 2008 to November 3, 2018	Beckman Coulter IMMAGE800 Olympus Au5811 and Au5821	0.020%
Jinhua People's hospital, Zhejiang Province	8/17150	November 1, 2010 to December 1, 2018	Biosystems A25	0.047%
The Second Affiliated hospital of Zhejiang University School of Medicine, Zhejiang Province	6/102213	January 2, 2012 to November 16, 2018	Siemens BNII	0.006%
Taizhou Hospital of Zhejiang Province	6/39192	June 6, 2017 to November 6, 2018	Beckman Coulter Au5800	0.015%
Hwa Mei Hospital, University of Chinese Academy of Sciences, Zhejiang Province	4/23013	January 1, 2016 to January 18, 2019	Siemens XP	0.017%

2.3 | Statistical analysis

Analyses were performed using the GraphPad Prism5. The numeric data were expressed as mean with standard deviation in respect to variables which were normally distributed. The categorical variables were shown as number and percentage.

3 | RESULT

3.1 | Geographical and prevalence distribution of SIgAD of Zhejiang Province in China

SIgAD is the most prevalent primary immunodeficiency, found at the highest frequency of 1 in 142 in Caucasians and a low of 1 in 18 550 among Japanese, with a prevalence among other ethnicities ranging between these values.[13] However, studies on the prevalence rate of SIgAD in China are scarce. Herein, we report our analysis of SIgAD of Zhejiang Province in China. The population we investigated to consist of 51 million population (exclude three white areas) (Figure 1). Then, the 555 180 (271 622 males 283 558 females) subjects who had received immunoglobulin assay for any reason from 9 hospitals at different areas in Zhejiang Province were investigated on the database of laboratory and hospital information system, including following cities: Hangzhou, Shaoxing, Wenzhou, Jiaxing, Lishui, Taizhou, Ningbo, and Jinhua (Table 1, Figure 1). Significantly, other secondary diseases causing hypo-IgA had also been excluded, including hematological and other solid tumor received chemotherapy which results in the hypo-IgA concentration. Finally, 109 SIgAD individuals who meet the international criteria of IgA < 0.07 g/L with normal levels of serum IgG and IgM of age over 4 years were found (Table 2). Thus, the prevalence of SIgAD was 109/555,180 (0.02%, compared to an estimated prevalence of 1 per 5000 persons), and the incidence in each city was indicated in the map by heatmap pattern (Figure 1). Additionally, these 109 SIgAD individuals consisted of 46 males and 63 females (male-to-female ratio is 1:1.37), which also included 22 children (Table 2). While 4 SIgAD subjects were from 64 978 physical examination subjects, 105 SIgAD subjects were for 490,202 hospital patients.

3.2 | The spectrum of clinical manifestations

3.2.1 | Infections

Among these 109 SIgAD individuals, 87 adults (≥18 years) and 22 children (18 > age > 4 years) were found, and then, the clinical manifestations were investigated separately. For adults, infection is the most common clinical manifestations in 43/87 patients (49.43%) (Table 3). Among them, pneumonia infections rank highest in 10/87(11.49%), upper respiratory tract infections rank secondary in 7/87 (8.05%), and bronchitis rank third in 3/87 (3.45%). Other infections including 3 gastritis cases, 3 intestinal infection cases, 2 bronchiectasis with infection cases, 2 urinary tract infection cases, 2 balanoposthitis cases, 2 tuberculosis cases, 2 fever cases, 2 hepatitis B cases, 1 otitis media case, 1 acute epiglottis case, 1 acute appendicitis case, 1 viral encephalitis case, and 1 skin infection case were found (Table 3). In contrast, 20/22 children were suffered with the infections, including 6 upper respiratory tract infections (27.27%), 5 bronchitis cases (22.73%), 2 pneumonia cases (9.09%), 2 otitis media cases (9.09%), 2 sinusitis cases(9.09%),

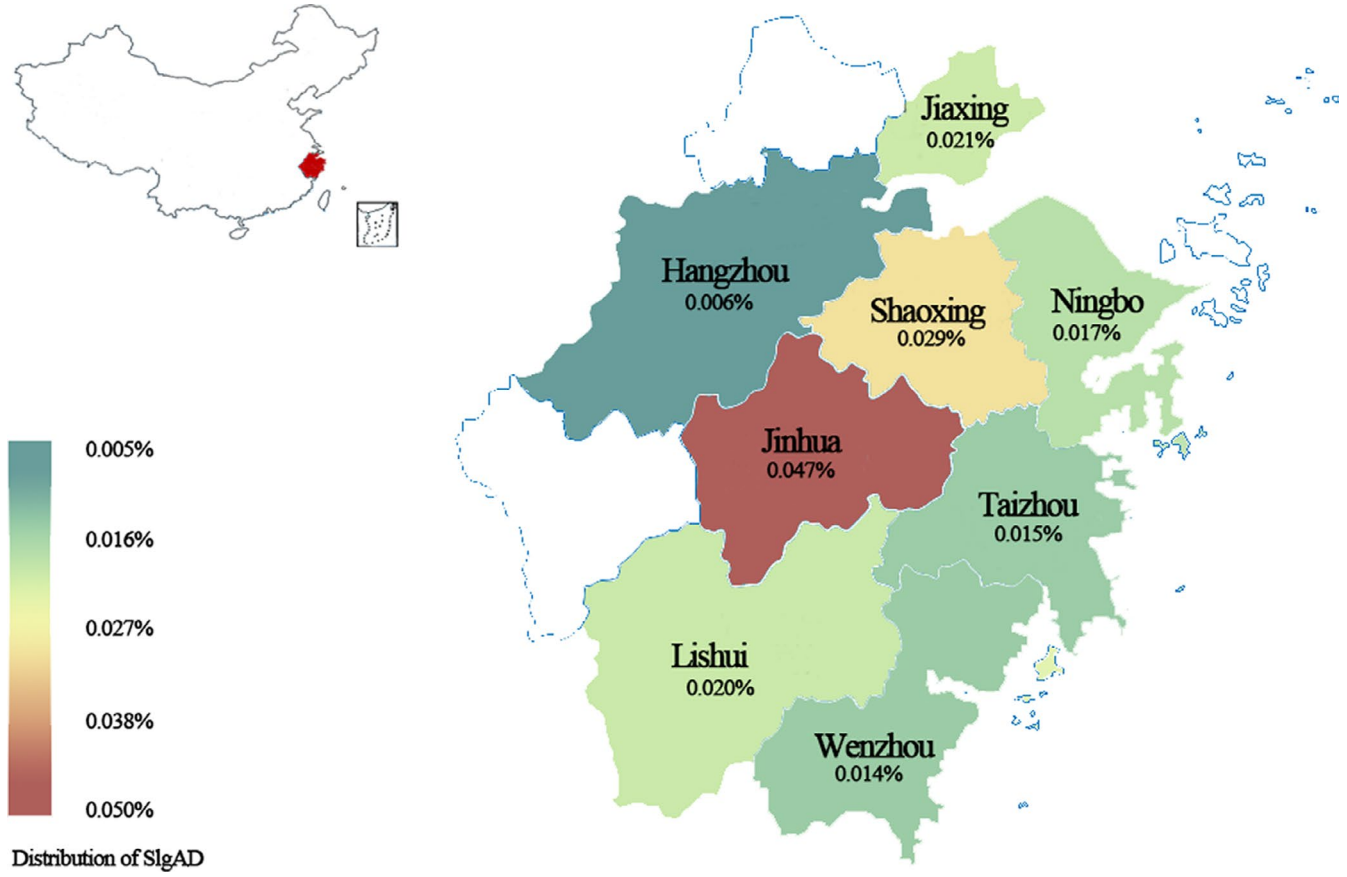

FIGURE 1 Distribution of SIgAD in 9 hospitals in Zhejiang Province

1 suppurative tonsillitis case(4.55%), 1 acute myelitis case (4.55%), and 1 varicella case (4.55%)(Table 4).

3.2.2 | Autoimmune disorders

For adult SIgAD individuals, autoimmune disorders were second most common clinical manifestation accounted for 31/87(35.63%), while the systemic lupus erythematosus had the highest ratio of 8/87(9.20%), and Sjogren's syndrome represented the second most frequent autoimmune disorders occurring in 6/87(6.90%) patients, arthritis accounted for 4/87(4.60%), while the 3 idiopathic thrombocytopenic purpura cases, 2 Evans syndrome cases, 2 rheumatoid arthritis cases, 1 graves case, 1 scleroderma case, 1 ankylosing spondylitis case, 1 adult onset still's disease case, 1 connective tissue disease case, and 1 psoriasis case were other diagnoses in these autoimmune diseases (Table 3). However, the rate of autoimmune diseases for children was lower than the adult, which account for 4/22(18.18%), including 2 systemic lupus erythematosus cases, 1 idiopathic thrombocytopenic purpura case, and 1 graves case (Table 4).

TABLE 2 Basic information of SIgAD patient

Patient characteristic	
No. of patients	109
Adult(≥18 y)	87
Children(18 > age>4 y)	22
Gender	
Male	46
Female	63
Age	43.22 ± 22.83
Total prevalence	109/555180 (0.020%)
Physical examination	4/64978 (0.006%)
Outpatient and inpatient	105/490202 (0.021%)

3.2.3 | Allergic disorders

Previous reports revealed that SIgAD individuals had high prevalence of allergic diseases.[9,14] However, 5/87 (5.75%) had allergic disorders among the SIgAD individuals, including 3 allergy, 1 bronchial asthma patients, and 1 urticaria patient (Table 3). Furthermore, for the children affected with SIgAD, only 1 bronchial asthma patient was found (Table 4).

3.2.4 | Tumor

Among SIgAD individuals, 4/87 (4.60%) adult SIgAD patients developed tumors, that is, stomach tumor, liver cancer, lung cancer, and

TABLE 3 The Clinical Manifestation of Selective IgA Deficiency in 87 Adults*

	No. of patients(%)
Infectious diseases	43 (49.43%)
Pneumonia	10 (11.49%)
Upper respiratory tract infection	7 (8.05%)
Bronchitis	3 (3.45%)
Gastritis	3 (3.45%)
Intestinal infection	3 (3.45%)
Bronchiectasis with infection	2 (2.30%)
Urinary tract infection	2 (2.30%)
Balanoposthitis	2 (2.30%)
Tuberculosis	2 (2.30%)
Fever	2 (2.30%)
Hepatitis B	2 (2.30%)
Otitis media	1 (1.15%)
Acute epiglottis	1 (1.15%)
Acute appendicitis	1 (1.15%)
Viral encephalitis	1 (1.15%)
Skin Infection	1 (1.15%)
Autoimmune disorders	31 (35.63%)
Systemic lupus erythematosus	8 (9.20%)
Sjogren's syndrome	6 (6.90%)
Arthritis	4 (4.60%)
Idiopathic thrombocytopenic purpura	3 (3.45%)
Evans syndrome	2 (2.30%)
Rheumatoid arthritis	2 (2.30%)
Graves	1 (1.15%)
Scleroderma	1 (1.15%)
Ankylosing spondylitis	1 (1.15%)
Adult onset still's disease	1 (1.15%)
Connective tissue disease	1 (1.15%)
Psoriasis	1 (1.15%)
Allergic disease	5 (5.75%)
Allergy	3 (3.45%)
Bronchial asthma	1 (1.15%)
Urticaria	1 (1.15%)
Tumor	4 (4.60%)
Stomach tumor	1 (1.15%)
Liver cancer	1 (1.15%)
Lung cancer	1 (1.15%)
Pancreatic cancer	1 (1.15%)
Others	44 (50.57%)
Hypertension or diabetes	24 (27.59%)
Normal medical examination	3 (3.45%)
Selective immunoglobulin A deficiency	2 (2.30%)
Respiratory failure	2 (2.30%)
Abortion	2 (2.30%)
Whole blood cell reduction	1 (1.15%)
Sheehan syndrome	1 (1.15%)
Lichen planus	1 (1.15%)
Liver disease	1 (1.15%)
Heart failure	1 (1.15%)
Headache	1 (1.15%)
Lumbago	1 (1.15%)
Colon polyps	1 (1.15%)
Chronic obstructive pulmonary diseases	1 (1.15%)
Pregnancy	1 (1.15%)
Fracture	1 (1.15%)

(Continues)

TABLE 3 (Continued)

*Many patients showed more than one clinical feature.

TABLE 4 The clinical manifestation of selective IgA deficiency in 22 children*

	No. of patients (%)
Infectious diseases	20 (90.9%)
Upper respiratory tract infection	6 (27.27%)
Bronchitis	5 (22.73%)
Pneumonia	2 (9.09%)
Otitis media	2 (9.09%)
Sinusitis	2 (9.09%)
Suppurative tonsillitis	1 (4.55%)
Acute myelitis	1 (4.55%)
Varicella	1 (4.55%)
Autoimmune disorders	4 (18.18%)
Systemic lupus erythematosus	2 (9.09%)
Idiopathic thrombocytopenic purpura	1 (4.55%)
Graves	1 (4.55%)
Allergic disease	1 (4.55%)
Bronchial asthma	1 (4.55%)
Others	10 (45.45%)
Selective immunoglobulin A deficiency	3 (13.64%)
Common variable immune deficiency	2 (9.09%)
Normal medical examination	1 (4.55%)
Immunodeficiency disease	1 (4.55%)
Simple hematuria	1 (4.55%)
Raynaud's phenomenon	1 (4.55%)
Primary enuresis	1 (4.55%)

*Many patients showed more than one clinical feature.

pancreatic cancer (Table 3). In contrast, no children SIgAD patients developed tumor (Table 4).

3.2.5 | Other diseases

Additionally, many patients showed more than one clinical feature. The medical history for 24 cases was significant for hypertension and diabetes. Other diagnoses including respiratory failure, abortion, whole blood cell reduction, Sheehan syndrome, lichen planus, liver disease, heart failure, headache, lumbago, colon polyps, chronic obstructive pulmonary diseases, pregnancy, and fracture were found for the adult SIgAD patients (Table 3). For children SIgAD patients, common variable immune deficiency, immunodeficiency disease, simple hematuria, Raynaud's phenomenon, and primary enuresis were found (Table 4). However, whether the SIgAD are associated with these diagnoses need further investigation. Additionally, 4 healthy individuals were asymptomatic upon the normal medical examination. Most importantly, only 5 SIgAD diagnoses were included in these 109 SIgAD subjects on the hospital information system.

4 | DISCUSSION

Unlike Western countries, the adult immunology specialist is still lacking in China. To the best of knowledge, adult clinical immunology service for the care of adult immunodeficiency became available in Hong Kong in 2016, and there was no adult immunology specialist service for the adult immunodeficiency patients in mainland. Therefore, general consciousness for the care of these adult immunodeficiency patients still lags behind in China.[15]

SIgAD is the most prevalent primary immunodeficiency, found at the highest frequency of 1 in 142 in Caucasians and a low of 1 in 18,550 among Japanese, with a prevalence among other ethnicities ranging between these values.[13] In China, Feng [11] investigated 22 609 healthy blood donors from single blood center on the criteria of IgA < 0.05 g/L, and 14 SIgAD individuals were found, and the prevalence is 0.062% in Shanghai blood donors in 2011. Another 7989 Peking suburb residents in 1987 showed that the incidence of SIgAD was 0.037%, and the epidemiological study of SIgAD individuals among 6 nationalities in China showed that the incidence of SIgAD was 0.024% in 1992. However, children below 4 years old were also included in these two studies in 1987 and 1992. In this study, the incidence of hospital patients (including outpatient and inpatient) and physical examination is 0.021% and 0.006% separately, lower than three previous Chinese reports in healthy blood donors and hospital patients. Furthermore, when compare to the hospital patients 0.033% in Japan, 0.021% for hospital patients in this study were lower than Japan.[4] Similarly, the 0.006% in physical examination in this study was similar for the 0.004% and 0.005% incidence for the blood donors in Japan. However, all these SIgAD subjects were defined as IgA level < 0.05 g/L. Therefore, the incidences cannot be compared on the different diagnosis criteria.[4] These different incidences may due to the changing diagnostic criteria for SIgAD or different genetic backgrounds.[13]

In agreement with previous studies, respiratory tract infection is the most frequent illnesses associated with SIgAD. But the proportion of respiratory infections was not as high as they are.[16,17] In addition, two patients developed bronchiectasis due to repeated respiratory infections. Two patients were infected with tuberculosis, one had pulmonary tuberculosis and another had bronchial tuberculosis. Moreover, recurrent infection may contribute to the scar of lung, which results in the respiratory failure. Interestingly, the infection rate in children SIgAD was significantly higher than the adult SIgAD (90.91% vs 49.43%), while 90.91% children SIgAD had suffered from the infectious diseases. Therefore, more attention should be paid on the children SIgAD while these children were more prone to get infection.

Significantly, IgA is found in tissues and in secretions especially from the GI tract and the respiratory tract in the form of saliva, tears, breast milk, but has very low levels in serum. This reflects its role in mucosal immunity and the development of tolerance. Interestingly, previous reports showed that the SIgAD individuals are susceptible to gastrointestinal diseases and also widely reported diseases, such as gastroenteritis, celiac disease, giardiasis, lactose intolerance, especially the celiac disease. However, only 6 gastritis or intestinal infection patients were found in this study, whether the geological distribution or other causes lead to this phenomenon still needs to be clarified.

Furthermore, the high prevalence of autoimmune disorders within SIgAD individuals had been reported.[4] In this study, a high incidence of autoimmune disorders (35.63%) was found for the adult SIgAD, as the second most frequent clinical manifestation of adult SIgAD. However, the rate of autoimmune disorders among the children SIgAD was significantly lower than the adult SIgAD (18.18% vs 35.63%). Significantly, the prevalence of systemic lupus erythematosus ranks first in adult and children SIgAD. Therefore, it does appear to be associated with SIgAD. For instance, one systematic review found an average SLE prevalence of 3.8% inpatients with SIgAD, with prevalence varying based on ethnicity.[13]

In current study, a significantly lower prevalence of allergic disease (5.75%) was observed within the SIgAD individuals. This rate is significantly lower than previous reports on SIgAD, ranging from 12.7% to 83.3%, while allergic diseases had not attracted enough attention in China may explain this phenomenon.[18] Similarly, specialists or consultants of allergy of these 9 hospitals of Zhejiang Province are lacking, which may contribute to the low incidence of allergies among these 109 SIgAD individuals. Moreover, for the allergy patients, except the IgE and allergen tests, other immunological tests including IgA, IgM, and IgG may not be ordered and then lead to the low incidence of allergy in for SIgAD in this study.

Additionally, other 32 patients with the diagnosis of hypertension, diabetes, respiratory failure, abortion, common variable immune deficiency, immunodeficiency disease, whole blood cell reduction, simple hematuria, Sheehan syndrome, lichen planus, liver disease, heart failure, headache, lumbago, colon polyps, chronic obstructive pulmonary diseases, pregnancy, fracture, Raynaud's phenomenon

and primary enuresis were found. However, whether the SIgAD are associated with these diseases need further investigation.

However, our study had limitations. In this retrospective study, the information of these 109 SIgAD individuals was mainly from the department of endocrinology, rheumatology, hematology, pediatrics, respiratory, cardiovascular, and emergency. These doctors are not professional immunodeficiency doctors who may not have a comprehensive understanding of SIgAD, so there may be a possibility of missed diagnosis for these SIgAD individuals. Similarly, specialists or consultants of allergy of these 9 hospitals of Zhejiang Province are lacking, which may contribute to the low incidence of allergies among these 109 SIgAD individuals.

5 | CONCLUSION

In conclusion, for the first time, we reported the prevalence and clinical manifestations of 109 SIgAD individuals in 9 hospitals within a large cohort of 555 180 subjects of Zhejiang Province in China. However, our research has its limitations, retrospective study design and long-time follow-up of these SIgAD individuals are lacking. Further, national registry of these SIgAD individuals will help to determine and discover the common characteristics of these subjects in China.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data are available upon request.

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