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Respiratory and allergic disorders in children with severe and partial Immunoglobulin A immunodeficiency

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List of abbreviations: FENO- Fraction of exhaled nitric oxide; FVC - Forced vital capacity; FEV1 - Forced expiratory volume in 1 second; IgA – Immunoglobulin A; IgG – Immunoglobulin G; IgM – Immunoglobulin M; IgAD - Immunoglobulin A deficiency; MEF50 - The maximal expiratory flow at 50 % of the forced vital capacity; PEF – Peak expiratory flow; PID – Primary immunodeficiency disorders;

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SCH – Srebrnjak Children's Hospital; sIgAD – selective Immunoglobulin A deficiency; tIgE – total Immunoglobulin E

Abstract

Background: Immunoglobulin A deficiency (IgAD) is the most common primary immunodeficiency. Although most people with selective IgAD (sIgAD) are asymptomatic, many patients often suffer from recurrent respiratory infections and different allergic disorders. Our aim was to investigate connection between subtypes of sIgAD and incidence of respiratory and allergic disorders, as well as connection with lung function changes in children.

Methods: Children with IgAD were divided into two groups; severe IgAD in patients was defined as serum IgA level < 7 mg/dL, while partial IgA deficiency diagnosis was made when serum IgA levels were higher than 7 mg/dL but at least two standard deviations (SD) below mean normal concentrations for their age. All patients were evaluated by their clinical and laboratory investigation parameters and compared to control group of children.

Results: Group of children with IgAD, severe as well as partial, showed higher prevalence of allergic diseases and total number of infections, compared to controls. There was a statistically significant difference in lung function for peak expiratory flow (PEF), the maximal expiratory flow at 50 % of the forced vital capacity (MEF50) and fraction of exhaled nitric oxide (FENO) between group of patients with severe as well as partial IgAD and control group, where children with IgAD showed reduced lung function.

Conclusions: Children with sIgAD are at increased risk for higher number of respiratory infections and developing allergic diseases, resulting in significantly lower pulmonary function which is related with the severity of sIgAD.

Keywords: Allergic diseases, partial and severe IgA deficiency, lung function, recurrent infections

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1. Introduction

Primary immunodeficiency disorders (PIDs) are identified as a heterogeneous group of inherited disorders and are characterized by impairment of one or more components of the immune system. It is estimated that PIDs affect between 1:10000 and 1:600 individuals in over 40 countries, but the real number of incidence and prevalence is still unknown^(1,2). Nowadays, 330 disorders with 320 different gene defects have been identified, which include different disorders and immune dysregulation with defects in innate and intrinsic immunity^(1,3). The most

frequent type of PIDs is primary antibody deficiency⁽⁴⁾. The most common primary immunodeficiency in many ethnic populations is selective immunoglobulin A deficiency (SIgAD) and its incidence varies from 1:163 to 1:18500⁽⁵⁻⁷⁾. IgA deficient (IgAD) individuals are mostly asymptomatic but they can also suffer from mucosal infections, autoimmune disorders and allergic diseases, from which recurrent sinopulmonary infections seem to be the most common clinical manifestation^(5,6,8). Because of higher prevalence of different disorders among children with immunodeficiency, we wanted to investigate connection between more frequent clinical manifestation (recurrent respiratory infections and allergic disorders) and subtypes of IgA deficiency (severe and partial IgAD). In both subtypes of SIgAD, the defect leading to IgA deficiency is associated with a failure of terminal B cell differentiation^(9,10). The difference is that the impairment in B cell differentiation in severe IgAD occurs before, while in partial IgAD after class switching^(10,11). Because of the fact that patients with partial IgAD have more cases of spontaneous remission, this type of IgAD is considered less serious and is not given enough attention in the literature. Our aim was to better understand the association between immunodeficiency and respiratory and allergic disorders in children with both subtypes of IgAD and to assess whether the incidence of these disorders is associated with the severity of IgA deficiency and possibly related with the impairment of pulmonary function.

2. Materials and methods

2.1. Patient selection

Children (4-18 years old) with SIgAD were recruited in Paediatric Clinic of Pulmonology, Allergology and Immunology at Srebrnjak Children's Hospital (SCH), Zagreb, Croatia, from 2009 to 2015. The study was approved by the SCH Ethics Committee. All subjects were acquainted with study objectives and methods used, and signed the informed consent for the study. The study protocol was executed according to the ethical principles of the World Medical Association Declaration of Helsinki. Follow-up period, where respiratory infections, development of allergic diseases and pulmonary function were assessed, lasted for 3 years. Inclusion criteria was to have SIgAD; severe or partial. Patient's diagnosis of SIgAD was made according to the ESID criteria⁽¹²⁾. Severe IgAD was defined as serum Immunoglobulin A (IgA) level < 7 mg/dL, with normal levels of serum Immunoglobulin G (IgG) and Immunoglobulin M (IgM) levels^(13,14), in children over 4 years

old. Partial IgAD diagnosis was made when serum IgA levels were higher than 7 mg/dL but at least two standard deviations below mean normal concentrations for their age, with normal IgG and IgM levels ⁽⁹⁾. All patients were evaluated by their clinical and laboratory investigation parameters and allergy disorders data (eczema, rhinitis, asthma), and compared to control group of children with normal immunoglobulin levels. All diagnosis of allergic diseases were made by allergy specialist: asthma according to GINA guidelines⁽¹⁵⁾, allergic rhinitis according to BSACI and ARIA guidelines^(16,17), while atopic dermatitis was diagnosed according to Guidelines for Management of Atopic Dermatitis⁽¹⁸⁾. Diagnosis of upper or lower respiratory tract infection was established by a paediatric specialist based on clinical symptoms and signs (eg. combination of rhinitis, cough, sore throat, wheeze), fever, physical examination findings and elevated inflammatory parameters (leukocytosis or leukopenia, elevated CRP) ⁽¹⁹⁾.

2.2. Laboratory analyses

In order to assess their health status, different diagnostic measurements and tests were performed in all participants at baseline. For IgA, IgG, IgM and total Immunoglobulin E (tIgE) measurement, blood samples from all of the subjects were drawn up to 4 ml in serum separation vacuum tubes and sent to the laboratory. Upon centrifugation at 2000 g for 10 min, a serum sample from every subject was kept at -20°C (storage under 24 hr) or at -80°C (long-term storage), until the analysis was performed. Concentrations of IgA, IgG and IgM, in patients' serum, were quantitatively measured by commercial turbidimetry assay on an Olympus AU680 automated system (Beckman Coulter Inc., USA), while concentrations of tIgE were measured by a chemiluminescent technology on IMMULITE 2000 XPi Immunoassay System (MMULITE® 2000 XPi, Siemens, Germany), according to the manufacturer's assay protocols. Complete blood count (absolute and/or relative) was measured using the cell counter Sysmex XT-1800i (Automated hematology analyzer, Sysmex Canada Inc., Canada), according to the manufacturers' assay protocols.

2.3. Lung function measurements

All participants underwent lung function measurements and measurements of FENO, as a marker of eosinophil inflammation in lower airways. Spirometry was done using a computerized

pneumotach (Ganzhorn, Germany) in accordance with ATS guidelines⁽²⁰⁾ and presented as percentage of predicted values according to Quanjer et al. ⁽²¹⁾. This included measurement of FEV1, FVC, PEF and MEF50. FENO was measured with the single exhalation method at 50 mL/s during 10 s using a NiOX analyzer (Aerocrine, Stockholm, Sweden) according to current ERS/ATS recommendations ⁽²²⁾.

2.4. Statistical analysis

The analyses were performed using SPSS Statistics, version 22 (IBM®, Corp., Armonk, New York, USA). Continuous variables were presented as mean, median and standard deviation. Since the variable distribution was not normal, differences between the three groups (severe IgA, partial IgA and control) were done using Kruskal-Wallis with adjusted significance, and between the two groups (IgAD: severe + partial; and control) were done using the Mann-Whitney test. For testing relationships between categorical variables the Pearson's chi square statistic was used. $p < 0.05$ was considered statistically significant for all tests performed.

3. Results

3.1. General characteristics

Ninety-five children with sIgAD were identified during a routine clinical assessment and enrolled in the study. They were divided into two groups: 1) severe IgA deficiency (serum IgA level < 7 mg/dL) and 2) partial IgA deficiency (serum IgA levels were higher than 7 mg/dL, but 2 SD below normal for age). Children were over 4 years old and with normal serum IgG and IgM levels, in both groups. Mean age at initial diagnosis for the whole cohort was 9.3 years (4-18 years old). Severe IgAD was recorded in 45 children (27,78%, M=24; F=21), and partial IgAD in 50 children (30,86%, M=28; F=24). Results of different clinical manifestations were compared with control group of children, who were also over 4 years old, with normal levels of IgA, IgG and IgM (N=67, mean age 9.2 years, M=34, F=33). Both children with IgAD and control group were longitudinally followed-up and analysed for prevalence of allergic disorders, upper and lower respiratory infections and pulmonary function. Statistical analysis showed that there was no significant difference between groups, in sex or age.

3.2. Clinical characteristics

3.2.1. Number of infections

Data on total number of infections during a 3-year period was analysed and compared between children with severe and partial sIgAD and healthy controls. Infections for all patients were defined by a clinician, according to their clinical symptoms and signs and by measuring markers of inflammation. Samples for only some patients were sent to outer microbiology lab, for additional identification of agents causing the infection, which is why data about microorganisms causing the infections are not provided. In a group of children with sIgAD the most represented were lower respiratory infections (35 cases of bronchitis, 16 patients with radiologically confirmed pneumonia). There was 12% of upper respiratory tract infections confirmed (laryngitis, pharyngitis, sinusitis, tonsillitis) in the same group, with two cases of ear infection and one case of eye infection. In control group of children bronchitis and pneumonia were also the most often infection, with 5 cases of bronchitis and 3 cases of pneumonia. There were also 2 cases of fever and nasopharyngitis and one case of sinusitis and tonsillitis, in the same group. Our results indicate that there is a statistically significant difference in the number, as well as severity of infections between children with severe IgAD, partial IgAD and controls ($p=0,0002$), whereas children with severe IgAD had the highest number of infections during a 3-year period. Also, the rate of infections was statistically higher in the combined immunodeficiency group (severe + partial), when compared with the control group ($p=0,0005$) (Figure 1). During three years of follow up, none of the patient with sIgAD developed COVID.

3.2.2. Allergic diseases

Children in this study were analysed for three different allergic diseases: asthma, allergic rhinitis (AR) and atopic dermatitis (AD) (Figure 2). Data analysis showed that there was a statistically significant difference for asthma between children with severe IgAD, partial IgAD and control group of children ($p<0.0001$), where children with severe and partial IgAD showed higher prevalence of asthma compared to controls. Also, there was a statistically significant difference when control group was compared with the whole cohort of children with immunodeficiency (severe + partial), ($p<0.0001$). Similar results can be seen for AR, where it was found that children with severe and partial IgAD showed higher prevalence of AR compared to controls

($p < 0.0001$). The same result was given when control group was compared to the whole cohort of children with immunodeficiency (severe + partial) ($p < 0.0001$). There was no statistically significant difference for AD between group of patients with IgA deficiency and control group, although there was a higher prevalence of AD in children with low IgA.

3.2.3. Lung functions and lower respiratory inflammation

Data analysis of spirometry test showed that there was a statistically significant difference for FENO, where children with severe IgAD and partial IgAD had higher values, compared to control group (Table 1). The same pattern was seen when control group was compared with combined immunodeficiency group (severe + partial) (Table 2). Also, there was a statistically significant difference for PEF and MEF 50 between children with severe IgAD, partial IgAD and control group, where children with deficiency had lower values of PEF and MEF50 (Table 1). Results of data comparison between the whole cohort of children with immunodeficiency (severe + partial) and controls also indicate that there was a statistically significant difference for PEF and MEF50 (Table 2). There was no statistically significant difference between the three groups for FEV1, although children with selective and partial IgAD showed lower values of FEV1 (Table 1). When control group was compared with the whole cohort of children with immunodeficiency (severe + partial), results showed that there was a statistically significant difference (Table 2). Data analysis showed that there was no statistically significant difference for FVC between group of patients with IgAD and control group, nor between control group and the whole cohort of children with immunodeficiency (severe + partial).

4. Discussion

Frequent infections as well as allergic diseases are a common reason for paediatric visits to the clinic. Many children who come to our outpatient clinic are often presented with recurrent respiratory infections and are in need for additional diagnostic evaluation, including assessment of the immune status, especially if they have recurrent pneumonia. As sIgAD is the most common primary immunodeficiency in children, it is important to do additional diagnostic tests, to prove or exclude partial or severe sIgAD. Partial IgAD is often considered as a mild type of sIgAD with less complications and overall less required assistance from the clinicians. Also, patients with

partial IgAD are more likely to have a spontaneous remission than those with severe IgAD⁽⁹⁾, which is why most available data is focused only on severe IgAD. Because of limited data on partial sIgAD, we wanted to study both subtypes and help clinicians to better understand different conditions in both IgA deficiencies. Recurrent infections of the respiratory tract are the most common clinical manifestation in immunodeficiencies, especially in sIgAD ^(23,24). Since children with PIDs have recurrent infections that may have a significant role in morbidity and death (30-65%), early detection and management of pulmonary disorders related with PID is essential for optimal therapy and management of the disease ⁽¹⁾. Earlier studies have demonstrated that early diagnosis could reduce the number of infections in patients with antibody deficiencies ^(1,25,26) and is the reason why we wanted to compare control group of children with patients with sIgAD and to investigate the connection between pulmonary function and infections with clinical features of PID. Also, it has been reported that asthma and allergic symptoms were significantly more common in children with low IgA levels and that there is a greater risk of infection, which is why we believe that serum IgA levels should be an important diagnostic factor in asthmatics ⁽²⁷⁻²⁹⁾. Low levels of IgA cause disruption of the barrier in mucosal immunity and disables exclusion, neutralization and excretion of infectious antigens, which increases infection susceptibility in the lung. It has been demonstrated that allergic and infectious diseases in IgAD are mainly associated to the respiratory tract, which could be associated to the less efficient compensation by IgM in the respiratory mucosa, compared to the gut and/or to the supposed IgD proinflammatory activity, predominant in the upper airways ⁽³⁰⁾. Indeed, our data analysis confirmed that children with IgAD had higher number of respiratory infections compared to controls, with the highest number of those suffering from bronchitis and pneumonia. Also, there was a higher prevalence of allergic diseases, specifically asthma, allergic rhinitis and atopic dermatitis in children with low IgA, which is in accordance to previous studies ^(1,5,28,31). Because of the fact that diagnosis of sIgAD depends on serum IgA concentration levels with monomeric IgA1 being dominant, whereas secretory IgA with dominant IgA2 form is not determined, we are not sure if both subclasses are being affected and why some immunocompromised children can be asymptomatic, despite the important protective role of IgA2. It is possible that some children diagnosed with sIgAD may have some IgA in the mucosa, enough to have a protective role. On the other hand, it has been demonstrated that secretory

IgA has a protective role against allergic disorders and eliminating allergens at the mucosal level⁽⁹⁾. Since our results show a higher prevalence of allergic disorders among children with sIgAD, this could mean both subclasses are being affected. Beside the connection with infections and allergic disorders, it has been shown that spirometry test results can give additional information on lung performance and be very useful in clinical assessment of patients with PID, especially abnormal readings of FVC and FEV1, which indicate restrictive and obstructive lung disease, respectively^(32,33). Our results showed that there was a significant difference in PEF, MEF50 and FENO parameters in children with sIgAD, compared to healthy controls. Decreased FEV1, PEF and MEF50 values and increased values of FENO in children with sIgAD could be connected to higher prevalence of respiratory infections and asthma in the same group and to allergic airway inflammation, specific for asthmatic patients. A longitudinal study in which we monitor pulmonary function in asthma control in patients with sIgAD is ongoing. Our results have shown that patients with sIgAD have decreased pulmonary function compared to controls, which can be associated with more frequent infections and more frequent asthma in these patients. According to our research, in patients with sIgAD lung function monitoring should be recommended at least once a year. The limitation of this study is that measurements from only one time point (initial visit) were used when comparing spirometry results between immunodeficient children and healthy controls. Additional study with spirometry results from different time points and detailed characterization of patients with different PIDs, including IgE deficiency, should be done and analysed for different comorbidities. This kind of study would lead to a better understanding of possible connection between PID and decreased lung function and association with other diseases, which would allow better management of the disease. Also, it would be interesting to study if IgAD could affect lung microbiome. It is known that some of the most important signals received by cells associated with mucosa, come from microbiota. This interaction between host and microbe is essential for induction of appropriate immunologic answer that reduces microbial invasion⁽³⁴⁾. Pasquali et al. demonstrated that oral administration of the bacterial extract in patients was able to increase IgA and lead to improved mucosal immunity in the airways and that oral administration of bacterial extract alone could be enough to improve induction of IgA barrier immunity in the respiratory tract⁽³⁴⁾. This supports the idea that IgAD can have an effect on lung microbiota, caused by disrupted IgA barrier and invasion and replication of aspirated foreign

bacteria causing an infection, and could be additional information for better understanding of the complications connected to IgAD, especially respiratory infections. Also, different abnormalities in immune cells could be of great importance in clinical assessment of PID, which is why we started to perform immunophenotyping of B and T cell populations and plan to include these results in future publications. Together with routine diagnostic tests, testing for genetic abnormalities should be performed in order to define different genotypes of PID. This kind of combined diagnosis of PID and appropriate therapy could prevent or at least slow down the development and course of respiratory complications of PIDs.

5. Conclusion

The knowledge of the detection and management of pulmonary disorders related to sIgAD is critical for optimal management. A lot of children who are predisposed to infections are in need for detailed immunologic evaluation in order to prevent the development of different comorbidities and complications. Further studies of connection between PID and other disorders are needed to better understand the course of the disease and allow prompt and adequate therapy. As our results show that there is a difference in prevalence of respiratory infections and allergic diseases with impaired pulmonary function between children with sIgAD and healthy controls, this type of approach highlights the importance of their early diagnosis, regardless if a child has a severe or just a partial immunodeficiency. All of this, including higher suspicion of clinicians, should lead to a better quality of life and much better outcomes for children with immunodeficiencies.

Author contribution

Jelena Živković collected all of the clinical and laboratory data from the hospital digital medical records, assembled and analysed all of the final data, designed and wrote the manuscript.

Lipej Marcel has analysed and interpreted the data with appropriate statistical analysis.

Ivana Banić collected clinical and laboratory data from the hospital digital medical records and participated in the statistical analysis.

Bulat Lokas Sandra collected clinical and laboratory data from the hospital digital medical records and analysed published data.

Boro Nogalo and Lulić Jurjević Rajka participated in selection of the study participants and were involved in diagnosing children with immunodeficiency and allergic diseases and data analysis and interpretation.

Mirjana Turkalj supervised the project and participated in research design as a highly specialized paediatrician, being involved in assessing the patients' stage of the disease and selecting the participants for the study and analysed all of the final data, designed and wrote the manuscript.

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Figure 1. Number of infections - comparison between control group and children with Immunoglobulin A deficiency (IgAD). Results show that there was a statistically significant difference ($p < 0.05$) between children with selective Immunoglobulin A deficiency (slgAD) and control group of children, with the highest number of infections among children with severe IgAD.

Figure 2. Prevalence of allergic diseases - comparison between control group and children with Immunoglobulin A deficiency (IgAD). There was a higher prevalence of asthma and allergic rhinitis among patients with IgAD, compared to control group of children. There was no statistically significant difference for atopic dermatitis.

Table 1. Spirometry test results – difference between controls, severe IgAD and partial IgAD

	Severe IgA deficiency Mean	Partial IgA deficiency Mean	Controls Mean	Severe IgA deficiency St.Dev.	Partial IgA deficiency St.Dev.	Controls St.Dev.	H	p Value
FENO	22,18	24,72	13,75	18,10	22,24	9,57	13,59	0,0011
PEF	85,16	84,28	92,84	16,23	22,91	13,31	7,519	0,0233
MEF50	85,98	85,4	94,57	22,77	22,45	19,37	6,153	0,0461
FEV1	89,24	89,16	95,22	17,81	12,94	12,32	5,367	0,0683
FVC	90,78	87,92	91,07	11,93	12,09	10,79	0,9214	0,6308

Values in boldface are statistically significant.

FENO, the fraction of exhaled nitric oxide; PEF, Peak expiratory flow; MEF50, the maximal expiratory flow at 50 % of the forced vital capacity; FEV1, forced expiratory volume in one second

St.Dev., standard deviation; H,Kruskal-Wallis H Test; P, Probability value

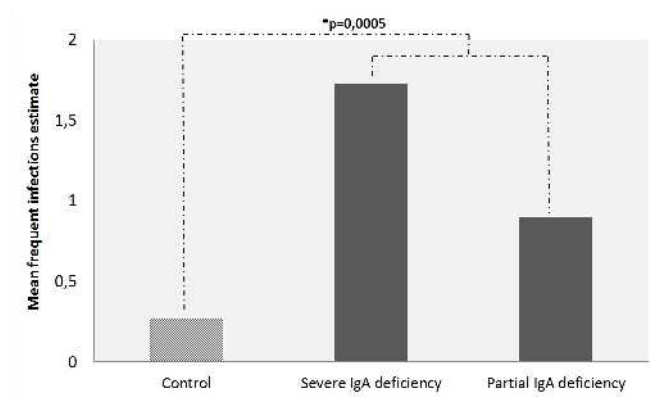
Table 2. Spirometry test results – difference between controls and IgA deficiency group (severe + partial)

	Severe+ Partial IgA deficiency Mean	Controls Mean	Severe+ Partial IgA deficiency St.Dev.	Controls St.Dev.	U	p Value
FENO	23,52	13,75	20,32	9,57	2112	0,0002
PEF	84,69	92,84	19,93	13,31	2351	0,006
MEF50	85,68	94,57	22,48	19,37	2404	0,0177
FEV1	89,2	95,22	15,35	12,32	2504	0,0207
FVC	89,27	91,07	12,04	10,79	3000	0,5351

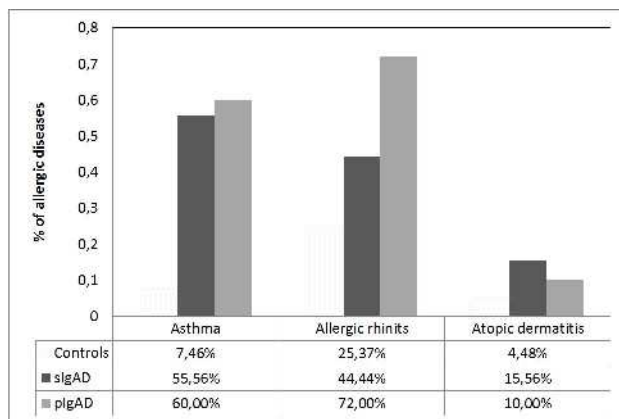
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St.Dev., standard deviation; H,Kruskal-Wallis H Test; P, Probability value



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