

DOES SERUM IMMUNOGLOBULIN AND COMPLEMENT C3 DEFICIENCY CAUSES BRONCHIAL ASTHMA?Usha¹, Kavyanjali Sharma^{2*}, Shailja Singh³, Niladri⁴, Ranjan Singh Rana⁵, Sajjan Kumar Meena⁶, Deepa Rani⁷, J. K. Mishra⁸, Rajosri Das⁹¹Professor, Department of Pathology & Incharge at UGC Advance Immunodiagnostic Training and Research Centre.^{2,3,4,5}Research Scholar, Department of Pathology.⁶Junior Resident, Department of TB & Respiratory Disease.⁷Assistant Professor, Department of Pathology.⁸Professor, Department of TB & Respiratory Disease.⁹Laboratory Attendant, Department of Pathology.

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ABSTRACT

Background & Objective: Etiopathogenesis of allergic diseases is not known. Both genetic factors and environmental factors have been blamed for it. Immunodeficiency (ID) is also one of the factor. Aim of the present study was to find out prevalence of C3 and immunoglobulin deficiency in patients presenting with asthma and or allergic rhinitis or urticaria. **Material & Method:** Serum immunoglobulins and complement C3 test were done by turbidometric method. Serum IgE test was done by ELISA method. **Result:** Total 58 cases of allergy and 20 healthy controls were studied. Serum IgE was elevated in all cases. In 43 cases (82.76%) all immunoglobulin and complements were normal. Partial C3 deficiency (pC3D) was present in 12.07% cases. Out of seven deficient cases, one case also had associated with IgAD in 28 years male and another one case (1.72%) was associated with IgGD. In 5 cases it was isolated C3 deficiency (8.62%). After C3D, another common ID was selective partial IgMD, which was detected in four cases (6.90 %). All immunodeficient patients also had recurrent respiratory tract infection in between allergic attack. In C3D four were females and three were males, while IgMD was more common in females and IgAD was seen only in male patient only, similarly IgGD was seen in adult male. **Interpretation & Conclusion:** Thus our study concludes that not only IgAD but C3D, IgMD and IgGD can also produce allergic diseases. Hence in every case of allergy, immunoglobulin and complement levels should be done. Intravenous immunoglobulin may benefit these patients.

KEYWORDS: Allergic Dermatitis, Urticaria, Bronchial Asthma, Serum IgE, IgM deficiency, IgA deficiency, IgG deficiency, C3 deficiency.

INTRODUCTION

Primary Immunodeficiency (PID) refers to a heterogenous group of disorder characterized by defective or absence of function of a component of immune system. It is usually due to genetic defect or developmental defect. Now more than 130 types of PID are seen. PID may involve T cells, B cells or combine T and B cells of acquired immunity or it may involve defect in innate immunity (phagocyte cells, complement system and NK cells).^[1] B cells immunodeficiency or humoral immunity deficiency is more common and accounts for 77% cases of PID. It includes X linked agammaglobunemia, common variable immunodeficiency syndrome (CVID), selective IgA deficiency (IgAD), selective IgM deficiency (IgMD) and selective IgG subclass deficiency (IgGD). Among these,

major groups are formed by CVID (38.4%) followed by IgG subclass D (19.4%), IgAD (7.8%), X linked agammaglobunemia (6.6%), selective IgMD (0.1%) and transient hypogammaglobunimemia (0.7%).^[2,3]

CVID usually occurs in second and third decades of life and some cases may manifest in childhood also. Incidence may vary from 1:10000 to 1: 50000.^[4] It presents with recurrent infections, diarrhoea, otitis media, meningitis, cytopenia and autoimmune diseases.^[5] Some authors have claimed that IgAD is the commonest immunodeficiency and its incidence may vary from 1:300 to 1:500 births. It presents predominantly as sinopulmonary infection, allergy and diarrhea.^[6,7] T cell immunodeficiency includes mostly DiGeorge syndrome and chronic candidiasis. Since T cell also help B cells to produce antibody hence T cell ID is also associated with

B cell ID and is called as combined ID. Some of them are very severe in nature and called as severe combined immunodeficiency (SCID). This is due to deficiency of ADA enzyme or PNP enzyme or mutation of common γ chain of cytokine IL-2, IL-4, IL-7, IL-9, IL-11, IL-15, IL-21 or deficiency of JAK3 or recombinase activating 1, 2 enzyme. Loss of MHC II Ag may also give rise to SCID.^[7] Ommen syndrome is also a SCID characterized by erythroderma, alopecia, dermatitis, increased TH2 cells, low serum immunoglobulin and eosinophilia.^[3,8] Comparatively less severe combined ID includes Wiskott's Aldrich syndrome characterized by eczema, bleeding, thrombocytopenia, infection, low IgM and increased serum IgE.^[7] T cell PID presents with atypical mycobacterial infection, salmonella infection, mucocutaneous candidiasis, autoimmune endocrinopathy, diaper rash and graft versus host disease. Isolated T cell PID is uncommon. It includes Digeorge syndrome which present as facial and cardiac abnormality, parathyroid hypoplasia, tetany and recurrent intracellular microbial infection. B cell ID presents with recurrent bacterial and viral infection, sinopulmonary infection, diarrhoea, haemolytic anemia, thrombocytopenia and autoimmune disease.^[4,9]

Combined immunodeficiency have features of both T and B cell ID along with some other physical finding like eczema, ataxia, telangiectasia, cartilage hair hypoplasia, tetany rashes and recurrent opportunistic infection, failure to thrive diarrhoea and rash.^[4,9,1] Phagocytic and complement deficiency manifest as antibody deficiency.

Allergic manifestations are less common in PID. It is mostly described in IgAD. Here we are reporting study of 58 cases that were having recurrent cough, asthma; elevated IgE along with allergic rhinitis (in 8 cases) and four cases had rashes on hand. Aim of the study was to see immunoglobulin and C3 deficiency in allergy cases.

MATERIAL AND METHODS

Sample: Total 58 cases (34 males with mean age 24.94 ± 13.76 years and 24 female with mean age 25.92 ± 13.74 years) of allergic disease especially asthma with allergic rhinitis and/or urticaria and 20 healthy controls (11 males with mean age 34.73 ± 9.19 years and 9 females with mean age 28.78 ± 8.84 years) were studied within a period of one year during November 2013 to December 2014. Twenty healthy controls were medical staff who were not suffering from any allergic diseases. Cases were taken from chest OPD and medicine OPD. It was a preliminary study and sample size was decided on the

basis of consent and availability of patients and also for controls within duration of study.

Inclusion and Exclusion criteria: Patients with bronchial asthma and/or allergic rhinitis or urticaria having typical features in clinical examination was selected for the study. Only those patients who had active disease but were not taking any medication were included in the study. Those cases who were taking any kind of drugs for allergic diseases were excluded from the study.

Methods: Serum IgE test was done by ELISA kit of Demeditec Diagnostics GmbH, Germany. Serum IgG, IgA, IgM, C3 tests were done by immunoturbidometric method. Kits of Spinreact company, Spain and standards of Bioscientifica Ltd, UK were used.

RESULT

All patients had asthma like symptoms and in all patient serum IgE was elevated above 165 mg/dl. Serum C3 level below 60 mg/dl was seen in 12.06 % cases while in control none of the case had C3 level below 60 mg/dl. Mean value of C3 in patients was significantly reduced (p value - 0.047) (Table II). Out of these seven patients three were males (12, 20 and 28 years) and four patients were female (19, 15, 26 and 15 years). Serum C4 level below 10 mg/dl was found in 15% controls and 3.45% patients. Contrary to C3, C4 levels were significantly elevated in allergic diseases (Table III). C3 values in reduced cases were 29.0, 27.9, 35.0, 42.0, 54.8, 42.3 and 49.5 mg/dl. Serum IgA was reduced in two patients (3.45%). This reduction was border line (54 mg/dl and 55 mg/dl), while in control cases none of the person had low IgA value (below 60 mg/dl). Both IgA deficient patients were males (31 years, 55 years). (Table IV).

Interestingly serum IgM was reduced (below 50 mg/dl) in four patients (6.90 %) and 22.41 % patients had elevated IgM level also. Hence mean value and chi-square test did not show any significant results (Table V). In deficient patients only one patient was male (20 years) while three were female (36, 25 and 20 years). All had asthma and cough with allergic rhinitis. Level of serum IgM was 37, 37, 38 and 47 mg/dl. Serum IgG was deficient in only one case (1.72%) and this patient was having asthma, cough and allergic rhinitis. None of the patient had elevated IgG and mean value of patient IgG did not show any significant changes (Table VI). This patient had very low serum IgG (216 mg/dl).

Table I: Showing Age and Sex of the patients and healthy control.

		Group A	Group B
Female	No. (%)	24 (41.4%)	9 (45%)
	Age (Mean \pm SD)	25.92 \pm 13.74	28.78 \pm 8.84
Male	No. (%)	34 (58.6%)	11 (55%)
	Age (Mean \pm SD)	24.94 \pm 13.76	34.73 \pm 9.19

(Note: Group A-Patients group with elevated IgE serum level. Group B-Healthy control group, SD-Standard deviation).

Table II: Showing serum complement 3 in control and respiratory allergy cases.

Groups	Serum C3 level			Mean \pm SD	t value	P value
	< 60 mg/dl	60-180 mg/dl	>180 mg/dl			
	No. (%)	No. (%)	No. (%)	mg/dl	A vs. B	A vs. B
Group A	7 (12.07 %)	47 (81.03 %)	4(6.90 %)	133.2 \pm 48.4	2.022	0.047*
Group B	0 (0.00%)	15 (75.00%)	5 (25.00 %)	157.8 \pm 42.4		

(Note: Group A-Patients group with elevated IgE serum level. Group B- Healthy control group, SD- Standard deviation, *- P value is significant).

Table III: Showing comparison between control and patients for serum C4 level.

Groups	Serum C4 level			Mean \pm SD	t value	P value
	< 10 mg/dl	10-40 mg/dl	>40 mg/dl			
	No. (%)	No. (%)	No. (%)	mg/dl	A vs. B	A vs. B
Group A	2 (3.45 %)	34 (58.62 %)	22 (37.93 %)	35.58 \pm 16.37	3.876	0.0002*
Group B	3 (15.00 %)	16 (80.00 %)	1 (5.00 %)	20.39 \pm 10.48		

(Note: Group A-Patients group with elevated IgE serum level. Group B- Healthy control group, SD- Standard deviation, *- P value is significant).

Table IV: Showing serum IgA level in respiratory allergy and control cases.

Groups	Serum IgA level			Mean \pm SD	t value	P value
	< 60 mg/dl	60-400 mg/dl	>400 mg/dl			
	No. (%)	No. (%)	No. (%)	mg/dl	A vs. B	A vs. B
Group A	2 (3.45 %)	55 (94.83 %)	1 (1.72 %)	199.60 \pm 83.07	1.782	0.079
Group B	0 (00.00 %)	17 (85.00 %)	3 (15.00 %)	245.64 \pm 137.87		

(Note: Group A-Patients group with elevated IgE serum level. Group B-Healthy control group, SD-Standard deviation).

Table V: Showing serum IgM level in respiratory allergy and control cases.

Groups	Serum IgM level			Mean \pm SD	t value	P value
	< 50 mg/dl	50-230 mg/dl	>230 mg/dl			
	No. (%)	No. (%)	No. (%)	mg/dl	A vs. B	A vs. B
Group A	4 (6.90 %)	41 (70.69 %)	13(22.41 %)	161.76 \pm 103.72	0.384	0.702
Group B	0 (0.00%)	18 (90.00%)	2 (10.00 %)	151.87 \pm 85.27		

(Note: Group A-Patients group with elevated IgE serum level. Group B-Healthy control group, SD-Standard deviation).

Table VI: Showing serum IgG level in respiratory allergy and control cases.

Groups	Serum IgG level			Mean \pm SD	t value	P value
	216 mg/dl	600-1600 mg/dl	>1600 mg/dl			
	No. (%)	No. (%)	No. (%)	mg/dl	A vs. B	A vs. B
Group A	1 (1.72 %)	57 (98.28 %)	0 (00.00 %)	1155.53 \pm 209.64	1.34	0.183
Group B	0 (00.00 %)	20 (100.00 %)	0 (0.00 %)	1225.15 \pm 167.182		

(Note: Group A-Patients group with elevated IgE serum level. Group B-Healthy control group, SD-Standard deviation).

DISCUSSION

Allergic diseases are mediated by IgE antibody. IgE bound on the surface of mast cells which interacts with allergens in sensitized person and triggers degranulation of mast cells which releases presynthesized mediators (histamine, neutral proteases, heparin) and synthesizes lipid mediators from membrane phospholipids and brings about collection of eosinophils, mast cells, Th2 cells and macrophages and sustains the response for several days.^[10,7]

Both genetic and environmental factors are responsible for it. Polymorphism of IL-4, IL-3, ADAM predisposes to hypereactivity to pollens, dust, mite, fungi and viruses.

Immune dysregulation including suppression of TH1 response, hyperreactivity of B cells and TH2 cells, decrease in T regulatory cells specially of CD4, CD 25, Fox P3 positive cells and good hygiene are other important factors.^[11,12]

Role of humoral immunity is also important in allergic diseases. Among the immunoglobulin deficiency IgAD is the foremost common ID for producing food allergy, atopic dermatitis and Asthma. IgA immunoglobulin binds to toxin, agglutinates bacteria and prevents its binding to mucosal epithelium. It also protects against IgE mediated food allergy and maintains tolerance to

food. Earlier study reported that 50 % patients of IgAD have allergy.^[13] Same type of study was also reported by that 58% patients of IgAD have some kind of atopic diseases.^[14] One study of 127 cases of IgAD showed that 50% patients of IgAD have recurrent respiratory infection, 28% had autoimmune diseases and 13 % had Asthma and allergy.^[15]

One of the study found that 83% patients of IgAD between the ages of 4 to 32 years suffered from allergic diseases like asthma, atopic dermatitis, allergic rhinitis, conjunctivitis, urticaria, food and drug Allergy.^[16] Recent study also have found that recurrent infection, allergic diseases and autoimmune diseases are seen in 84% patients of IgAD and incidence of Asthma and Allergic Rhinitis is 3.5 times high in IgAD persons than controls.^[17]

Surprisingly in our study we found IgAD in only two cases (3.45%) of allergic diseases. Our study supports the views of those who found mostly food allergy in IgAD cases.^[18] They did not report increased frequency of respiratory allergy. One case of IgGD also had Asthma and Rhinitis. We found that among immunoglobulin deficiency IgMD is more common (6.90%) in allergic disorder.

Similar to our study other workers in the past also found cases of selective IgMD having diarrhea, recurrent respiratory infection and dermatitis.^[19] Another study also reported that 14% cases of antibody deficiency present with Allergy.^[20] A study from Minnesota has shown that 55% of PID has coexisting atopic diseases.^[20] To our surprise complement C3D in our study was more common in which isolated C3D was seen in 13.79% and combined IgG and C3 deficiency was found in 1.72% and combined IgM, IgA, C3 deficiencies were found in 3.45% cases. Complement system protects host from invading microorganism by initiating inflammatory and phagocytic response and by promoting lysis.^[22]

It also stimulates respiratory burst in macrophage, neutrophils and eosinophils.^[23] Contrary to our findings some studies have reported that deficiency of C3a receptor or C3 decreases airway hyperresponsiveness and eosinophilia while C5D have opposite effect.^[24,25,26] But similar to our study a group of workers have found association between 4896 C/T in the C3 gene and childhood and adult Atopic asthma.^[27] C3 4896 C/T polymorphism was associated with adult bronchial asthma whereas 1526 G/A of C3 were associated with severity of childhood bronchial Asthma. They also identified high risk haplotype of the C3 gene of childhood and adult Asthma. C3D in human is strongly associated with recurrent bacterial infection involving ear, meningitis, lungs and manifests mostly in childhood because in adults opsonizing antibody develops which act as opsonins. These patients also have impaired primary and secondary immune response, abnormal IgG switching and reduced level of IgG2 and IgG4.^[28]

One study has shown that C3D produces defect in memory cells and functional defect of dendritic cells and regulatory T cells.^[29] It is well known that defect in regulatory T cells is responsible for allergic inflammation probably persistent inflammation due to immunoglobulin and complement deficiency drives to TH2 response and produce allergy.^[30]

Thus our study concludes that selective IgMD and C3D is more important for producing upper and lower respiratory allergic disease rather than IgAD. Study shows that IgM immunoglobulins and C3 also protects respiratory mucosa like IgA immunoglobulin. Hence in all patients of allergy, immunoglobulin and C3 level should be tested. It may possible that intravenous immunoglobulin may benefit the patients.

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