Serum levels of immunoglobulin A (IgA) class in patients with COVID-19 and asthma

ABSTRACT

Background: Growing interest in the importance of the mucosal immune system, coupled with an improved understanding of the functional properties of IgA has re-engineered interest in this previously neglected immunoglobulin class ~~(IgA)~~. Research into IgA ~~levels and~~ roles and levels might open ~~its~~ a novel ~~uses~~ approach in therapeutic settings and mucosal vaccination. Both COVID-19 and asthma are broncho-mucosal inflammatory diseases. However, the exact role of IgA in the pathogenesis of these diseases is unclear.

Objective: To investigate the role of IgA as a potential differentiating biomarker of patients with COVID-9 and asthma.

Methodology: Serum IgA levels were measured in 30 patients with bronchial asthma and 30 COVID-19 patients with their 30 corresponding age- and sex-matched healthy control subjects using enzyme-linked immunosorbent assay.

Results: The mean value of serum IgA was significantly increased in COVID-19 patients at admission (p=0.001) or COVID-19 patients at discharge (p=0.031) compared with the level in the control. The mean value of serum IgA was similar in COVID-19 patients at admission compared with COVID-19 patients at discharge. The mean value of plasma IgA was significantly decreased (p=0.018) in asthma patients compared with the level in the control.

Conclusions: Serum IgA could be a useful biomarker to differentiate patients with COVID-9 from patients with asthma.

Keywords:Adaptive immunity, Immunoglobulin A class, Lung diseases.

INTRODUCTION

A deeper understanding of the mechanisms of diseases could lead to the development of highly specific methods of treatment. However, the exact etiology of COVID-19 and asthma is yet not been fully clarified.[1]IgA is one of the most abundant immunoglobulin classes ~~produced~~ secreted into external fluids and binds various receptors on granulocytes, monocytes, macrophages, dendritic cells (DC), and eosinophils, as it was first described in 1953.[2]These cells are particularly important in the pathogenesis of COVID-19 and asthma. Although IgA is present in the serum as a monomer, its main known functions are elicited at the mucosal level in the form of dimeric secretory IgA (s-IgA).[3] The luminal epithelium is continuously exposed to exogeneous antigens, which are endocytosed by subepithelial ~~antigen~~ antigen-presenting cells (APC) forprocessing and presentation to immune cells in the nasopharynx, across the nasal epithelium and tonsils and adenoids (Waldeyer's ring).[4]

Thus, it is important to determine the levels of IgA during respiratory diseases, but this is grossly understudied.

Asthma is a chronic inflammatory condition of the airways with intricate and complex pathophysiologyinvolving airway inflammation, intermittent airflow obstruction, and bronchial hyperresponsiveness initiated by IgE antibodies which respond to certain triggers in the environment and bind to high-affinity mast cells and basophils. Inhaled pollutant or risk factor causes mast cell degranulation, the release of cytokines histamine, prostaglandins, and leukotrienes. As a result of inflammation and bronchoconstriction, there is an intermittent airflow obstruction, resulting in increased difficulty~~of~~ inbreathing.Studies suggested that asthma is associated with impaired innateand adaptive immunity or the existence of selective IgA deficiency (sIgAD).[5,6]IgE is the most studied immunoglobulin class in patients with asthma [7], neglecting bronchial-associated immunoglobulin (IgA).

Comment [CEO1]: Asthma is not only produced by IgE antibodies, but may be produced by Non-IgE-mediated hypersensitivities, I recommend the reading and citation of:
Olivier CE, Pinto DG, Teixeira APM, Santana JLS, Santos RAPGS, Lima RPS, et al. Evaluating non—IgE-mediated Allergens' Immunoreactivity in Patients Formerly Classified as "Intrinsic" Asthmatics with Help of the Leukocyte Adherence Inhibition Test. European Journal of Clinical Medicine. 2023;4(2):1-7. https://www.ej-clinicmed.org/index.php/clinicmed/article/view/238

Formatted: Highlight

The novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was a global pandemic with wide-ranging health and socioeconomic implications.[8] SARS-CoV-2 enters human cells by attachment to and subsequent internalization of angiotensin-converting enzyme 2 receptors that are highly expressed by Type II pneumocytes in the deep bronchial system,[9] where immunoglobulin (Ig) A, produced in the bronchial-associated lymphoid tissue, is the main line of humoral defense.[10] Indeed, specific IgA production against the SARS-CoV-2 spike protein has been shown to appear early in infected patients.[11] However, despite the important role of IgA in mucosal immunity, the level of total IgA generated in response to SARS-CoV-2 infection remain unexplored. IgA ~~has been shown to be~~is very effective at tackling viruses in virus-infected epithelial cells and in redirecting antigens to the lumen when they enter the lamina propria.[12] Upper airway infection with certain viruses such as rhinovirus,[13] influenza,[14] and SARS-CoV2 [15] has shown to induce an increase of IgA in the nasal lavage and for influenza, playing an important role in the protection against viral infection in humans.[14] This is supported by murine studies where transfer of nasal IgA from immunized to naïve mice leads to protection against influenza infection [16] and mice lacking S-IgA have increased viral load after intranasal challenges.[17] No articles are currently discussing the role of IgA in COVID-19 patients at admission and ~~at~~ discharge.

The ~~aim of this study was~~is study aimed to explore whether IgA could be used to differentiate or prognosticate patients with lung diseases such as COVID-19 or asthma. The outcome

could be applied in the suggestion for the use of the IgA strategy in the treatment of lung mucosal diseases.

METHODOLOGY

Ethics Committee Approval: Ethical approval from the Institutional (UI/UCH) EthicsReview Committee (Approval number: UI/EC/20/0283) and informed consent from participants or relatives to participate were obtained.

Study Design and Laboratory Procedures: The study was acase–control study which included 90 subjects recruited from University College Hospital, Ibadan, and Infectious Diseases Center (IDC), Olodo, Ibadan, Nigeria. Study The study population were was30newly diagnosed asthma patients with 30 corresponding control and 30 newly diagnosed COVID-19 patients followed up till dischargedcompared with 30 corresponding control. COVID-19 patients were recruited from IDC, Olodo, were enrolled into this study. The COVID-19 cases were confirmed by detection of hCoV nucleic acid using real-time reverse-transcriptase polymerase-chain chain-reaction (RT-PCR) assay in nasal and pharyngeal swab specimens following recommended guidelines apart from clinical signs of dry cough, high fever, sore throat and shortness of breath.[18]Patients with asthma as per the definition of the American Thoracic Society[19] were chosen for the study. They were newly diagnosed from atthe Medical Outpatient Clinic, University College Hospital, Ibadan, Nigeria. Subjects on medication (antihistamines, steroids, and compulsory drugs) and those with skin disorders or dermatographia were excluded. None of the subjects was pregnant or had co-existing diseases like diabetes, cardiac disease, renal and/or liver dysfunction.

Other exclusion criteria wereare: smoking, subjects with secondary immune deficiency, diabetes hypertension, and malignancy or subjects taking medications including antiepileptics sulfasalazine, D penicillamine, thyroxine, captopril, levamisole, systemic corticosteroids, and cyclosporine or history of immunosuppressive medications and co-morbid conditions such as rheumatoid arthritis, lupus, celiac disease, or inflammatory bowel disease to avoid the confounding effect.Whole blood collected into a plain tube was allowed to clot and retract before being spun at 2,000 x g for 10 minutesfor the collection of serum. The serum was stored at -20^{0}C until analysedanalyzed.

Venous blood samples were collected from all subjects in 5ml vacutainer tubes without anti-coagulants. All samples were processed at the Department of Immunology laboratory at the College of Medicine, University of Ibadan, Nigeria. Serum samples were frozen and stored at

-80^{0}C until analysis was performed. Samples were analyzed for the levels of IgA using based on the method described by the manufacturer (Elabscience, USA, Catalogue number E-EL-H6071) as follows: 50µl per well of appropriate sample dilution buffer, antigen standard cocktail or experimental sample was pipetted into microtiter plates. This was incubated at room temperature (27°C). The ELISA immunoplate was washed 3 times with 350µl/well of washing buffer. 100µl per well of detection antibodies was added. This was incubated at room temperature for 60 minutes. The immunoplate was re-washed 3 times with 350µl/well of washing buffer. 100µl/well of diluted Avidin-HRP conjugate was added, after which the plate was incubated at room temperature for 30 minutes avoiding light rays. The plate was washed 4 times and 100µl per well of developing solution was added. The reaction was stopped with 100µl/well of Stop Solution and absorbance optical density (O.D) was read at 450nm within 30 minutes following the addition of stop solution. The average absorbance value of each O.D. was plotted against corresponding cytokine values to plot a standard curve. The average absorbance of each serum sample was used to determine corresponding cytokine values by interpolating from the curve.

Statistical Analysis: Data were analyzed using SPSS and the values were presented as mean (±SD). Mean (±SD) between and within the two groups were compared using the Student t-test. A p-value ≤0.05 was reported as significant.

RESULTS

Table 1: The mean level of IgA (mg/dL) in COVID-19 patients at admission compared with control

Groups	N	Mean	SD	t-value	P-value
COVID-19 patients at admission	30	250	40.00		
Controls	30	245	59.00	3.40	<0.001

Table 2: The mean level of IgA (mg/dL) in COVID-19 patients at discharge compared with control

Groups	N	Mean	SD	t-value	P-value
COVID-19 patients at discharge	30	251	61.00		
Controls	30	245	59.00	2.25	<0.031

Table 3: The mean level of IgA (mg/dL) in COVID-19 patients at admission compared with COVID-19 patients at discharge.

Groups	N	Mean	SD	t-value	P-value
COVID-19 patients at admission	30	250	40.00		
COVID-19 patients at discharge	30	251	61.00	0.088	>0.50

Table 4: The mean level of IgA (mg/dL) in COVID-19 patients in asthmatic patients compared with control

Groups	N	Mean	SD	t-value	P-value
Asthma	30	248	40.00		
Controls	30	255	20.00	4.37	<0.018

Table 5: Frequency of COVID-19 patients or asthma patients or control having IgA values outside the normal reference ranges (70-400mg/dL)

Groups	% of participants having IgA values outside the normal reference ranges
Asthma	0%
COVID-19	0%
Control	0%

The mean value of serum IgA was significantly increased in COVID-19 patients at admission ($p<0.001$) or COVID-19 patients at discharge ($p<0.031$) compared with the level in the control. See Tables 1 and 2.The mean value of serum IgA was similar in COVID-19 patients at admission compared with COVID-19 patients at discharge ($p>0.50$). See Table 3. The mean value of plasma IgA was significantly decreased ($p=0.018$) in asthma patients compared with the level in the control (Table 4). None of the participants have IgA values outside the normal reference values (70-400mg/dL). See Table 5.

DISCUSSION

Unlike in gastro-intestinal diseases, the role of IgA in airway disease remains largely understudied. ~~Reported~~ The reported ~~on~~function of IgA ~~were~~ wasdetermined in chronic obstructive pulmonary disease (COPD),[20] asthma,[20] and cystic fibrosis.[21]Moreso, patients with secretory IgA deficiency ~~were seem~~seemed to present with more frequent respiratory infections, allergies, and auto-immune diseases compared to patients with normal

IgA levels.[22, 23]The current study has provided information concerning serum IgA levels in two lung mucosal diseases (COVID-19 and asthma). Based on the results of this study, it was found that there was a statistically significant decrease ~~regarding~~ inserum IgA in the asthma patients than in the control patients. This supported previousfindings.[24, 25, 26] Reduced IgA in asthmatic patients might ~~possibly~~ be the reason for the increased risks of bacterial infections in them.[24]Asthma patients on treatment were excluded from this study because serum IgA level was reported to be significantly lower among asthma patients using inhaled corticosteroids.[27]

Asthma, a disease of the airways of no fixed etiologyis known to involve eosinophil degranulation, cytokine secretion, and raised level of IgE[7] but the involvement of IgA in asthma pathophysiology is largely unknown. ~~Previous~~ A previous study suggested ~~a~~ theparticipation of IgA in eosinophil degranulation in ~~the~~ patients with atopic asthma.[28] Furthermore, IgA facilitates the phagocytosis of antigens due to the presence of specific IgA Fc receptors.[29]Also, the role of IgA in the pathogenesis of IgA nephropathy has been extensively studied, and deposits of IgA together with Complement components are observed in the mesangial area of the kidney.[30] IgA might be the cause of lung injury in asthmatics, as shown by the presence of IgA immune complex-mediatedin acute lung injury of rats.[31] The capacity of IgA to trigger therelease of mediators from inflammatory cells and to activate the Complement System explains IgA's role in inflammation.[29]

Various cell types have been found to bind IgA as depicted by the presence of prototype Fc receptor for IgA FcαRI (CD89) on neutrophils, eosinophils, monocytes, and macrophages.[29] This leads to the activation of a variety of effector functions in asthmatics, including phagocytosis, production of reactive oxygen intermediates, degranulation, and production of cytokines.[32-37]Moreover, the levels of IgA in broncho-alveolar fluid and sputum from patients with asthma are higher than those in controls.[28] In addition, complexes of IgA and IL-8 have been detected in induced sputum, and the levels of these complexes were higher in atopic asthmatics compared withhealthy non-atopic control participants.[38] Increased IgA levels in pulmonary secretions can be explained by increased leakage of IgA from the circulation among other mechanisms. There is evidence from in vitro studies that cytokines implicated in the pathogenesis of asthma may enhance the transport of IgA across the epithelium. IL-4 and interferon (IFN)-gammasynergistically enhance the expression of secretory components and binding of IgA to cultured epithelial cells.[39] In line

with this observation, IFN-gamma and IL-4 were found to increase secretory component-mediated transport of IgA across epithelium in cell culture.[40] All these mechanisms might explain the decreased level of serum IgA found in our asthmatics compared with controls.

In this study, we measured total IgA in COVID-19 patients at admission or ~~at~~ discharge compared with control of similar ages and gender.A previous finding showed a marked elevation of total IgA in severe SARS-CoV-2 infection.[11, 15] These data support our hypothesis that a strong IgA-driven immune response was stimulated in the bronchial-associated lymphoid tissue when SARS-CoV-2 infects and persists in the respiratory system.[41]Thus explainingour findings of raised IgA in COVID-19 patients at admission and dischargecompared with controls or similar levels of IgA in COVID-19 patients at admission compared with COVID-19 patients at discharge.~~A d~~Data supported a link between IgA and multisystem inflammatory syndrome in COVID-19 (MIS-C),which is a novel COVID-19–related disease.[42, 43]Our present study ~~therefore~~, therefore, suggests that elevated total IgA might have a causal role in MIS-C.

The role of IgA in asthma has been less explored. A study linked significantly lower serum IgA levels in asthmatics with recurrent infections,[24], and it was well documented that IgA-deficient individuals have an increased incidence of autoimmune disease ofthe gastrointestinal tract. About 1% of individuals with coeliac disease were IgA-deficient.[41]~~Authors~~ The authors of the present study ~~hypothesised~~ hypothesized thatreduced IgA in asthma patientsmight beliable for the ~~responsible~~future occurrence of recurrent infection and autoimmune disorders in them. However, none of the participants had serum IgA levels below or above the normal reference range (70-400mg/dL).Binding of IgA to myeloid-cell-specific type I Fc receptor for IgA (FcαRI or CD89), the Fcα/Fcμ receptor, the asialoglycoprotein receptor, and the transferrin receptor[44] results ~~to~~ inboth pro-inflammatory as well anti-inflammatory pathways. Anti-inflammatory signals are generated by FcαRI upon binding of monomeric IgA, whereas pro-inflammatory FcαRI-dependent responses are induced by IgA immune complexes.[45] Thus, raised monomeric serum IgA in COVID-19 patients might be a strategy to produce anti-inflammatory signals through binding with FcαRI to dampen excessive inflammationin COVID-19 patients.

IgA production typically occurs in response to transforming growth factor-β1 (TGFβ1), ~~that~~which activates the specific promoters responsible for IgA class switching. It has been described that IgA switching can also occur through B-cell activation in combination with

other cytokines, such as interleukin-2 (IL-2), IL-4, IL-5, IL-6, and IL-10.[46, 47]These cytokines have been reported to raised during episodes of “cytokine storm”in COVID-19 patients, thus an increased level of IgA is expected and as reported in this study. Also, lipopolysaccharide (LPS) via Toll-like receptors (TLRs) or polysaccharides through the B-cell receptorproduce non-specific, polyreactive IgA in a T-cell independent way by directly activating B cells or induce a selective IgA class switch in B cells.[48]LPS, TLR, and polysaccharides are increased in COVID-19 patients[49] which might stimulate the production of polyreactive IgA[50]. These polyreactive antibodies recognize multiple antigens and are therefore able to provide limited protection against a plethora of pathogens.[51] Therefore, increased IgA in COVID-19 patients might be another protective advantage ~~to~~ forthese patients.In support of its role as a neutralizing antibody that excludes antigens, IgA has also been found to be elevated following vaccination against SARS-CoV-2 in a cohort of high-risk first responders.51 Ideally, this is another support for the protective role of IgA during SARS-CoV-2 infection.

The main limitation of the current study was the small size of its sample. Hence, it is recommended for future research to conduct larger studies. Nevertheless, the inclusions of extensive exclusion criteria are the major strength~~s~~ of the study.

Conclusion

This novel data concluded that a vigorous antiviral IgA response was triggered in the bronchial mucosaof COVID-19 patients and that serum IgA levels differentiate COVID-19 patients from asthma patients. This is a similar trend to a recent report from our laboratory using activities of plasma indoleamine-2, 3-dioxygenase enzyme (IDO) in patients with asthma, pulmonary tuberculosis, and COVID-19.[52] The major importance of the present study is that IgA is protective in COVID-19 patients and that IgA might be one of the ~~neutralising~~ neutralizing antibodies stimulated by COVID-19 vaccines. However, IgA ~~was~~contributed to the pathology of lung injury in asthma patients.

Abbreviations

COVID-19 = Coronavirus Disease 2019

DC = Dendritic cells

ELISA = ~~Enzyme~~ Enzyme-linked immunosorbent assay

HRP = ~~Histidine~~ Histidine-Rich Protein

IDC = Infectious Diseases Center

IDO = Indoleamine-2, 3-dioxygenase enzyme

IFN = interferon

IgA = Immunoglobulin class A

IgE= Immunoglobulin class E

IL 2, 4 = Interleukin 2, 4

LPS = Lipopolysaccharide

MISC-C = Multisystem Inflammatory Syndrome in COVID-19

O.D = Optical density

SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2

TLR = Toll-like receptors

UI/UCH = University of Ibadan/University College Hospital

Ethics Committee Approval: Ethical approval from Institutional EthicsCommittee (Approval number: UI/EC/20/0283) and consent from participants or relatives to participate were obtained.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

REFERENCES

1. Busse WW, Lemanske RF. Asthma. N Engl J Med. 2001;344:350–362. doi:10.1056/NEJM200102013440507.
2. Kerr MA, Loomes LM, Bonner BC, Hutchings AB, Senior BW. Purification and characterization of human serum and secretory IgA1 and IgA2 Using Jacalin. Methods Mol Med.1998; 9:265–78. doi: 10.1385/0-89603-396-1:265. PubMed Abstract | CrossRef Full Text | Google Scholar
3. Mkaddem SB, Christou I, Rossato E, Berthelot L, Lehuen A, Monteiro RC. IgA, IgA receptors, and their anti-inflammatory properties. Curr Top Microbiol Immunol.2014; 382:221–35. doi: 10.1007/978-3-319-07911-0_10. PubMed Abstract | CrossRef Full Text | Google Scholar

4. Brandtzaeg P. Immunobiology of the tonsils and adenoids. In: Mestecky J, Strober W, Russell MW, Kelsall BL, Cheroutre H, Lambrecht BN, editors. Mucosal Immunology.2015; Amsterdam: Elsevier.pages. 1985–2016. Google Scholar
5. Marenholz I, Kerscher T, Bauerfeind A, et al. An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma. J Allergy Clin Immunol. 2009; 123(4):911–916. doi:10.1016/j.jaci.2009.01.051
6. Habibzay M, Saldana JI, Goulding J, et al. Altered regulation of Toll-like receptor responses impairs antibacterial immunity in the allergic lung. Mucosal Immunol. 2012; 5(5):524–534. doi:10.1038/mi.2012.28
7. Oluwole O, Arinola OG, Mary D. Adu, AdedayoAdepoju, Babatunde O. Adedokun, Olufunmilayo I. Olopade, and Christopher O. Olopade. Relationships between Plasma Micronutrients, Serum IgE, and Skin Test Reactivity and Asthma among School Children in Rural Southwest Nigeria, Volume 2014. Article ID 106150, 9 pages
8. Ali OH, Bomze D, Lorenz Risch, Silvio D Brugger, Matthias Paprotny, Myriam Weber, Sarah Thiel, Lukas Kern, Werner C Albrich, Philipp Kohler, Christian R Kahlert, Pietro Vernazza, Philipp K Bühler, Reto A Schüpbach, Alejandro Gómez-Mejia, Alexandra M Popa, Andreas Bergthaler, Josef M Penninger, Lukas Flatz.Severe Coronavirus Disease 2019 (COVID-19) is Associated With Elevated Serum Immunoglobulin (Ig) A and Antiphospholipid IgA Antibodies, Clinical Infectious Diseases, 2012; 73, Issue 9, 1 November 2021, Pages e2869–e2874, https://doi.org/10.1093/cid/ciaa1496
9. Monteil V, Kwon H, Prado P , et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell. 2020; 181: 905–913.e7.Google Scholar, Crossref, PubMed, WorldCat
10. Brandtzaeg P, Jahnsen FL, Farstad IN. Immune functions and immunopathology of the mucosa of the upper respiratory pathways. Acta Otolaryngol. 1996; 116:149–59. Google Scholar, Crossref, PubMed, WorldCat
11. Yu H, Sun B, Fang Z, et al. Distinct features of SARS-CoV-2–specific IgA response in COVID-19 patients. Eur Respir J. 2020; 56: 2001526. Google Scholar, Crossref, PubMed, WorldCat
12. Brandtzaeg P. Induction of secretory immunity and memory at mucosal surfaces. Vaccine.2006; 25:5467–84. doi: 10.1016/j.vaccine.12.001. PubMed Abstract | CrossRef Full Text | Google Scholar
13. Igarashi Y, Skoner DP, Doyle WJ, White MV, Fireman P, Kaliner MA. Analysis of nasal secretions during experimental rhinovirus upper respiratory infections. J Allergy Clin

Immunol.1993; 92:722–31. doi: 10.1016/0091-6749(93)90016-9. PubMed Abstract | CrossRef Full Text | Google Scholar

14. van Riet E, Ainai A, Suzuki T, Hasegawa H. Mucosal IgA responses in influenza virus infections; thoughts for vaccine design. Vaccine. 30:5893–900. doi: 10.1016/j.vaccine.2012.04.109. PubMed Abstract | CrossRef Full Text | Google Scholar
15. Russell MW, Moldoveanu Z, Ogra PL, Mestecky J. Mucosal immunity in COVID-19: a neglected but critical aspect of SARS-CoV-2 infection. Front Immunol. 2020; 11:611337. doi: 10.3389/fimmu.2020.611337. PubMed Abstract | CrossRef Full Text | Google Scholar
16. Tamura S, Funato H, Hirabayashi Y, Suzuki Y, Nagamine T, Aizawa C, et al. Cross-protection against influenza A virus infection by passively transferred respiratory tract IgA antibodies to different hemagglutinin molecules. Eur J Immunol.1991; 21:1337–44. doi: 10.1002/eji.1830210602. PubMed Abstract | CrossRef Full Text | Google Scholar
17. Asahi Y, Yoshikawa T, Watanabe I, Iwasaki T, Hasegawa H, Sato Y, et al. Protection against influenza virus infection in polymeric Ig receptor knockout mice immunized intranasally with adjuvant-combined vaccines. J Immunol.2002; 168:2930–2938. doi: 10.4049/jimmunol.168.6.2930. PubMed Abstract | CrossRef Full Text | Google Scholar
18. Li T. Diagnosis and clinical management of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection: an operational recommendation of Peking Union Medical College Hospital (V2.0). Working Group of 2019 Novel Coronavirus, Peking Union Medical College Hospital. 2020: Pages 582-585. https://doi.org/10.1080/22221751.2020.1735265
19. National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug. Section 2, Definition, Pathophysiology and Pathogenesis of Asthma, and Natural History of Asthma. Available from: https://www.ncbi.nlm.nih.gov/books/NBK7223/
20. 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. doi: 10.1164/rccm.201703-0561OC. PubMed Abstract | CrossRef Full Text | Google Scholar
21. Collin AM, Lecocq M, Noel S, Detry B, Carlier FM, Aboubakar Nana F, et al. Lung immunoglobulin A immunity dysregulation in cystic fibrosis. EBioMedicine.60:102974. doi: 10.1016/j.ebiom.2020.102974. PubMed Abstract | CrossRef Full Text | Google Scholar

22. Yel L.Selective IgA deficiency. J Clin Immunol.2010; 30:10–6. doi: 10.1007/s10875-009-9357-x. PubMed Abstract | CrossRef Full Text | Google Scholar
23. Aytekin C, Tuygun N, Gokce S, Dogu F, Ikinciogullari A. Selective IgA deficiency: clinical and laboratory features of 118 children in Turkey. J Clin Immunol.2012; 32:961–6. doi: 10.1007/s10875-012-9702-3. PubMed Abstract | CrossRef Full Text | Google Scholar
24. Abo Ali FH, Mahmoud NE, El-Sayed AYM, Abdelmaksoud MF, Shata AK, Fouad SH.Selective IgA Deficiency a Probable Risk of Recurrent Chest Infections in Asthmatics. J Asthma Allergy. 2021; 14:1323-1333. https://doi.org/10.2147/JAA.S329531.
25. Rachid R, Castigli E, Geha RS, et al.TACI mutation in common variable immunodeficiency and IgA deficiency. Curr Allergy Asthma Rep. 2006; 6:357–362. doi:10.1007/s11882-996-0004-9
26. Janzi M, Melen E, Kull I, et al. Rare mutations in TNFRSF13B increase the risk of asthma symptoms in Swedish children. Genes Immun. 2012; 13:59–65. doi:10.1038/gene.2011.55
27. Fukushima C, Matsuse H, Saeki S, et al.Salivary IgA and oral candidiasis in asthmatic patients treated with inhaled corticosteroid. J Asthma. 2005;42(7):601–604. doi:10.1080/02770900500216259
28. Peebles RS Jr, Liu MC, Lichtenstein LM, Hamilton RG.IgA, IgG and IgM quantification in bronchoalveolar lavage fluids from allergic rhinitis, allergic asthmatics, andnormal subjects by monoclonal antibody-based immunoenzymetric assays. J Immunol.Methods.1995. 179:77–86.
29. Morton HC, van Egmond M, van de Winkel JG. Structure and function of human IgA Fc receptors (Fc alpha R). Crit Rev Immunol 1996; 16: 423–440.
30. Galla JH. IgA nephropathy. Kidney Int. 1995; 47: 377–387.
31. Jones ML, Mulligan MS, Flory CM, Ward PA, Warren JS. Potential role of monocyte chemoattractant protein 1/JE in monocyte/macrophage-dependent IgA immune complex alveolitis in the rat. J Immunol.1992. 149: 2147–2154.
32. Onifade A.A and Arinola O.G. Albendazole reduces serum levels of inflammatory cytokines: Potential strategy for the management of cytokine storm". Saudi Journal of Biomedical Research. 2020; 5 (11):320-324. DOI : 10.36348/sjbr.2020.v05i11.006
33. Arinola OG, Edem VF, Alonge TO. Respiratory Burst Functions in COVID-19 Nigerian Patients. Journal of Basic and Applied Research in Biomedicine. 2021; 7(1): 24-28.
34. Akinwumi JA, Edem VF, Arinola OG. Cellular inflammatory indices in hospitalised Nigerian COVID-19 patients. Journal Health Science Research. 2021; 6(2): 19-26.

35. Arinola GO, Edem VF, Fashina OA, Olaniyan OA, Alonge TO. Cellular and Humoral Factors of Oxidative Burst in COVID-19 Patients with Malaria Parasiteamia. Annals of Epidemiology & Public Health.2021. 4(1): 1060-1065.
36. Arinola OG, Rahamon SK, Edem VF, Yaqub SA, Fashina OA, Alonge TO. Elevated plasma level of circulating immune complexes in Nigerian adults infected with Severe Acute Respiratory Syndrome Corona Virus-2. Arch. Basic and Applied Medicine. 2021; 9: 69-72
37. Arinola O.G, Edem VF, Alonge TO. Levels of Plasma C-reactive protein, Albumin and Pre-Albumin in Nigerian COVID-19 Patients. Annals of Medical Research. 2022, 29(1): 46-51
38. Louis R, Shute J, Biagi S, et al. Cell infiltration, ICAM-1 expression, and eosinophil chemotactic activity in asthmatic sputum. Am J Respir Crit Care Med.1997; 155: 466–472.
39. Phillips JO, Everson MP, Moldoveanu Z, Lue C, Mestecky J. Synergistic effect of IL-4 and IFN-gamma on theexpression of polymeric Ig receptor (secretory component) and IgA binding by human epithelial cells. J Immunol.1990; 145: 1740–1744.
40. Loman S, RadlJ, Jansen HM, Out TA, Lutter R.Vectorialtranscytosis of dimeric IgA by the Calu-3 human lungepithelial cell line: upregulation by IFN-gamma. Am J Physiol.1997; 272 (5 Pt 1): L951–L958.
41. Pilette C, Ouadrhiri Y, Godding V, Vaerman JP, Sibille Y.Lung mucosal immunity: immunoglobulin-A revisited. Eur Respir J. 2001; 18: 571–88. Google ScholarCrossrefPubMedWorldCat
42. Toubiana J, Poirault C, Corsia A, et al.Kawasaki-like multisystem inflammatory syndrome in children during the COVID-19 pandemic in Paris, France: prospective observational study. BMJ.2020; 369: m2094. Google ScholarPubMedWorldCat
43. VerdoniL, Mazza A, Gervasoni A, et al.An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020; 395: 1771–1778. Google ScholarCrossrefPubMedWorldCat
44. Mkaddem SB, Christou I, Rossato E, Berthelot L, Lehuen A, Monteiro RC.IgA, IgA receptors, and their anti-inflammatory properties. Curr Top Microbiol Immunol.2014; 382:221–35. doi: 10.1007/978-3-319-07911-0_10. PubMed Abstract | CrossRef Full Text | Google Scholar
45. Bakema JE, Van Egmond M.The human immunoglobulin A Fc receptor FcαRI: a multifaceted regulator of mucosal immunity. Mucosal Immunol.2011; 4:612–24. doi: 10.1038/mi.2011.36. PubMed Abstract | CrossRef Full Text | Google Scholar

46. Brandtzaeg P. Immunobiology of the tonsils and adenoids. In: Mestecky J, Strober W, Russell MW, Kelsall BL, Cheroutre H, Lambrecht BN, editors. Mucosal Immunology. Amsterdam: Elsevier. 2015. p. 1985–2016. Google Scholar
47. Fagarasan S, Honjo T. T-Independent immune response: new aspects of B cell biology. Science. 2000; 290:89–92. doi: 10.1126/science.290.5489.89. PubMed Abstract | CrossRef Full Text | Google Scholar
48. Peng SL. Signaling in B cells via Toll-like receptors. CurrOpinImmunol. 2005; 17:230–6. doi: 10.1016/j.coi.2005.03.003. PubMed Abstract | CrossRef Full Text | Google Scholar
49. Khanmohammadi S, Rezaei N.Role of Toll-like receptors in the pathogenesis of COVID-19. J Med Virol. 2021; May;93(5):2735-2739. doi: 10.1002/jmv.26826. Epub 2021 Feb 9. PMID: 33506952; PMCID: PMC8014260.
50. Macpherson AJ, Uhr T.Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria. Science.2004; 303:1662–5. doi: 10.1126/science.1091334. PubMed Abstract | CrossRef Full Text | Google Scholar
51. Montague, B.T., Wipperman, M.F., Chio, E. et al.Elevated serum IgA following vaccination against SARS-CoV-2 in a cohort of high-risk first responders. Sci Rep. 2022.12, 14932 https://doi.org/10.1038/s41598-022-19095-7.
52. Arinola, G.O., Abdullahi, I., Rahamon, S.K. et al.Activities of plasma indoleamine-2, 3-dioxygenase (IDO) enzyme in Nigerian patients with lung diseases: basis for tryptophan supplementation or IDO inhibitor use. Egypt J Bronchol. 2023;17, 2 https://doi.org/10.1186/s43168-022-00174-2