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Diagnostic Significance of Reduced IgA in Children

Jasmina Nurkic¹, Fatima Numanovic¹, Lejla Arnautalic², Nijaz Tihic¹, Dzenan Halilovic³, Mahira Jahic¹

¹Policlinic for laboratory diagnostic. University Clinical Centre Tuzla, Tuzla, Bosnia and Herzegovina

²Clinic for Radiology. University Clinical Centre Tuzla, Tuzla, Bosnia and Herzegovina

³Clinic for Pulmonary Disease. University Clinical Centre Tuzla, Tuzla, Bosnia and Herzegovina

Corresponding author: Jasmina Nurkić, MD. Department of Immunology, Policlinic for laboratory diagnostic, University Clinical Centre Tuzla, Tuzla, Bosnia and Herzegovina. Phone: +987 61 284 704; E-mail: jnurki@yahoo.com

ABSTRACT

Introduction: The finding of reduced value of immunoglobulin A (IgA) in children is frequent in daily medical practice. It is important to correctly interpret the findings as adequate further diagnostic evaluation of the patient in order to make the determination on the significance of such findings. In children younger than 4 years always consider the transient impairment of immunoglobulins, maturation of child and his immune system can lead to an improvement in the clinical picture. In older children decreased IgA may lead to serious illnesses that need to be recognize and acknowledge through the appropriate diagnostic methods. At the University Clinical Center Tuzla, children with suspected deficient immune response due to reduced values of IgA, goes through further diagnostic evaluation at the Polyclinic for Laboratory Medicine, Department of Immunology and Department of Microbiology, as well as the Clinic of Radiology. **Material and methods:** Our study followed 91 patients, for the year 2013, through their medical charts and made evaluation of diagnostic and screening tests. **Conclusion:** The significance of this paper is to draw attention to the importance of diagnostic approach to IgA deficient pediatric patient and relevance of knowledge of individual diagnostic methods as well as to the proper interpretation of the results thereof. **Key words:** IgA deficiency, children, diagnostic evaluation.

1. INTRODUCTION

Understanding of the advantages and limitations of laboratory tests and their correct interpretation prerequisites rational diagnosis of any disease. In pediatrics that interpretation is even more complex due to the need to understand child development especially in the first few years of life. In practice, often in the evaluation of children with frequent infections are done numerous serological tests which attempts to prove the etiology of infection by measuring specific immunoglobulins. In addition to infections, serum immunoglobulins should be determined in each child with unclear elevated erythrocyte sedimentation rate, paraproteinemia in electrophoresis and suspected chronic inflammatory disease of any organic system (post infectious, autoimmune and/or auto inflammatory).

Immunoglobulin (Ig) A deficiency is defined as decreased or absent level of serum IgA in the presence of normal serum levels of IgG and IgM in a patient older than 4 years of age, in whom other causes of hypogammaglobulinemia have been excluded (1). The threshold of 4 years of age is used to avoid premature diagnosis of IgA deficiency which may be transient in younger chil-

dren due to delayed ontogeny of IgA system after birth. Most individuals are present with recurrent infections of the respiratory and gastrointestinal tracts, allergic disorders, and autoimmune manifestations. Subclass IgA1 in monomeric form is mainly found in the blood circulation, whereas subclass IgA2 in dimeric form is the dominant immunoglobulin in mucosal secretions. Monomeric IgA in the circulation may have a role in activation of phagocytic system by means of the FcR α receptors (2, 3, 4). More than 95% of secretory IgA is produced locally. In the gastrointestinal system, organized Payer's patches or isolated lymphoid follicles as well as non organized lamina propria can be sites for local IgA production by T cell-dependent as well as T cell-independent mechanisms (5). Secretory IgA level is not determined; therefore, it is possible that the individuals diagnosed with selective IgA deficiency may still have some IgA in the mucosal systems enough to provide some protective functions. In IgA-deficient patients, the common finding is a maturation defect in B cells to produce IgA (6). The defect appears to involve the stem cells since IgA deficiency can be transferred by bone marrow transplantation (7). An intrinsic B cell defect, T helper cell dysfunction, and suppressor T cells have all

been reported in IgA deficiency. Abnormalities in the cytokine network such as lack of IL-4, IL-6, IL-7, IL-10, TGF-β, and most recently IL-21 have also been proposed to play a role in IgA deficiency (6, 8).

The aim was to make an insight into the analysis conducted on immunoglobulins at Department of Immunology, Polyclinic of Laboratory Medicine, University Clinical Centre Tuzla and other diagnostic tests in patients with reduced values of immunoglobulin A.

2. PATIENTS AND METHODS

In the period of year 2013, there were a total of 91 patients with reduced values of IgA, age up to 13 years, of which 55 boys and 36 girls. The average age was 2.6 for boys and 2.4 years for girls. Of the total number of patients, 27 boys and 24 girls were hospitalized, the rest were outpatients or patients treated on an outpatient basis.

With Nephelometry method (BN II analyzer, Siemens) were determined immunoglobulin-A, M, G and E. The results are interpreted according to the age of patients (Table 1).

IgG	IgA	IgM	IgE
Newborn to 1 week	Infant 0.10-0.70 g/L	Infant 0.20-1.00 g/L	Newborn <1.5 IU/ml
7.00-20.00g/L	Children 1-3 years	Children from 1-3 years	Infant <15 IU/ml
Newborn and infant 1-12 weeks	0.20-1.30 g/L	0.50-2.00 g/L	Children 1-5 years <60IU/ml
1.50-9.00 g/L	Children 4 years and older	Children 4 years and older	Children 6-9 years
Infant from 12 weeks to 12 months	0.40-2.40 g/L	0.50-2.20 g/L	<90 IU/ml
2.00-8.00 g/L	Others	Others	Children from 10-15 years
Children from 1-3years	0.70-4.00 g/L	0.40-2.30 g/L	<200 IU/ml
4.00-13.00 g/L			Adults <100 IU/ml
Children from 4-7 years			
6.90-16.00 g/L			
Children 8 years and older			
7.00-18.00 g/L			
Adults			
7.00-16.00 g/L			

Table 1. Reference values of immunoglobulins are interpreted in relation to the age of the patient.

3. RESULTS AND DISCUSSION

The standard 1:20 dilution of samples that takes place in the process of automated BN II nephelometry means that immunoglobulin A values less than 0.24 g/L are automatically display as a result of <0.24 g/L. Because IgA deficiency is covered only if the values are reduced or absent with normal serum levels of IgG and IgM in patients older than 4 years with the exclusion of other causes of hypogammaglobulinemia, in our study population, nine boys and five girls meets the above criteria. Mean values of immunoglobulin G, M and E are shown in Table 2.

Imunoglobulins	Mean value (males)	Mean value (females)
IgG	5.98 g/L	7.57 g/L
IgM	0.8 g/L	0.84 g/L
IgE	150.5 IU/ml	46.6 IU/ml

Table 2. Mean values of immunoglobulin in the total population of analyzed patients

There is a wide spectrum of clinical findings in IgA deficiency. Patients with IgA deficiency may be identified among blood bank donors, without any clinical findings [6]. In fact, 85–90% of IgA-deficient individuals are asymptomatic. Some patients with IgA deficiency have a tendency to develop recurrent sinopulmonary infections, gastrointestinal infections and disorders, allergies, autoimmune conditions, and malignancies. Infections of the respiratory system are the most common findings in individuals with IgA deficiency (6, 9). These infections are mostly due to bacteria, e.g., Haemophilus influenzae and Streptococcus pneumoniae. Some patients may develop end organ damage such as bronchiectasis secondary to recurring or chronic infections (10).

At the Department of Microbiology, Polyclinic for Laboratory Diagnostic, University Clinical Centre Tuzla was analyzed 50 samples (54.9%) of the total number of patients with analysis of throat and nose swabs, urine culture, coproculture, TORCH (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex Virus), ASTO (antistreptolysine O antibodies) and anti-DN ase antibodies (antibodies at Streptococci A). Results of TORCH exam in all patients indicated elevated levels of IgG which is in line with previous immunization according to the calendar of vaccination and age of the patient. Urine culture was positive in six patients, mainly Escherichia coli and Enterococcus faecalis. Throat swab was positive in one patient, with isolated Haemophilus influenzae. Nasal swab was positive in two patients with isolated Pseudomonas aeruginosa and Klebsiella pneumoniae. In one patient was isolated from stool Salmonella enteritidis. ASTO and antiDN ase were significantly increased in two patients.

Microbiology analyses	Males (n=25)	Females (n=25)
TORCH	5 (20%)	1 (4%)
ASTO	6 (24%)	2 (8%)
Urine culture	11 (44%)	14 (56%)
Coproculture	5 (20%)	7 (28%)
Swab of nose and throat	4 (16%)	1 (4%)

Table 3. Relation of number of recusted microbiology analysis to the gender of patients

At Clinic for Radiology, University Clinical Centre Tuzla was processed 30 (32.9%) patients, 15 males and 15 females with chest X ray, paranasal sinuses x ray, Magnetic Resonance Imaging (MRI) of head, stomach or sinuses (Table 4).

Radiology exams	Male (n=15)	Female (n=15)
Chest X ray	10 pulmonary infiltration (66,7%)	9 pulmonary infiltration (60%)
Sinuses X ray	1 sinusitis (6,7%)	0
MRI head	1 normal findings (6,7%)	2 heterotopy of grey mass (13.3%) 1 intraventricular hemorrhage (6,7%)
MRI stomach		1 multicystic renal dysplasia (6.7%)

Table 4. Relation of number of radiology exams to the gender of patients

IgA-deficient individuals have a tendency to develop infections and disorders of the gastrointestinal tract [6]. Giardiasis, malabsorption, lactose intolerance, celiac dis-

Immunology laboratory tests	Males (n=21)	Females (n=19)
Tissue transglutaminase (tTg) IgA antibody	7 (33.3%)	8 (42.10%)
Anti Nuclear Antibodies	4 (19.04%)	2 (10.5%)
Autoimmune liver profile (antimitochondrial antibody, smooth muscle antibody, liver/kidney/microsomal antibody)	2 (9.5%)	0
Circulating Immune Complexes (CIC)	4 (19.04%)	1 (5.3%)
Anti gliadin antibodies IgG	7 (33.3%)	6 (31.6%)
Anti Myeloperoxidase and Anti-Proteinase 3 antibodies (MPO, PR3)	1 (4.8%)	1 (5.3%)
Rheuma factor	1 (4.8%)	0
Nose smear for eosinophiles	4 (19.04%)	3 (15.8%)
Specific antigen IgE (egg, milch, wheat)	4 (19.04%)	5 (26.3%)

Table 5. Immunology laboratory tests

ease, ulcerative colitis, nodular lymphoid hyperplasia, and malignant proliferation are among the associated diseases. Since the protective barrier of the gastrointestinal system is impaired in IgA deficiency, protozoa such as *Giardia lamblia* can adhere to the epithelium, proliferate, and cause infection (11). Malabsorption may ensue secondary to structural damage to the intestinal villi. Even in the absence of infection, some molecules may enter the subepidermal and submucosal tissue because of the impaired mucosal clearance of macromolecules and proteins. This process may facilitate antibody production against certain antigens and intolerance to certain foods (12). For instance, patients with IgA deficiency have a higher chance of developing celiac disease (13). Patients with IgA deficiency are not expected to develop IgA isotype antibodies against gliadin, tissue transglutaminase, or endomysium; however, they may have IgG isotype antibodies against those antigens. Inflammatory bowel diseases, mostly ulcerative colitis, have also been reported in association with selective IgA deficiency (6). At Immunology department, Polyclinic for Laboratory diagnostic, University Clinical Centre Tuzla were analyzed samples of 40 patients, 21 (52.5%) males and 19 (47.5%) females (Table 5).

Results of immunology laboratory tests indicated one positive anti gliadine antibodies IgG in males and one in females. Two girls were positive for nose smear for eosinofile.

IgE is elevated for 6 males and 7 females age 1-5 years and in 11 males and 3 girls younger than 1 year. Specific IgE for egg white was positive for one female. Allergic disorders appear to be common in patients with IgA deficiency. In 40.5% of the patients, allergic manifestations were the presenting symptoms. It is thought that 25% of patients with IgA deficiency are identified during evaluation for allergic disorders (6). Autoimmune diseases are among the most important clinical manifestations in IgA deficiency (6). It has been long known that several autoimmune disorders may occur in association with IgA deficiency. In a study from year 2004, the second most common association with IgA deficiency after recurrent infections was autoimmunity (28%) (9). Autoimmunity was more prevalent in adults (median age 29 years) and in females (24 autoimmune conditions in females versus 14 in males in a total of 34 subjects). In a younger population, autoimmune disorders, i.e., thyroid disease, arthropathy, celiac disease, anemia, and systemic lupus erythematosus,

were detected in 19% of patients. This figure varies from 20% to 30% based on the age range of studied populations (14). Celiac disease screening should include IgG isotype antibodies against gliadin and tissue transglutaminase since IgA isotype antibodies may not be detected because of the IgA deficiency.

In our study from the total of 91 patients with reduced IgA, 9 (9.9%) boys and 5 (5.5%) girls suits age criteria for the diagnosis of true IgA deficiency. Radiological methods in the four boys demonstrated pulmonary infiltration and in one infiltration of the paranasal sinuses. Microbiological tests were processed for all males but results indicated only high ASTO levels for one male and culture of nasal swab of one male indicated *H. Influenzae*. Immunology tests for this true IgA deficiency group were same as for other patients in study but only one male was positive for anti gliadine IgG antibodies. Of the five girls diagnosed with true IgA deficiency, two showed heterotopy gray mass on head MRI, one inflammation of the paranasal sinuses and the only one microbiological treated was with normal titers of ASTO and anti DN ase.

4. CONCLUSION

Repeated infections are undoubtedly the most frequent indication for determination of serum immunoglobulins in children. Such an approach is rational because most of the primary disorder of the immune system in children occurs as a result of impaired development or function of B lymphocytes (about 50%). Evaluation of a suspected IgA deficiency would generally include a diversity of diagnostic procedures. In addition, pertinent laboratory testing for the associated conditions, e.g., recurrent infections, allergies, or celiac disease, should be performed. Therefore, a patient with IgA deficiency, once identified, would deserve a regular follow-up of clinical and immunological findings.

CONFLICT OF INTEREST: NONE DECLARED.

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