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Original article

Selective immunoglobulin A deficiency and recurrent infections in children: how deep is this issue?

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Abstract

Background: Selective immunoglobulin A deficiency (SIgAD) is the most common primary immunodeficiency. Although most patients with SIgAD do not develop symptoms, some conditions related to SIgAD have been reported, particularly recurrent respiratory tract infections and infections caused by encapsulated microorganisms. Our objective was to evaluate the association of SIgAD with other pediatric conditions and extract data to establish an individualized protocol for managing patients with SIgAD.

Methods: We conducted a 3-year retrospective epidemiological study of 57 pediatric patients (aged 4-17 years) diagnosed with SIgAD after admission to the Pediatrics Department of "Grigore Alexandrescu" Emergency Children's Hospital in Bucharest, Romania. The type of infection (location, etiologic agent, and severity) and associated allergic and immune disorders were analyzed.

Results: Respiratory tract infections were the main conditions observed in patients with SIgAD (86.0%), and recurrence was reported in over half of the patients (54.4%). Overall, 42.1% of patients had acute digestive involvement. Of the 93 infections (positive culture), in 37 cases (39.8%)

encapsulated germs were involved. Among the encapsulated germs, *Klebsiella pneumoniae* was isolated in 11 cases (29.7%), *Staphylococcus aureus* in 9 cases (24.3%), *Escherichia coli, Streptococcus pneumoniae* and *Haemophilus influenzae* each in 5 cases (13.5%), and *Pseudomonas aeruginosa* was identified in 2 cases (5.4%). Several patients had recurrent or multiple infections – for 20 (35.1%) out of the 57 children, 2 microorganisms were identified at different points in time during the study period, and for 8 children (14.0%), 3 microorganisms were identified at the same time. Allergic-associated markers or allergic events were found in 20 children (35.1%) and celiac disease was diagnosed in 3 patients (5.3%).

Conclusions: Although SIgAD is a primary immunodeficiency that is not immediately life-threatening, infections are potentially disabling. Therefore, primary care physicians and pediatricians should closely monitor patients with SIgAD.

Keywords

Selective IgA deficiency, recurrent respiratory infections, digestive infections, encapsulated microorganisms, allergic disorders, immune diseases.

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Introduction

Immunoglobulin A (IgA) is involved in the immune defense of respiratory, gastrointestinal, and genitourinary mucous membranes, and its serum level is the second highest of all immunoglobulins after immunoglobulin G (IgG) [1].

IgA deficiency can have primary or secondary causes. Primary IgA deficiency is usually sporadic, but familial cases secondary to autosomal or recessive transmission have been reported. Primary IgA deficiency may be caused by the lack of or suppression of B-cell maturation. Secondary IgA deficiency is usually reversible and can be iatrogenic (e.g., due to antiepileptic medications, sulfasalazine, or captopril) or occur after viral infections (e.g., following hepatitis C, Epstein-Barr, or rubella viral infections) [2, 3].

IgA is mainly involved in neutralizing viruses, binding toxins, agglutinating bacteria, and preventing them from binding to epithelial cells in the mucous membranes. It is also involved in binding food antigens, preventing them from crossing the mucosa into circulating blood [4]. Systemically, serum IgA plays a role in limiting inflammation and allergic reactions and in modulating the activation of the complement system by IgG.

An increased level of immunoglobulin E (IgE) has been reported in patients with low IgA, which may explain the greater prevalence of atopic disease among patients with IgA deficiency. Furthermore, a decrease in secretory IgA triggers a rise in secretory immunoglobulin M (IgM), explaining why some IgA-deficient patients experience fewer infections than others. Selective IgA deficiency (SIgAD) results in colonic dysbiosis. Owing to the ability of IgM and IgG to compensate for IgA deficiency, only a small proportion of patients develop simultaneous respiratory and gastrointestinal infections [2, 5].

There are two subclasses of IgA (IgA1 and IgA2), both of which exist in monomeric and dimeric forms: IgA1 is prevalent in airways, whereas IgA2 is prevalent in the digestive tract [2].

According to the International Consensus, SIgAD is diagnosed in individuals aged > 4 years with blood IgA levels of < 7 mg/dl (0.07 g/l) but normal levels of IgG, IgM, and IgE after excluding other causes of hypogammaglobulinemia or other T-cell defects [2]. IgA deficiency can be selective or partial; selective deficiency is defined as a serum IgA level of < 0.07 or < 0.05 g/l (depending on assay sensitivity) and it is a severe condition, while partial IgA deficiency is defined as a serum IgA level of ≥ 0.07 g/l but below the lower limit of normal (> 2 standard deviations for the age) [4, 6-8].

In the general population, SIgAD affects 1 in 600 individuals and is most common in Caucasians [9]. Its recorded incidence varies from 1 in 143 to 1 in 18,500 individuals, depending on ethnic

background. In reality, however, the incidence may be higher because many individuals with SIgAD are asymptomatic and there are no screening programs [10]. Although patients with SIgAD are often asymptomatic, some associated conditions have been reported, particularly recurrent viral or bacterial respiratory infections such as otitis, tonsillitis, sinusitis, bronchitis, and community-acquired pneumonia [5]. Patients with ≥ 4 episodes of sinusitis/otitis or ≥ 2 episodes of pneumonia per year are more likely to be diagnosed with SIgAD [6, 11].

Aim

The aims of this study were to evaluate the characteristics of pediatric patients with SIgAD, focusing on the following four clinical features: (a) infectious complications and their recurrence; (b) colonization of the respiratory tract mucosa with encapsulated microorganisms; (c) autoimmune-associated diseases (e.g., celiac disease, Crohn's disease); and (d) associated allergies. This research aims to facilitate the development of an individualized protocol that would be useful for managing patients with recurrent infections related to SIgAD.

Material and methods

We performed a retrospective study, reviewing the electronic medical records for laboratory data of patients admitted to the Pediatrics Department of "Grigore Alexandrescu" Emergency Children's Hospital in Bucharest, Romania, over a 3-year period (2018-2020). We reviewed immunological serum tests for IgA value, and the identified patients were divided in 2 groups, based on their IgA serum level: children with normal IgA and children with low IgA. We excluded from the research patients with partial IgA deficiency, which was defined as a serum IgA level ≥ 0.07 g/l but below the lower limit of normal (> 2 standard deviations for the age) according to the European Society of Immunodeficiencies (ESID) and the European Academy of Allergology and Clinical Immunology (EACCI) definition; children with other causes of hypogammaglobulinemia (IgG or IgM deficiency); children with T-lymphocyte deficiency; children with viral infections (hepatitis B or C, rubella, cytomegalovirus, toxoplasma or Epstein-Barr virus); or children receiving drugs (sulfasalazine, D-penicillamine, gold salts, phenytoin, valproic acid, thyroxin, captopril, levamisole, cyclosporine) that may cause a transient decrease in serum IgA.

We selected patients aged 4-17 years with SIgAD – serum IgA level below 0.07 g/l, with normal serum IgG and IgM levels, and normal blood cell count, according to the definition of the ESID and EACCI guidelines [12-14]. Patients were recruited from the General Pediatrics Department, where they were admitted for recurrent respiratory, digestive of urinary infections.

Written informed consent was obtained from the legal guardians of all patients included in the study group.

We analyzed the frequency, severity, and recurrence of respiratory, enteral, and urinary tract infections, isolated or in association with celiac disease or allergies, in all eligible patients. We aimed to evaluate current clinical and laboratory features. Analyzing efficacy of different treatment regimens was not the purpose of the study. Microsoft® Office® 2010 software (Word® and Excel®) was used to organize and analyze the results.

Results

From 2,957 immunological serum tests for IgA reviewed, 2,714 were identified to have normal serum IgA, while 243 children had a low level of serum IgA. Patients with a low level of serum IgA were analyzed. Children with partial IgA deficiency (58 patients), the ones with low IgG or IgM serum levels (95 children), viral infections (23 children) and the ones who received contraindicated medication (10 cases) were excluded from the study group. After applying the inclusion and exclusion criteria, 57 patients with severe decrease of IgA value (1.93%) were selected.

In our cohort, all 57 patients with SIgAD presented with symptoms. Respiratory infections were reported in 49 patients (86.0%), of which 31 (54.4%) had recurrent infections. Acute digestive symptoms were reported in 24 patients (42.1%), of which 7 (12.3%) suffered from recurrent or chronic diarrhea. Furthermore, 4 patients (7.0%) had recurrent pyelonephritis.

According to the location of the respiratory disease, among 49 children with respiratory symptoms, 24.3% were hospitalized for rhinopharyngitis, 20.2% for acute nonspecific interstitial pneumonia, 16.6% for bacterial pneumonia, 14.2% for otitis media, 12.1% for bronchitis, 8.6% for tonsillitis, 2.0% for laryngitis, and 2.0% for infected bronchiectasis (**Fig. 1**). Patients

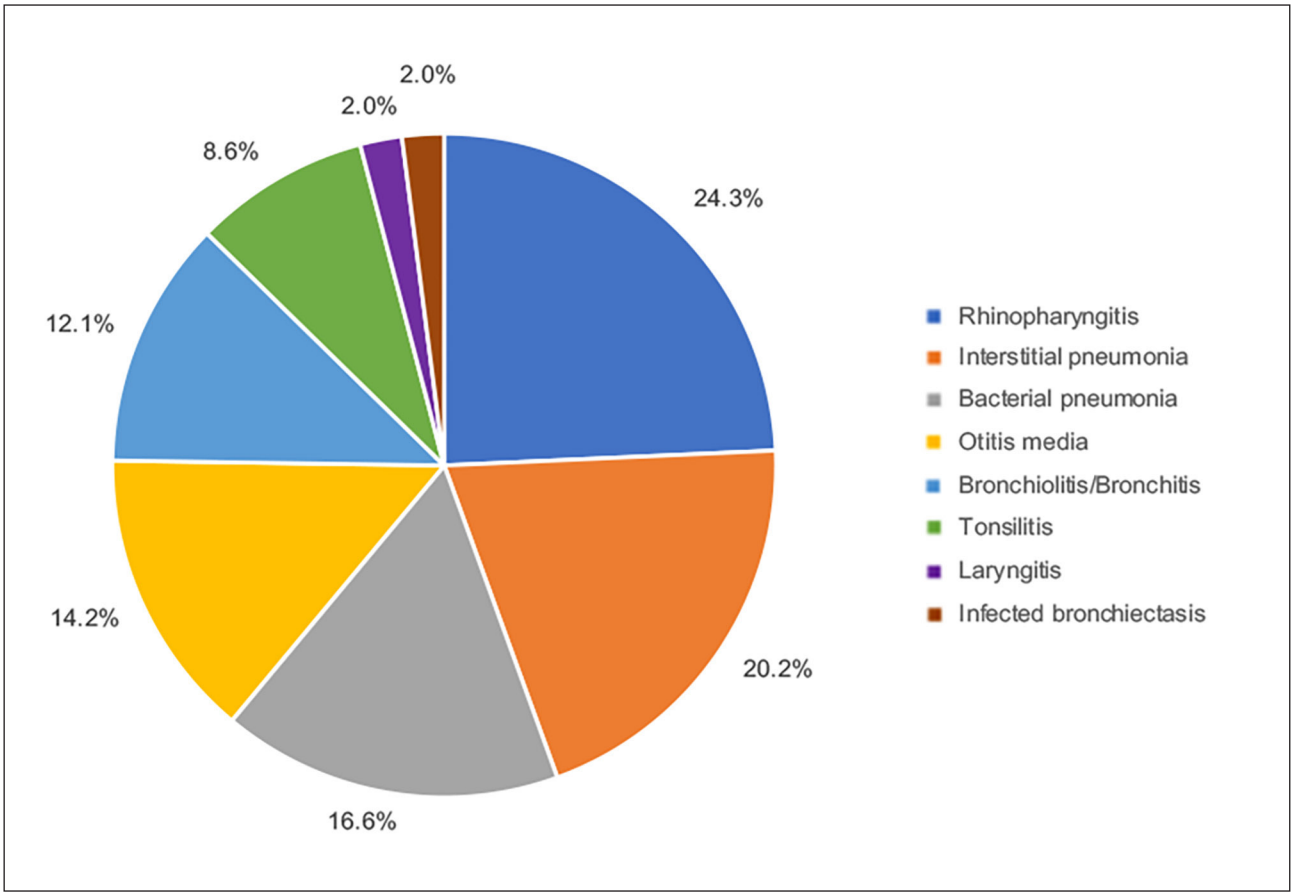

Figure 1. Type of respiratory involvement.

previously diagnosed with bronchiectasis who were admitted with fever and no other localization of the infection identified were considered to have infected bronchiectasis, when laboratory tests showed leukocytosis and high inflammatory markers.

In patients with SIgAD, the etiologic microorganisms causing infection were identified in 93 culture or antigen tests: the majority of them presented *Candida albicans*, in 15 cases (16.1%), followed by rotavirus in 14 children (15.1%) and *Klebsiella pneumoniae* in 11 (11.8%) tests. The rest of the results are presented in **Fig. 2**. Of all 93 infections for which the etiologic agent was identified, in 37 patients (39.8%) encapsulated germs were involved, which comprised of *Klebsiella pneumoniae* isolated in 11 cases (29.7%), *Staphylococcus aureus* identified in 9 cultures (24.3%), *Escherichia coli*, *Streptococcus pneumoniae* and *Haemophilus influenzae* found each in 5 cases (13.5%), and *Pseudomonas aeruginosa* isolated in 2 samples (5.4%) (**Fig. 3**).

Some of the patients experienced recurrent or multiple infections: for 20 patients (35.1%) 2 microorganisms were identified as etiologic agents of 2 different infections, while for 8 patients (14.0%) 3 microorganisms were identified simultaneous, during the same infectious episode. Acute digestive involvement was reported in 24 patients (42.1%), including 15 children (26.3%) diagnosed with infectious gastroenteritis, 8 cases (14.0%) of stomatitis, and 1 case (1.8%) diagnosed with *Enterobius vermicularis* infestation. Three patients (5.3%) had transient lactose intolerance due to recurrent or persistent diarrhea, unrelated to SIgAD.

In terms of infection recurrence, 31 patients (54.4%) had recurrent respiratory infections, 7 children (12.3%) had recurrent or chronic diarrhea, and 4 (7.0%) had recurrent pyelonephritis.

Overall, 20 children (35.1%) in the study group had allergic-associated markers or allergic events. Seven (12.3%) were diagnosed with asthma (1 was sensitized to house dust mites), each of allergic rhinitis and cow's milk protein allergy were identified in 3 cases (5.3%). Urticaria, atopic dermatitis and eosinophilia without clinical manifestations were present each in 2 patients (3.5%). One patient (1.8%) had a high serum IgE level (**Fig. 4**).

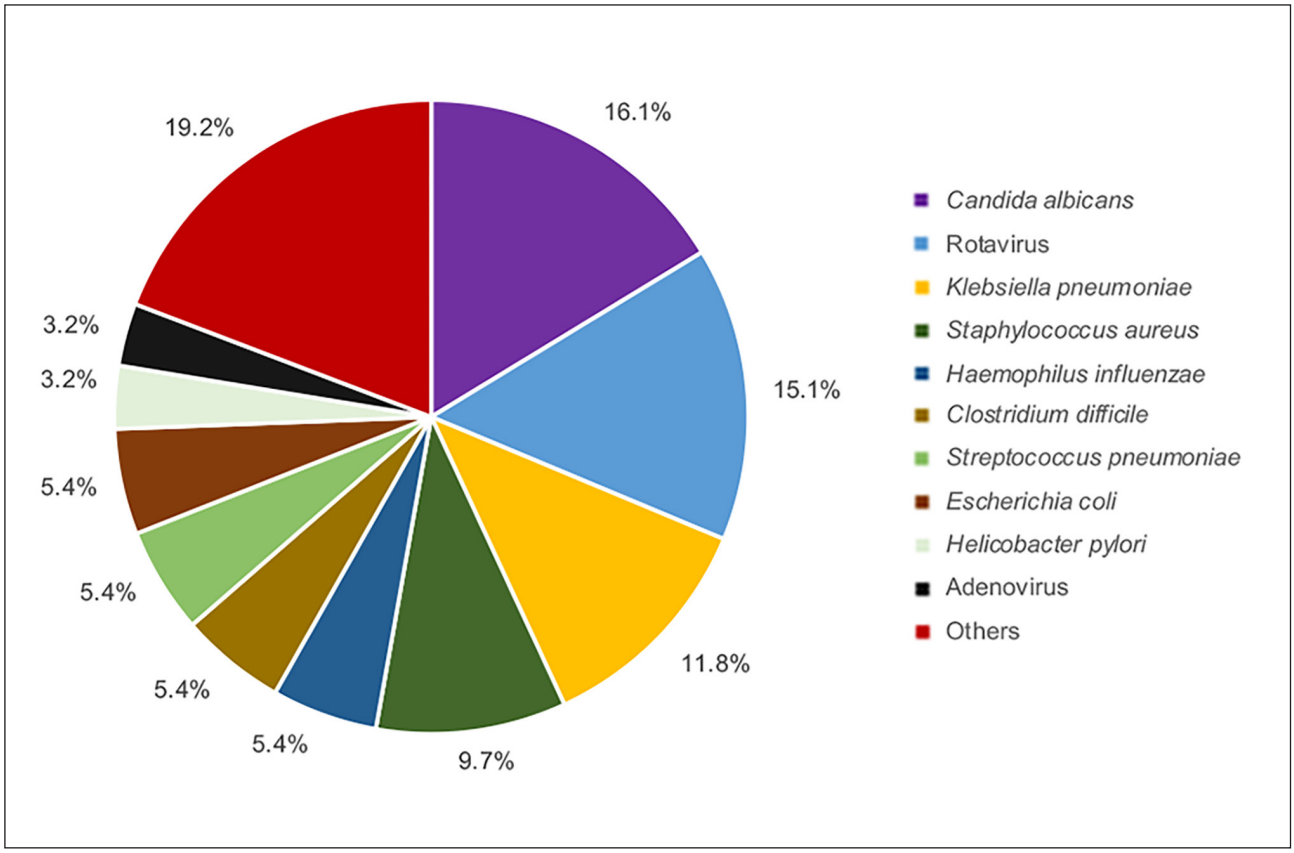

Figure 2. Distribution of infectious organisms.

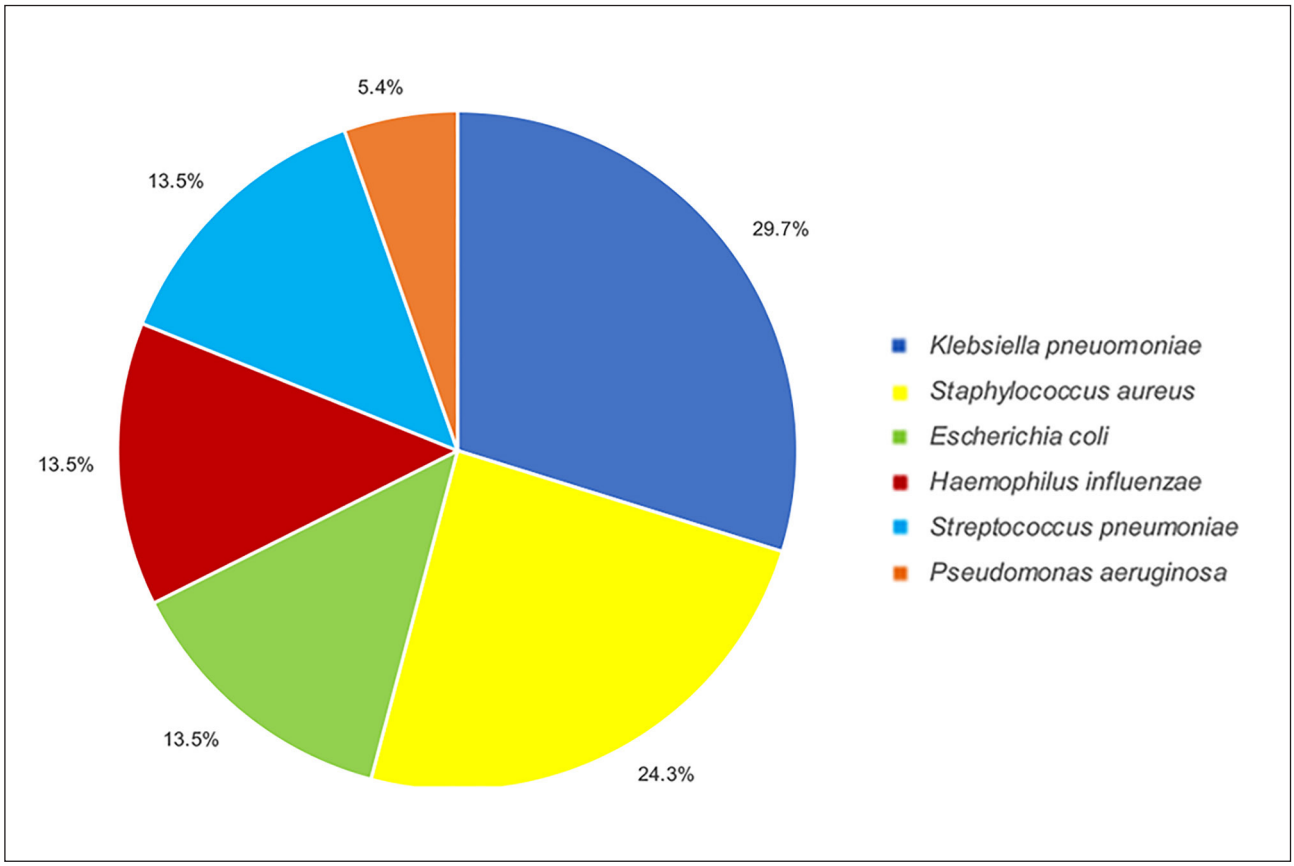

Figure 3. Species of encapsulated microorganisms.

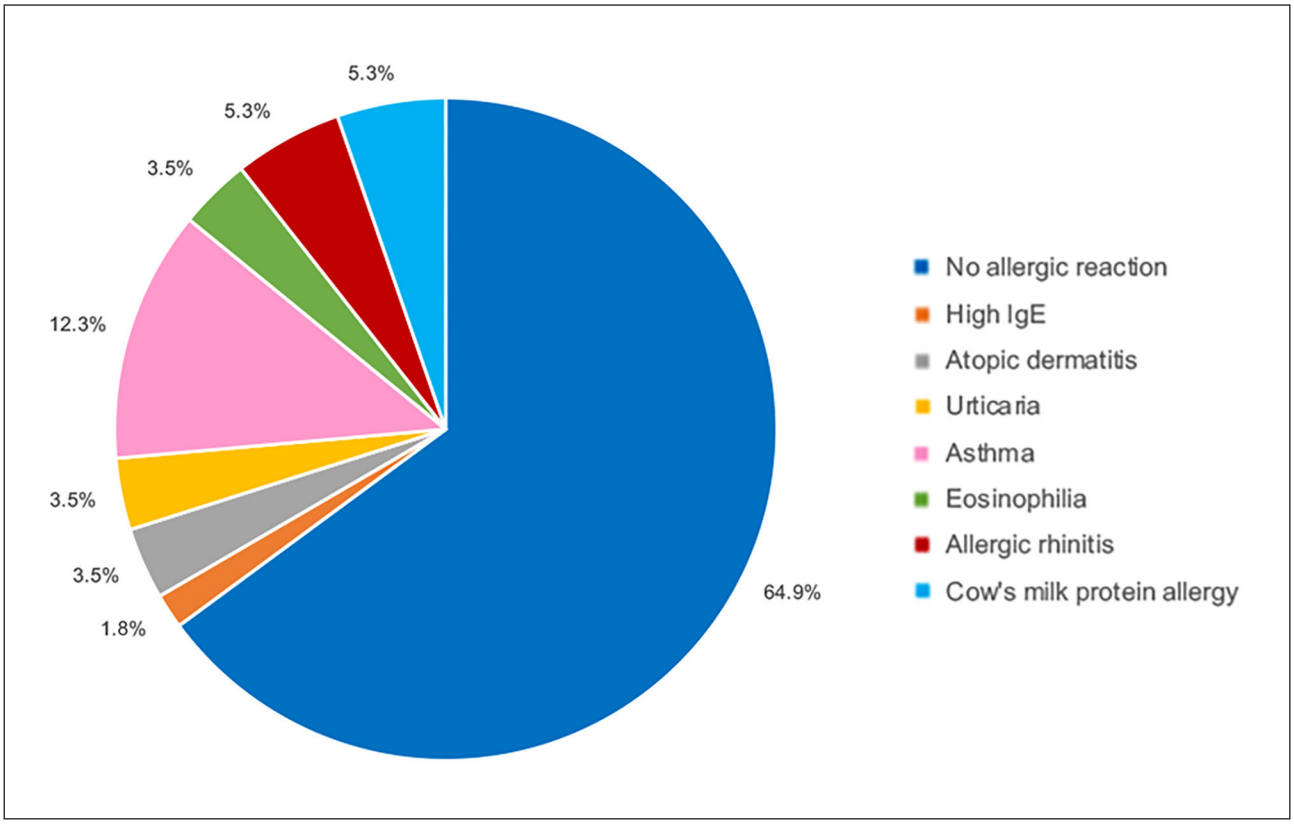

Figure 4. Allergic diseases associated with selective immunoglobulin A (IgA) deficiency (SIgAD).

Of the 57 patients with SIgAD included in this study, 3 children (5.3%) were diagnosed also with celiac disease. When analyzing the association of SIgAD with other immune conditions, we found that 2 patients (3.5%) had been previously diagnosed with Crohn's disease and 1 patient (1.8%) had been previously diagnosed with cutaneous mastocytosis.

Discussion

SIgAD is the most common immunodeficiency in children, with an estimated incidence ranging from 1:3,000 to 1:150, depending on the report [14]. According to Rawla et al., the incidence of IgA deficiency in the general population varies from 1:143 to 1:965 in different regions, with a median of 1:600. [2]

In our study, from 2,957 tests performed for serum IgA, we discovered 57 cases of SIgAD (1.93%), meaning 1:52, and 58 cases of partial IgA deficiency (1.96%), meaning 1:51. Our reported incidence is 10 times the incidence described in children in the literature and 3 times the incidence recorded in the general population. The difference of numbers could be explained by the selected population – our research included patients hospitalized for infectious respiratory and digestive diseases. This could be considered a study limitation.

SIgAD, in itself, is a benign condition, but it can have a significant impact on the child's health and quality of life due to severe associated infections, as well as recurrent or chronic diarrhea, which may affect the patient's nutritional status [8, 15].

In children aged < 4 years, especially those with partial IgA deficiency, the diagnosis of SIgAD should be considered preliminary and their IgA levels should be monitored over time to see if they return to normal as they age. In children aged 6 months to 4 years, SIgAD may be transient or may progress to variable degrees of immunodeficiency [1].

In 2015, Yazdani et al. attempted to divide the clinical SIgAD phenotypes into five main categories (asymptomatic, minor infections, autoimmunity, allergy, and severe), but they did not identify a correlation between the serum IgA levels and the clinical phenotype or disease severity [16]. In our cohort, there were no asymptomatic patients because we only enrolled hospitalized children, which may be a limitation of our study. However, it is difficult to apply the term "severe disease" because all of the patients were hospitalized, in which case they may all be presumed to have severe disease.

Recurrent respiratory tract infections are reported in 20-30% of children aged < 5 years, but the incidence decreases significantly beyond this age [17].

A randomized study published in Italy in 2019, which included 184 children with SIgAD, notes that respiratory disease is the most frequent form of presentation in these patients (62% incidence among the study population), followed by digestive disorders (27% of patients). Allergic phenomena have a high prevalence in patients with SIgAD, of about 39% – 23% being present at the time of diagnosis, the other 16% arising during follow-up [18]. In our cohort, all patients were hospitalized for symptoms suggestive of respiratory, digestive or urinary infections.

Respiratory infections were reported in 86.0% of patients, with a frequent recurrence supporting the defining role of IgA in the antibacterial defense of the respiratory tract. Lower respiratory infections, viral or bacterial, were diagnosed in 51.0% of the patients (including viral or bacterial pneumonia, bronchiolitis, and infected bronchiectasis). In prior reports, the respiratory infections in SIgAD patients were mostly bacterial, and the frequent etiologic agents were *Haemophilus influenzae* and *Streptococcus pneumoniae*. Some patients may develop end-stage organ damage, such as bronchiectasis secondary to recurrent or chronic infection [10]. Respiratory infections prevailed in our cohort, but the most frequent etiologic pathogens were *Haemophilus influenzae* and *Staphylococcus aureus*, and *Streptococcus pneumoniae* was the third most common pathogen. The geographical variation in antibiotic resistance and the distribution of microorganisms in certain population groups may explain the differences in results among studies. Another factor that might influence the etiology of respiratory infections in our geographic region is the recent introduction of a pneumococcal vaccine in the national vaccination program.

We were not able to make assumptions regarding susceptibility to specific infections or long-time prognosis of patients in our cohort, given the small sample and the failure to determine specific patterns.

Digestive infections (including parasitic infestation) were found in a large proportion (42.1%) of patients with SIgAD in our cohort. The most common etiologic pathogen involved in gastrointestinal infections was rotavirus, possibly because rotavirus vaccination is optional in Romania. Other etiologic microorganisms involved in digestive infections were *Candida albicans*, *Klebsiella pneumoniae*, and *Clostridium difficile*. In earlier studies, *Giardia lamblia* was the main pathogen involved in gastrointestinal infections [10, 19].

IgA deficiency alters the gastrointestinal mucosal barrier, allowing microorganisms to adhere to the epithelium, proliferate, and thus facilitate the impairment of the intestinal villi, leading to malabsorption. IgA deficiency also alters the clearance of food antigens, allowing them to penetrate the mucosa and induce antibody production, leading to food sensitivity or allergies [10, 14]. Allergic conditions such as conjunctivitis, rhinitis, urticaria, atopic dermatitis, and asthma are often associated with SIgAD, although their prevalence has not been widely studied [7].

Allergic-related events were reported in 35.1% of patients, including asthma (12.3%), allergic rhinitis (5.3%), cow's milk protein allergy (5.3%), urticaria (3.5%), atopic dermatitis (3.5%), eosinophilia (3.5%), and elevated IgE (1.8%). In prior studies, allergic disorders or atopic diseases were reported in 13-58% of children or adults with IgA deficiency [10, 20]. In a study of 126 Brazilian children and adolescents with SIgAD, respiratory allergies and atopic dermatitis were reported in 48% [21].

The prevalence of allergies is likely to be underestimated in patients with SIgAD. Therefore, a systematic evaluation of allergic events should be conducted. In one study, the allergic status was determined based on clinical findings and skin prick tests for the 14 most common standard allergens, revealing allergic events in 84% of patients aged 4-32 years with SIgAD [22].

Immune diseases are the most common conditions associated with SIgAD. SIgAD is associated with a number of immune-mediated conditions, including celiac disease or inflammatory bowel disease. In patients with celiac disease, the frequency of SIgAD was increased 10-fold [23]. In our study, screening for celiac disease revealed 3 new cases, and 2 additional patients had been previously diagnosed with Crohn's disease. Screening for SIgAD should be considered for patients with recurrent respiratory tract infections (e.g., otitis media, bronchitis, pneumonia) accompanied by fever, chronic sinusitis refractory to antibiotics or requiring surgical treatment, celiac disease, recurrent or chronic diarrhea, failure to thrive, or *Giardia lamblia* intestinal infestation [1, 8, 10].

Although recurrent respiratory and intestinal infections were reported in our patients, their

prognosis was favorable, with no cases of major respiratory distress, severe infection, or malignancy.

The current research emphasizes clinical and laboratory aspects of pediatric patients with SIgAD, but limitations of the study must be mentioned: the retrospective approach – collecting data from electronic folders of previously hospitalized patients, some of them incomplete (no relevant information regarding the patient's medical history, family history or lifestyle), in the absence of a control group; the relatively small cohort of patients from a single center; no data collected regarding the treatment of these patients.

Conclusions

SIgAD is the most common primary immunodeficiency. Many patients with SIgAD are asymptomatic; however, when present, the most frequent symptoms are recurrent respiratory and digestive infections caused by encapsulated microorganisms. Thus, SIgAD should be considered in all pediatric patients with a history of recurrent respiratory, gastrointestinal, or urinary tract infections, especially those caused by encapsulated microorganisms. SIgAD can be associated with allergic or immune disorders, which may delay the diagnosis of some of them, as celiac disease. If SIgAD is identified in children < 4 years old, it may be a transient condition or may progress to overt immunodeficiency of varying severity, and such patients require close clinical and immunological follow-up by a multidisciplinary healthcare team for an extended period.

Institutional Review Board statement

The research was reviewed and approved by the Ethics Committee of "Grigore Alexandrescu" Emergency Children's Hospital, Bucharest, Romania (no. 28749, approval date 21 October 2021).

Informed consent statement

Informed consent was obtained from the legal guardians of all participants.

Declaration of interest

The Authors declare no conflict of interest. Funding: this research received no external funding.

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