Frequency of Low Immunglobuline level in Pre-School Recurrent Wheezing

Okul Öncesi Tekrarlayan Vizing ile İzlenen Hastalarda İmmünglobulin Düşüklüğü Sıklığı

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ABSTRACT

Objective: Immunoglobulin lowering may be associated with recurrent wheezing symptoms and clinic by increasing the tendency to viral respiratory tract infections. This study aimed to investigate the frequency of immunoglobulinemia in preschoolers with wheezing.

Material and Methods: The study was conducted between 01.01.2013 - 01.01.2016 between T.C. University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training, and Research Hospital, The Pediatric Allergy and Immunology Clinic included patients who had been followed up and treated for at least one year with recurrent wheezing attacks within 72 months. The patients' immunoglobulin (G, A, M) values were retrospectively analyzed. Immunoglobulin levels were determined to be normal and low according to age limits.

Results: The study included 585 patients (65.6% male, 34.4% female) under the age of 6 years with a mean age of 26.9 months. The mean follow-up period of the patients is 2.2 years. In 33.7% of these patients, at least one immunoglobulin was low. None of these patients had any signs or symptoms of immunodeficiency. Immunoglobulin A was low in 21% of the patients, immünglobulin G in 18%, and immünglobulin M in 7.5% of all patients.

Conclusion: Hypogammaglobulinemia was found in approximately 1/3 of the patients. There were no signs of immunodeficiency in these patients. Whether this is a special group in preschooler recurrent wheezing and hypogammaglobulinemia combination should be etiologically investigated.

Key Words: Immunoglobulin A, Immunoglobulin G, Immunoglobulin M, Low immunoglobulin, Pre-school recurrent wheezing

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ÖZ

Amaç: İmmünglobulin düşüklüğü viral solunum yolu enfeksiyonlarına eğilimi arttırarak tekrarlayan vizing semptomları ve kliniği ile ilişki olabilir. Bu çalışmada okul öncesi vizingli hastalarda immünglobulin düşüklüğü sıklığını araştırmak amaçlandı.

Gereç ve Yöntemler: Çalışmaya 01.01.2013 - 01.01.2016 tarihleri arasında T.C. Sağlık Bilimleri Üniversitesi Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim ve Araştırma Hastanesi Çocuk Allerji ve İmmünoloji Kliniği'nde 72 ay altında tekrarlayan vizing ataklarıyla en az bir yıldır takip ve tedavi edilen hastalar dahil edildi. Hastaların immünglobulin (G,A,M) değerleri geriye dönük olarak incelendi. İmmünglobulin düzeyleri yaş sınırlarına göre normal ve düşük olarak belirlendi.

Bulgular: Çalışmada ortalama başvuru yaşı 26.9 ay olan 6 yaş altı 585 (%65.6 erkek, %34.4 kız) hasta dahil edilmiştir. Hastaların ortalama takip süresi 2.2 yıldır. Bu hastaların %33.7 sinde en az bir immünglobulinde düşüklük saptanmıştır. Bu hastaların hiçbirinde immün yetmezlik düşündürecek semptom ve bulgular saptanmamıştır. Tüm hastaların %21'inde immünglobulin A, %18'inde immünglobulin G, %7.5'inde immünglobulin M değerlerinde düşüklük olduğu saptanmıştır.

Sonuç: Hastaların yaklaşık 1/3'ünde hipogamaglobulinemi saptandı. Bu hastalarda immün yetmezlik belirtileri yoktu. Okul öncesi tekrarlayan hışıltı ve hipogamaglobulinemi kombinasyonu saptanan hastaların özel bir grup olup olmadığı konusunda araştırmalar yapılmalıdır.

Anahtar Sözcükler: İmmunglobulin A, İmmunglobulin G, İmmunglobulin M, Düşük immunglobulin, Okul öncesi tekrarlayan vizing

INTRODUCTION

Wheezing is a common respiratory symptom in childhood. Almost half of the children report at least one wheezing episode in the first six years (1). Since airway narrowing and inflammation cannot be evaluated clearly in this age group; the diagnosis is according to physical examination and symptoms. These children may be incorrectly diagnosed with pneumonia and poor treatment. Children who experience preschool wheezing have an increased risk of asthma (2). Therefore, recognizing recurrent wheezing is very important. In a study conducted in Türkiye, according to the The International Study of Asthma and Allergies in Childhood (ISAAC) phase 2 protocol, the general prevalence of wheezing was 15.8%, and the widespread majority of bronchial hyperreactivity was 24.2% (3).

Transient hypogammaglobulinemia of infancy (THI) is a temporary immunodeficiency in which immunoglobulin G levels are below 2 standard deviations for age. Immunoglobulin M and immunoglobulin A deficiency may also accompany (4). THI is one of the most common primary immune disorders in childhood and usually resolves by six years of age (5). Although its incidence is unknown, it is considered more common than estimated since routine immunoglobulin levels are not checked in healthy children. It causes an increase in frequency, especially in upper and lower respiratory tract infections (6). Studies show low immunoglobulin levels increase susceptibility to respiratory virus infections, exacerbate asthma, and cause chronic obstructive respiratory diseases (7-9). In a study by Karaman et al. (10), immunoglobulin G4 levels were significantly lower in recurrent preschool wheezing. Coexistence can be observed between allergic diseases and immune deficiencies (11-14).

In patients followed up with recurrent wheezing, low immunoglobulin may be associated with recurrent wheezing symptoms by increasing the tendency to viral respiratory tract infections. Our study aimed to investigate the frequency of low immunoglobulin in patients with preschool wheezing.

MATERIALS and METHODS

The study was conducted between 01.01.2013 - 01.01.2016 between T.C. University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, Pediatric Allergy and Immunology Clinic. This study was approved by the Clinical Research Ethics Committee of Ankara Pediatrics Hematology Oncology Training and Research Hospital (14.06.20217/2017-084). Inclusion criteria of the patients were determined as followed-up in the clinic with recurrent wheezing for at least one year and under the age of 72 months. Patients who presented to the clinic with wheezing at least three times a year were considered recurrent wheezing. The criteria for the exclusion of cases were other causes that might lead to hypogammaglobulinemia (systemic disease, cellular immune deficiency, malignity, genetic syndromes). Laboratories such as lymphocyte subgroup analysis, vaccine responses, complement level measurement, and nitroblue tetrazolium test were performed on suspected patients. Patients thought to have a specific immunodeficiency were excluded from the study. Electronic health records and files of patients were evaluated retrospectively in terms of concomitant low immunoglobulin levels.

The patients' immunoglobulin (G, A, M) values were retrospectively analyzed. Immunoglobulin levels were determined to be normal and low according to age limits. All data about the patients were scanned in the patient follow-up files and the database in the information operating system. Immunoglobulin (IgG, IgA, IgM, IgE) measurement was performed nephelometrically with a device called Immunochemistry System-IMMAGE 800. Immunoglobulin measurements of the patients, which were made once at any time, were compared with the normal immunoglobulin values of Turkish children for age below -2 SD value (15) was considered as hypogammaglobulinemia.

All results were evaluated with the Statistical Package for Social Sciences 18.0 (SPSS Inc., Chicago, IL, 2009) program. Discrete variables were given as numbers and percentages, normally distributed continuous variables as mean ± standard

deviation, and non-normally distributed continuous variables as median (interquartile range). The Chi-square test was used to compare discrete variables.

RESULT

There were 585 patients (201 females (%34.4) and 384 males (%65.6) included in the study. All patients were diagnosed with wheezing under the age of 72 months. The mean age of initiation was 26.9 months. The current mean age of the patients was 4.2 years (min: 61 days, max: 72 months). The mean follow-up period of the patients was 2.2 years. Immunoglobulin G, Immunoglobulin M, and Immunoglobulin A levels were measured in all patients.

At least one immunoglobulin isotype was low in 33.7% of all patients. The prevalence values of low immunoglobulin levels were 22.7% for one immunoglobulin, 7.5% for two immunoglobulins, and 3.4% for three immunoglobulins. Immunoglobulin deficiency for isotypes was detected in 21.9% of Immunoglobulin A, 18.6% of immunoglobulin G, and 7.5% of immunoglobulin M. In female patients, the low immunoglobulin ratio was 28.4% at IgA, 16.4% at IgG, and 6.5% at IgM. The low immunoglobulin ratio in male patients was 18.5% at IgA, 19.8% at IgG, and 8.1% at IgM. Low immunoglobulin A frequency was significantly higher in the female gender (p<0.050) (Table I).

For patients between 61 days and five months, low immunoglobulin levels were detected in all girls and 75% of boys. For patients between 9-12 months, low immunoglobulin levels were detected in 47.6% of girls, in 75% of boys. For patients between 12-24 months, immunoglobulin deficiency was detected in 50.7% of girls, in 52.4% of boys (Figure 1).

Low immunoglobulin A was detected in all girls and 75% of boys between 61 days and five months, in 44% of girls and 30% of boys between 12-24 months, in 27% of girls and 16% of boys between 37-48 months (Figure 2). Low immunoglobulin M was evaluated in 15% of boys between 61 days and 5 months, 13% of girls, and 23.3% between 12-24 months (Figure 3). The results of low immunoglobulin G levels were between 9-12 months old patients in 28.6% of girls, in 14.8% of boys, between 12-24 months in 20.3% of girls, in 32% of boys, and between 49-72 months in 23.1% of girls, in 30% of boys (Figure 4).

Table I: Frequency of immunoglobulin A, M, G deficiency in female and male patients.

	Female n (%)	Male n (%)	Total n (%)	p
Low immunoglobulin A	57 (28.4)	71 (18.5)	128 (21.9)	=0.006
Low immunoglobulin G	33 (16.4)	76 (19.8)	109 (18.6)	>0.050
Low immunoglobulin M	13 (6.5)	31 (8.1)	44 (7.5)	>0.050

Table II: Frequency of any immunoglobulin deficiency in patients younger than four years old and over four years old

	Under 4 years old n (%)	Over 4 years old n (%)	p
Low in one Immunoglobulin	125 (22.2)	8 (34.8)	>0.050
Low in Two Immunoglobulins	43 (7.7)	1 (4.3)	>0.050
Low in Three Immunoglobulins	20 (3.6)	0 (0)	>0.050

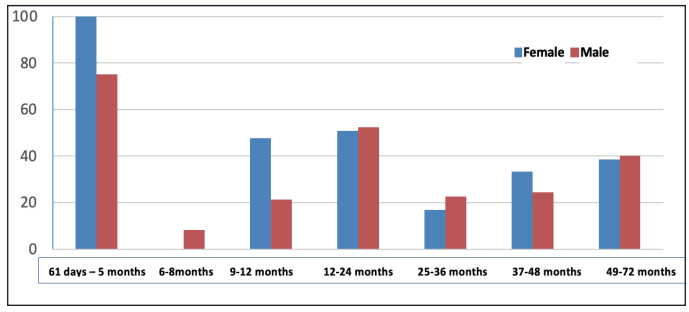

Figure 1: Frequency of patients with low levels of any Immunoglobulin by gender and age in different age groups.

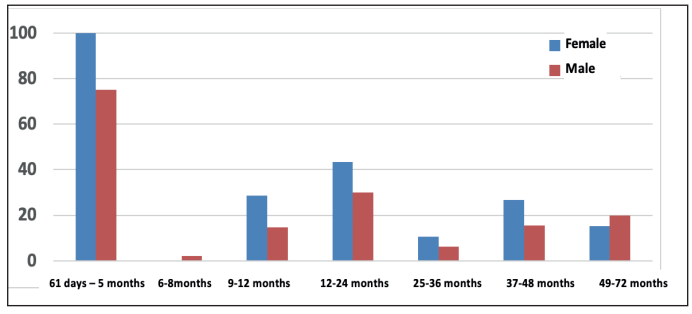

Figure 2: Frequency of patients with low immunoglobulin A according to gender and age in different age groups.

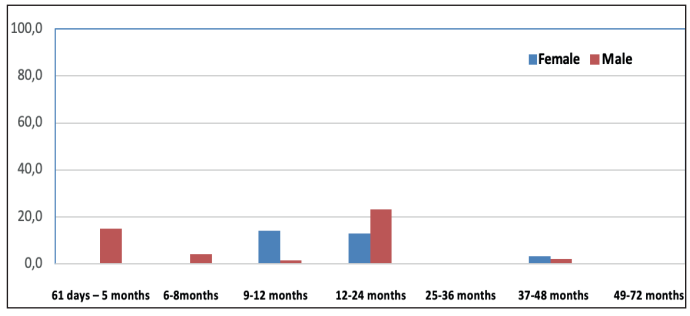

Figure 3: Frequency of patients with low immunoglobulin M according to gender and age in different age groups.

In patients under four years of age, the frequency of low levels of any immunoglobulin was 22.2%, 7.7% of two immunoglobulins, and 3.6% of three immunoglobulins. In patients over four years of age, the frequency of any immunoglobulin was 34.8%, and the frequency of low levels of two immunoglobulins was 4.3%. No patient had low levels of three immunoglobulins in patients over four years of age (Table II).

Among the 585 patients, there were 562 patients under four years old, and 23 were over four years old. The immunoglobulin

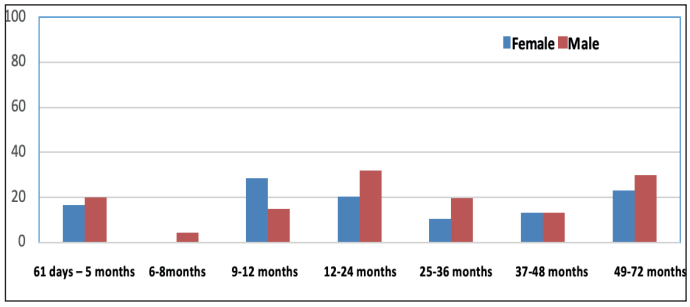

Figure 4: Frequency of patients with low immunoglobulin G levels by gender and age in different age groups.

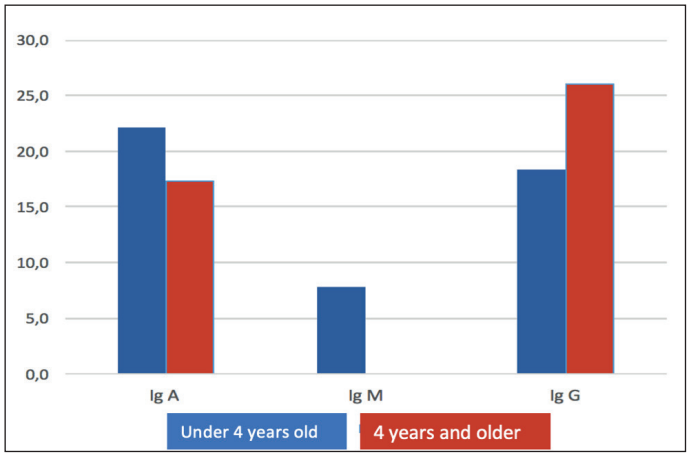

Figure 5: Frequency of low immunoglobulin A, M, and G values in patients younger than four years old and over four years old

A values of the patients were compared, and it was found that low immunoglobulin A was 22.1% in patients under four years and 17.4% in patients over four years. The immunoglobulin G values were compared. Low immunoglobulin G levels in patients under four years old were 18.3%, and low immunoglobulin G levels in patients over four years old were 26.1%. Immunoglobulin M values were compared; low immunoglobulin M levels were 7.8% in patients under four years. Immunoglobulin M levels were normal in patients over four years (Figure 5).

DISCUSSION

Our study found a decrease in at least one immunoglobulin isotype in 33.7% of the patients. Symptoms and signs of immune deficiency diseases were not detected during the evaluation of the patients, but the process related to the patients in the later stages is unknown. It is thought that low immunoglobulin levels in a group of patients with recurrent wheezing may cause recurrent viral infections or severe viral infections, leading to a preschool wheezing clinic. In addition, many studies indicate that there may be a relationship between immune deficiencies and allergic diseases (12,13,16,17).

Many factors, such as personal and environmental factors, play a role in the development of asthma, and the male gender is one of the risk factors (18). Low immunoglobulin A was found more frequently in females when the frequency of low immunoglobulin levels was evaluated according to the genders. Since all of these patients were under 72 months of age, they were not evaluated for selective or partial immunoglobulin A deficiency. No significant difference was found between both genders regarding immunoglobulin M and G levels.

Kaufman et al. (19) evaluated the relation with atopy by measuring the immunoglobulin level in 641 adult cases with recurrent allergic disease symptoms. They found immunoglobulin levels low in 6.7% of the cases (19). In our study, low immunoglobulin levels were more common. This result may be due to the temporary delay in immunoglobulin production because the patients we followed were younger than six. In addition, some of the patients we followed may have had transient infantile hypogammaglobulinemia. This difference may also be due to ethnic, genetic, and geographic disparities and differences between normal immunoglobulin values (20).

Immunoglobulin A:

The most important function of immunoglobulin A in the body is to form the first line of defense against pathogens by preventing the attachment of bacteria and toxins to epithelial cells. High levels of secretory immunoglobulin A antibodies can avoid the absorption of allergens by preventing the adhesion and penetration of antigens (21). Immunoglobulin A, the most abundant immunoglobulin in the mucosa, acts as an active barrier to inhaled and ingested antigens. Barrier changes and epithelial disorders are also prominent features of allergic asthma (22, 23). It is reported that immunoglobulin A secreted in breast milk reduces the risk of asthm (24, 25).

Our study found low immunoglobulin A levels in 21% of patients with recurrent wheezing. Our findings suggest that there may be a relationship between low immunoglobulin A levels and recurrent wheezing. In the saliva, secretory immunoglobulin A is protective against the development of recurrent wheezing in children (26, 27). Another study reported that high fecal immunoglobulin A levels in the first six months of life might reduce the risk of immunoglobulin E related disease development (28). It has been shown in various studies that infants with higher nasal immunoglobulin A levels have fewer respiratory tract infections and a lower incidence of wheezing during viral infection (29). In a study conducted in Iceland, babies with low immunoglobulin A levels had more asthma and otitis media than those with normal levels. A significant correlation was also found between the severity of allergic symptoms and low immunoglobulin A levels (30).

Selective immunoglobulin A deficiency is one of the immunodeficiencies most commonly associated with allergy and atopy. In a study conducted on patients diagnosed with selective immunoglobulin A deficiency, there was a correlation with allergic findings in 83.7%.

Immunoglobulin M:

Immunoglobulin M is the first immunoglobulin isotype synthesized in the neonatal period. Immunoglobulin M is an important antibody in most external secretions, particularly in saliva and respiratory epithelial fluid, and plays a role in the pathogenesis of some autoimmune diseases like rheumatoid arthritis. However, there needs to be more information about the role of immunoglobulin M in the pathogenesis of asthma (31). It has been reported that individuals with immunoglobulin M deficiency are more susceptible to opportunistic respiratory tract infections than healthy individuals (32). In addition to immunoglobulin A, secretory immunoglobulin M may be important for pulmonary mucosal barrier homeostasis (31). In our study, immunoglobulin M was low in 7.5% of all patients. In patients older than 48 months, low immunoglobulin M was not detected.

Immunoglobulin G:

Immunoglobulin G, the major immunoglobulin of the body, constitutes 75-80% of serum immunoglobulins (33). It is known that there is a transplacental transmission of immunoglobulin G (28). Based on this information, low immunoglobulin G levels were detected in patients between 61 days and five months in our study (female 16.7%, male 20%) had a higher percentage than expected.

In a study aiming to investigate humoral immunity in children with asthma, immunoglobulin G, M, A, and E levels were normal in cases with severe asthma, but immunoglobulin G (especially immunoglobulin G3) and immunoglobulin A subgroup deficiencies were found (16). In a study to determine the relationship between serum immunoglobulins and recurrent wheezing in patients with recurrent wheezing, serum immunoglobulin G subclasses were measured. Immunoglobulin G3 was significantly deficient in patients aged 2-6 years compared to the control group (34). In another study, immunoglobulin G3 levels were low in 39.6% of three years old patients with recurrent wheezing (35). It has been reported that low IgG4 levels may cause recurrent wheezing in infants (36,37). These studies suggest that wheezing in childhood may be associated with immunoglobulin G subclass deficiency. In our research, immunoglobulin G subclasses were not examined in patients, but new studies on this subject are needed in light of the significant results in previous studies. We found that 18% of all patients had low immunoglobulin G levels. These findings showed that low immunoglobulin levels in patients with recurrent wheezing might predispose them to wheezing attacks due to delayed maturation of the immune system.

In conclusion, our study found low immunoglobulin A in 21% of all patients. Our study has led us to think that the immunoglobulin A level improves in advancing ages, and the wheezing disappears. Further research is needed to determine whether this is a special group of patients with preschool wheezing. Future studies on immunoglobulin A may develop new therapeutic strategies to develop protective immunity against pathogens and help induce immune tolerance to allergens. In addition, the findings of this study support the idea that in case of delayed production of immunoglobulin G, the immune response may be affected, and a predisposition to recurrent wheezing attacks may occur.

REFERENCES

1. Bloom CI, Franklin C, Bush A, Saglani S, Quint JK. Burden of preschool wheeze and progression to asthma in the UK: Population-based cohort 2007 to 2017. J Allergy Clin Immunol 2021;147:1949-58.
2. Fitzpatrick AM, Bacharier LB, Guilbert TW, Jackson DJ, Szefler SJ, Beigelman A, et al. Phenotypes of recurrent wheezing in preschool children: identification by latent class analysis and utility in prediction of future exacerbation. J Allergy Clin Immunol Pract 2019;7:915-24. e7.
3. Civelek E, Cakir B, Boz AB, Yuksel H, Orhan F, Uner A, et al. Extent and burden of allergic diseases in elementary schoolchildren: a national multicenter study. J Investig Allergol Clin Immunol 2010;20:280-8.
4. Justiz Vaillant AA, Wilson AM. Transient Hypogammaglobulinemia of Infancy. 2022 Sep 5. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan.
5. Ameratunga R, Ahn Y, Steele R, Woon S. Transient hypogammaglobulinaemia of infancy: many patients recover in adolescence and adulthood. Clin Exp Immunol 2019 ;198:224-32.
6. Yorulmaz A, Artaç H, Reisli İ. Evaluation of patient follow-up with transient hypogammaglobulinemia in infancy diagnosis. Çağdaş Tıp Dergisi 2019;9:15-20.
7. Kim JH, Ye YM, Ban GY, Shin YS, Lee HY, Nam YH, et al. Effects of immunoglobulin replacement on asthma exacerbation in adult asthmatics with IgG subclass deficiency. Allergy Asthma Immunol Res 2017;9:526-33.
8. Berger M, Geng B, Cameron DW, Murphy LM, Schulman ES. Primary immune deficiency diseases as unrecognized causes of chronic respiratory disease. Respir Med 2017;132:181-8.
9. de Fays C, Carlier FM, Gohy S, Pilette C. Secretory Immunoglobulin A Immunity in Chronic Obstructive Respiratory Diseases. Cells 2022;11:1324.
10. Karaman Ö, Uğuz A, Uzuner N. IgG subclasses in wheezing infants. Indian J Pediatr 1999;66:345-9.
11. Frey A, Lunding LP, Ehlers JC, Weckmann M, Zissler UM, Wegmann M. More than just a barrier: the immune functions of the airway epithelium in asthma pathogenesis. Front Immunol 2020;11:761.
12. Aghamohammadi A, Cheraghi T, Gharagozlou M, Movahedi M, Rezaei N, Yeganeh M, et al. IgA deficiency: correlation between clinical and immunological phenotypes. J Clin Immunol 2009;29:130-6.
13. Urschel S, Kayikci L, Wintergerst U, Notheis G, Jansson A, Belohradsky BH. Common variable immunodeficiency disorders in children: delayed diagnosis despite typical clinical presentation. J Pediatr 2009;154:888-94.
14. Haskoloğlu ZŞ. To What Extent do Transient Hypogammaglobulinemia of the Infancy and Allergic Diseases Coexist? Asthma Allergy Immunol 2020;18:23-9.

15. Tezcan I, Berkel A, Ersoy F, Sanal O. Sağlıklı Türk çocukları ve erişkinlerde turbidometrik yöntemle bakılan serum immunoglobulin düzeyleri. Çocuk Sağlığı ve Hastalıkları Dergisi 1996;39:649-56.
16. de Moraes Lui C, Oliveira LC, Diogo CL, Kirschfink M, Grumach AS. Immunoglobulin G subclass concentrations and infections in children and adolescents with severe asthma. Pediatr Allergy Immunol 2002;13:195-202.
17. Erkoçoğlu M, Metin A, Kaya A, Özcan C, Akan A, Civelek E, et al. Allergic and autoimmune disorders in families with selective IgA deficiency. Turk J Med Sci 2017;47:592-8.
18. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. . Available from: wwwginasthmaorg. 2021.
19. Kaufman HS, Hobbs JR. Immunoglobulin deficiencies in an atopic population. Lancet 1970;2:1061-3.
20. Aksu G, Genel F, Koturoğlu G, Kurugöl Z, Kütükçüler N. Serum immunoglobulin (IgG, IgM, IgA) and IgG subclass concentrations in healthy children: a study using nephelometric technique. Turk J Pediatr 2006;48:19-24.
21. Hand TW, Reboldi A. Production and Function of Immunoglobulin A. Annu Rev Immunol 2021;39:695-718.
22. Frey A, Lunding LP, Ehlers JC, Weckmann M, Zissler UM, Wegmann M. More Than Just a Barrier: The Immune Functions of the Airway Epithelium in Asthma Pathogenesis. Front Immunol 2020;11:761.
23. Ladjemi MZ, Gras D, Dupasquier S, Detry B, Lecocq M, Garulli C, et al. Bronchial epithelial IgA secretion is impaired in asthma. Role of IL-4/IL-13. Am J Respir Crit Care Med 2018;197:1396-409.
24. Mosconi E, Rekima A, Seitz-Polski B, Kanda A, Fleury S, Tissandie E, et al. Breast milk immune complexes are potent inducers of oral tolerance in neonates and prevent asthma development. Mucosal Immunol 2010;3:461-74.
25. Järvinen KM, Martin H, Oyoshi MK. Immunomodulatory effects of breast milk on food allergy. Ann Allergy Asthma Immunol 2019;123:133-43.
26. Sandin A, Björkstén B, Böttcher MF, Englund E, Jenmalm MC, Bråbäck L. High salivary secretory IgA antibody levels are associated with less late-onset wheezing in IgE-sensitized infants. Pediatr Allergy Immunol 2011;22:477-81.
27. El Ansari YS, Kanagaratham C, Burton OT, Santos JV, Hollister BA, Lewis OL, et al. Allergen-Specific IgA Antibodies Block IgE-Mediated Activation of Mast Cells and Basophils. Front Immunol 2022;13:881655.
28. Kukkonen K, Kuitunen M, Haahtela T, Korpela R, Poussa T, Savilahti E. High intestinal IgA associates with reduced risk of IgE-associated allergic diseases. Pediatr Allergy Immunol 2010;21:67-73.
29. de Fays C, Carlier FM, Gohy S, Pilette C. Secretory immunoglobulin a immunity in chronic obstructive respiratory diseases. Cells 2022;11:1324.
30. Lúdvíksson BR, Arason GJ, Thorarensen O, Ardal B, Valdimarsson H. Allergic diseases and asthma in relation to serum immunoglobulins and salivary immunoglobulin A in pre-school children: a follow-up community-based study. Clin Exp Allergy 2005;35:64-9.
31. Jones K, Savulescu AF, Brombacher F, Hadebe S. Immunoglobulin M in Health and Diseases: How Far Have We Come and What Next? Frontiers in Immunology 2020;11: 595535.
32. Michaud E, Mastrandrea C, Rochereau N, Paul S. Human Secretory IgM: An Elusive Player in Mucosal Immunity. Trends Immunol 2020;41:141-56.
33. Bayram RO, Özdemir H, Emsen A, DAĞI HT, Artac H. Reference ranges for serum immunoglobulin (IgG, IgA, and IgM) and IgG subclass levels in healthy children. Turk J Med Sci 2019;49:497-505.
34. Oner AF, Caksen H, Celik A, Cesur Y, Uner A, Arslan S. Serum immunoglobulins and immunoglobulin G subclasses with recurrent wheezing. Indian J Pediatr 2000;67:861-4.
35. Ones U, Güler N, Somer A, Salman N, Yalçin I. Low immunoglobulin G3 levels in wheezy children. Acta Paediatr 1998;87:368-70.
36. Zaitsu M, Matsuo M. Transient low IgG4 levels cause recurrent wheezing requiring multiple hospitalizations in infancy. Pediatr Pulmonol 2022;57:1631-4.
37. Kim CK, Park JS, Chu SY, Kwon E, Kim H, Callaway Z. Low immunoglobulin G4 subclass level is associated with recurrent wheezing in young children. Asia Pacific Allergy 2020;10:e43.