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Original Article

The Significance of Immunoglobulins in Cystic Fibrosis: Normal or High?

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ABSTRACT

Aim: Cystic fibrosis (CF) is characterized by local and chronic inflammation accompanied by increased neutrophil and macrophage counts, high elastase levels, and inflammatory cytokines due to impaired haemostasis. Changes in immunoglobulin (Ig) levels may occur due to recurrent chronic infections and may be associated with the deterioration of respiratory functions. In this study, we aimed to evaluate the interaction of high Ig levels with respiratory functions and chronic infections in CF.

Materials and Methods: The diagnosis of the patients CF was made in accordance with the "National CF Diagnosis and Treatment Guidelines". The socio-demographic characteristics, Ig values, and the pulmonary function tests were evaluated according to age group.

Results: A total of 107 patients were included in this study. The patients' median age was 65 (6-200) months. It was found that those patients with high IgG (p=0.01) and IgA (p<0.001) values had more moderate-to-severe respiratory function than those with normal values. Also, there was no statistically significant difference when the patients were compared for *P. aeruginosa* colonization using IgG levels (p=0.51), IgA levels (p=0.16) and IgM levels (p=0.34).

Conclusion: Elevated IgG and IgA levels in patients with CF may be an indirect indicator of deterioration in pulmonary function tests. There was no significant difference in IgG, IgA, and IgM levels for *P. aeruginosa* colonization. We recommend that the results of our study be supported by cohort studies.

Keywords: Cystic fibrosis, immunoglobulins, chronic inflammation, respiratory functions

Introduction

The cystic fibrosis (CF) disease is caused by a defect in the CF transmembrane regulator gene, which produces a protein called CF transmembrane conductance regulator (CFTR) (1,2).

CF is characterized by local and chronic inflammation accompanied by increased neutrophil and macrophage counts, high elastase, and inflammatory cytokines due to impaired haemostasis. Changes in immunoglobulin (Ig) levels may occur due to recurrent chronic infections and inflammation in the respiratory tract (3-6). Mutations which cause disruptions in CFTR function lead to abnormal mucus viscosity and disruptions in mucociliary clearance, allowing permanent airway colonization, especially with pathogenic bacteria. Chronic colonization with *Pseudomonas aeruginosa* and *Staphylococcus aureus* usually occurs in CF. An association between chronic colonization with *P. aeruginosa* and elevated IgG levels and subtypes has been demonstrated (3,7,8). Higher IgG

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and IgA levels have been associated with worse clinical outcomes and increased impairment of lung function in CF patients (4,9,10). A study conducted on child and adult CF patients found positive correlations between IgG and CRP, and negative correlations between CT scores and spirometry. The use of IgG as a marker for CF disease activity is supported by the available literature (11). Interestingly, hypogammaglobulinemia has been reported to be associated with less severe lung disease and therefore, better prognosis (4,5,9). Although many mechanisms have been blamed for the pathogenesis of polyclonal Ig activity in CF, the real mechanism is not clear. IgG levels may reflect a hyperimmune state with no apparent effect on recurrent infections, possibly causing damage to the airways (11). Given this context, this study aimed to evaluate the interaction of high Ig levels with respiratory functions and chronic infections in CF.

Materials and Methods

Patients who were diagnosed with CF between 6 months and 18 years old and followed up by the Department of Paediatric Chest Diseases between December 2012 and December 2021 were evaluated. Approval was obtained from the Dicle University Faculty of Medicine Non-Invasive Research Ethics Committee (number: 507, date: 15.12.2021). The diagnosis of CF was evaluated according to the "National CF Diagnosis and Treatment Guidelines": Clinical findings of CF disease or sibling history with CF or neonatal screening test positivity and at least one of the following: showing 2 mutations of CF or measurement of nasal potential difference compatible with CF or two different sweat test results performed on the same day are ≥60 mEq/Lt (12,13).

The socio-demographic characteristics routinely checked, single Ig values, and laboratory parameters from the previous three months were evaluated. Levels of IgG, IgA, IgM, and IgE were expressed as being within the normal or above (hyper) two standard deviations from the age-corrected mean. The results were compared to the age-related national normal population data (14). Routine C-reactive protein (CRP) and haemogram values taken at the same time as Igs were evaluated.

Body weight, height measurements, and pulmonary function tests (PFT) recorded simultaneously with the last laboratory tests of the patients were evaluated according to age groups. Nutritional status was evaluated by calculating weight for height (BGA) percentiles for those patients in the first two years of life, and body mass index (BMI) percentiles for those aged between three to 18 years. The nutritional status of the patients whose BGAs and BMIs were below the 10^{th} percentile were considered inadequate (13).

The patients were evaluated during clinical stability. Those patients with a background of intervention with gamma globulin, cancer immunosuppression therapy, transplant or those with acute lung infection, or any immunodeficiency such as humoral and/or cellular immunodeficiency were excluded from the Ig analysis (15).

The patients' forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC, and maximum expiratory flow at 50% of vital capacity (FEF_{25-75}) were assessed. The severity of the lung disease was evaluated according to the FEV_1 percentages. Cases with a FEV_1 of 81% and above were accepted as normal, between 51% and 80% as mild, between 31% and 50% as moderate, and less than 30% as severe (16). PFTs within the last three months were evaluated. The Ig levels and PFT were evaluated during clinical stability.

Those patients with bronchiectasis on chest tomography taken within the last six months, and *P. aeruginosa* and *S. aureus* colonization in their sputum cultures over three consecutive months in the last six months were included this study.

Statistical Analysis

SPSS-18 was used to conduct statistical analyses for this study. Visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods were employed to verify whether the variables conformed to the normal distribution. Descriptive statistics are given, including the median for numerical non-normally distributed variables and the mean for normally distributed variables. The chi-square test (χ^2) was used to compare categorical variables. Correlation analyses were calculated using the Pearson test.

Results

The clinical characteristics and laboratory parameters of the patients are shown in Table I. A total of 107 patients were included in this study. Of these, 61 patients were male (57%) and their median age was 65 (6-200) months. Fourty-eight patients were diagnosed via new-born screening (44.9%). Genetic testing was carried out on 102 patients. Genetic mutation was detected in 82 patients (76.7%). Homozygous 3130delA/3130delA was the most common mutation. Chronic *P. aeruginosa* colonization was seen in 17 patients (15.8%). Median CRP was 0.07 (IQR=0.24).

The evaluation of IgG, IgA, and IgM levels according to the age of the patients is shown in Table II. Ig values were found to be normal in most of the patients. Eighty-three of the patients were below 10 years and 9 (10.8%) of them had high IgG.

The comparison between different parameters and IgG levels is shown in Table III. Sixty-four of the patients could perform PFTs. Three patients (5.6%) had normal to mild FEV_1 and high IgG. Also, three patients (30%) had moderate to severe FEV_1 and high IgG. This was statistically different (p=0.01). Forty patients were below 10 years of age and could perform a PFT. Four out of 40 patients (10%) had high IgG. Two of the other 24 patients (8%) who were above 10 years of age had high IgG. This was not statistically different (p=0.76). Nutritional status was inadequate in 25 patients. Five out of 25 patients (20%) had high IgG. Also, 6 out of 82 patients (7.6%) with a normal nutritional status had high IgG. This was not statistically different (p=0.08).

The interactions between the parameters and IgA levels are shown in Table IV. There was a significant difference between the groups in terms of FEV_1 (p<0.001). It was determined that those patients with high IgA levels had more moderate-to-severe respiratory function.

The interactions between the parameters and IgM levels are shown in Table V. There was no statistically significant difference between the groups in terms of FEV_1 (p=0.2), *P. aeruginosa* colonization (p=0.34), nutritional status (p=0.73), or age (below or above 10 years old) (p=0.18).

The relationships between Ig levels and CRP, absolute neutrophil, and eosinophil count are shown in Table VI. There was no significant correlation between increases in Ig levels and these laboratory parameters.

Discussion

Ig levels may be elevated because of aging, reflecting a deterioration in lung function and chronic lung infections in patients with CF (4,5,17). Therefore, monitoring IgG and IgA levels in CF patients may be useful for this purpose. In this study, the interaction of Ig changes with both *P. aeruginosa* colonization and PFT were evaluated in patients with CF.

Various mutations were found in 75% of the patients in the study that was conducted by Onay et al. (18). The most common mutation was the delta F508 mutation (18.8%), and the second most common mutation was 1677delTA (7.3%). Erdem et al. (19) found various mutations in 75% of their patients, and the delta F508 homozygous mutation

Table I. Clinical characteristics and laboratory parameters of the patients

Age, median (min.-max.), months		65 (6-200)
Age at diagnosis (months), median (min.-max.)		4 (0-244)
Follow-up durations (months), n (IQR)*		98 (51)
Gender, male/female (%)		57/43
Consanguineous marriage, n (%)		58 (54.2)
Newborn screening diagnosis, n (%)		48 (44.9)
Genetic mutation detected, n (%)		82 (76.7)
Most common mutation	Homozygous 3130delA/3130delA, n (%)	8 (7.5)
	Homozygous delta F508/delta F508, n (%)	7 (6.5)
Median FEV_1** (IQR)		89 (33)
Chronic *P. aeruginosa* colonization n (%)		17 (15.8)
Chronic *S. aureus* colonization n (%)		7 (6.5)
Median number of polymorphonuclear neutrophils (IQR)/mm^3		4000 (3580)
Median CRP, mg/dL (IQR)**		0.07 (0.24)
Malabsorption***, n (%)		18 (30.7)
The rate of bronchiectasis, n (%)		24 (22.4)
Age of first bronchiectasis occurrence, mean ± Standard deviation		102±39.4
Nutritional status****, inadequate, n (%)		25 (23.4)

*IQR: Interquartile range
**Sixty-four patients were able to perform pulmonary function test
*** Stool elastase >200 microgram/day was considered as malabsorption.
****Nutritional status was evaluated by calculating weight for height percentiles for patients in the first two years of age, and body mass index percentiles for patients aged between three to 18 years
min.-max.: Minimum-maximum, FEV_1: Forced expiratory volume in 1 second, CRP: C-reactive protein

(12.5%) was found most frequently. In our study, genetic mutation was detected in 82% of the patients. The most common mutations were homozygous 3130delA/3130delA (7.5%) and homozygous delta F508/delta F508 (6.5%). Due to the heterogeneous structure of the Turkish population, different regional genotypic results have been reported in studies. Due to these different genotypic features, genotype results in patients with CF in our country may vary locally, but in general, the homozygous delta F508/delta F508 mutations are common.

Moss's (3) study found that patients with CF had higher IgG levels than the control groups. Hypergammaglobulinemia was detected in 34.2% of the cases (3). During follow-up in a cohort study, Proesmans et al. (17) also found that the rate of hypergammaglobulinemia had increased from 16% to 25% over the years. Garside et al. (4) found hypergammaglobulinemia in 7.8% of CF patients below 18 years of age. In addition, this rate was found to be 1.2% in patients below the age of 10 and 15.5% in those above the age of 10, and this difference was significant (4). In the study by Matthews et al. (5), the rate of hypergammaglobulinemia in the paediatric population was found to be 6.5% for those below the age of 10, and 24.7% for those above the age of 10, and this was found to be statistically significant. The rate of hypergammaglobulinemia was found to be greater in those studies conducted on adults. Hassan et al. (20) found this rate to be 69% between the ages of 17 and 49 years and Pressler et al. (21) found it to be 32% between the ages of one and 36 years. We found that 11 (10.3%) of our patients had hypergammaglobulinemia and our results were very similar to other studies conducted with children. However, in terms of hypergammaglobulinemia values, no statistically significant difference was found between those patients below or above 10 years of age who were able to perform PFTs. In fact, the median age of our patients was 65 months. We know that chronic infections and inflammation are relatively rare at this age (22). It was stated by Ortega-López et al. (10) that hypergammaglobulinemia was the result of chronic airway inflammation due to chronic infection. Also, adult patients were not included in our study. The

Table II. Number and rates of cases with normal or high immunoglobulin levels by age groups

Ig values	Categorical age	Normal* n (%)	High* n (%)
IgG	Below 10 years, n=83	74 (89.2)	9 (10.8)
	Between 10-18 years, n=24	22 (91.7)	2 (8.3)
IgA	Below 10 years, n=83	74 (89.2)	9 (10.8)
	Between 10-18 years, n=24	19 (79.2)	5 (20.8)
IgM	Below 10 years, n=83	79 (95.2)	4 (4.8)
	Between 10-18 years, n=24	21 (87.5)	3 (12.5)
IgE	0-18 years, n=107	104 (97.2)	3 (2.8)

*Levels of IgG, IgM, IgA were assessed as being normal or above (hyper) the standard deviations from the age-corrected mean
Ig: Immunoglobulin

Table III. Interaction between the parameters and IgG levels

Parameters		Normal IgG n (%)	High IgG n (%)	p-value
FEV_1*	Normal to mild, n=54	51 (94.4)	(5.6)	0.01
	Moderate to severe, n=10	7 (70)	3 (30)	
Age*	Below 10 years old and those who could do pulmonary function test, n=40	36 (90)	4 (10)	0.76
	Above 10 years old and those who could do pulmonary function test, n=24	22 (91.7)	2 (8.3)	
Nutritional status, inadequate	Yes, n=25	20 (80)	5 (20)	0.08
	No, n=82	76 (92.7)	6 (7.3)	
Malabsorption**	Yes, n=18	15 (83.3)	3 (16.7)	0.32
	No, n=89	81 (91)	8 (9)	
P. aeruginosa colonization	Yes, n=17	16 (94.1)	1 (5.9)	0.51
	No, n=90	80 (88.9)	10 (11.1)	
S. aureus colonization	Yes, n=7	5 (71.4)	2 (28.6)	0.1
	No, n=100	91 (91)	9 (9)	
Bronchiectasis***	Yes, n=24	19 (79.1)	5 (20.9)	-
	No, n=7	7 (100)	0 (0)	

*Only 64 patients were able to perform pulmonary function tests.
**Stool elastase >200 microgram/day was considered as malabsorption.
***Computed tomography was performed in 26 of the patients in the normal IgG group with suspected bronchiectasis, and in 5 of the patients in the high IgG group
FEV_1: Forced expiratory volume in 1 second, Ig: Immunoglobulin

incidence of hypergammaglobulinemia is less common in children than in adults. This has been attributed to less *P. aeruginosa* colonization and the treatment of inflammation with antibiotics (4,5).

Further, it has been shown that CF patients with high IgG levels had more severe clinical outcomes and worse lung functions compared to those with normal levels (4,9). In our study, we found that lung functions were affected more severely in patients with hypergammaglobulinemia. This supports the results observed during the literature review. In addition, when evaluated in terms of *P. aeruginosa* colonization, no significant difference was found between the groups with or without hypergammaglobulinemia. Bronchiectasis was detected in all patients with hypergammaglobulinemia. It was difficult to evaluate the difference between colonization and the age groups based on our study. Cohort studies would be able to provide more accurate information. Our study supports previous findings that an increase in IgG may be an indicator of lung function damage (9,23).

It has been stated by Aanaes et al. (24) that IgA elevation is significant when *P. aeruginosa* is present in respiratory

Table IV. Interaction between the parameters and IgA levels

		Normal IgA n (%)	**High IgA n (%)**	**p-value**
FEV_1*	Normal to mild, n= 54	47 (87.1)	7 (12.9)	<0.001
	Moderate to severe, n=10	3 (30)	7 (70)	
Nutritional status, inadequate	Yes, n=25	20 (80)	5 (20)	0.24
	No, n=82	73 (89)	9 (11)	
P. aeruginosa colonization	Yes, n=17	13 (76.5)	4 (23.5)	0.16
	No, n=90	80 (88.9)	10 (11.1)	
Malabsorption**	Yes, n=18	14 (77.8)	4 (22.2)	0.2
	No, n=89	79 (88.8)	10 (11.2)	
S. aureus colonization	Yes, n=7	6 (85.7)	1 (14.3)	-
	No, n=100	87 (87)	13 (13)	
Age	Below 10 years, n=83	74 (89.2)	9 (10.8)	0.21
	Above 10 years, n=24	19 (79.2)	5 (20.8)	

*Only 64 patients were able to perform pulmonary function tests.
**Stool elastase >200 microgram/day was considered as malabsorption
FEV_1: Forced expiratory volume in 1 second, Ig: Immunoglobulin

Table V. Interaction between the parameters and IgM levels

		Normal IgM n (%)	**High IgM n (%)**	**p-value**
FEV_1*	Normal to mild, n=53	50 (94.3)	3 (5.7)	0.2
	Moderate to severe, n=11	10 (90.9)	1 (9.1)	
Nutritional status, inadequate	Yes, n=25	23 (92)	2 (8)	0.73
	No, n=82	77 (93.9)	5 (6.1)	
Malabsorption**	Yes, n=18	16 (88.9)	2 (11.1)	0.39
	No, n=89	84 (94.4)	5 (5.6)	
P. aeruginosa colonization	Yes, n=17	15 (88.2)	2 (11.8)	0.34
	No, n=90	85 (94.4)	5 (5.6)	
S. aureus colonization	Yes, n=7	6 (85.7)	1 (14.3)	-
	No, n=100	94 (94)	6 (6)	
Age	Below 10 years, n=83	79 (95.2)	4 (4.8)	0.18
	Above 10 years, n=24	21 (87.5)	3 (12.5)	

*Only 64 patients were able to perform pulmonary function tests.
**Stool elastase >200 microgram/day was considered as malabsorption
FEV_1: Forced expiratory volume in 1 second, Ig: Immunoglobulin

tract secretions and is an indicator of *P. aeruginosa* infection. In another study, it was found that the group with high IgA levels had a higher rate of *P. aeruginosa* colonization (71.4%) than the group with normal IgA (23.5%). Also, it was found that those patients with high IgA levels had a higher rate of severe FEV_1 classification (71.4%) than the group with normal IgA (8.8%) (10). Our study was not a cohort study. The median age of the patients was 65 months, and they were part of the age group with lesser bronchiectasis and chronic colonization. In our study, no significant difference was found in terms of *P. aeruginosa* colonization and IgA levels. Interestingly, it was observed that IgA elevation could be accompanied by a moderate to severe deterioration in PFT.

In a study evaluating 53 patients with CF, high levels of IgM were found in seven patients (13%). A similar rate of severe involvement in FEV_1 was found between the high IgM group (18.8%) and the normal group (28.6%). High IgM levels were detected in one patient below 10 years of age (14.3%) and in four patients above 10 years (57.1%). *P. aeruginosa* colonization (>three months) was detected in six patients with high IgM (18.8%) and in seven patients with normal values (100%). In addition, bronchiectasis was detected in 10 patients with high IgM (29.4%) and in six patients with normal IgM (85.7%). Malnutrition was observed in 11 patients with normal IgM (34.4%) and in three patients with high IgM (42.8%), all of whom were below 18 years of age. The significance of these differences was not mentioned (10). In our study, no significant association was found between FEV_1 level, age, nutritional status, *P. aeruginosa* colonization, and IgM elevation. Further research is needed to explain the importance of IgM elevation in CF. It is difficult to comment on this subject with the current literature knowledge.

Gur et al. (25) found a relationship between IgG and CRP levels in adult patients with CF. CRP is a marker for inflammation which increases during pulmonary exacerbations and decreases after antibiotic therapy (26). Even in stable patients, higher CRP levels were associated with worse FEV_1 values (27). Higher IgG and CRP levels were found to be associated with disease severity (26,28). We did not find a significant relationship between high IgG levels and CRP or neutrophil counts in our patients during clinical stability.

Table VI. The relationship between Ig levels and CRP, absolute neutrophil, and eosinophil count

		C-reactive protein (mg/dL)	Absolute neutrophil count	Absolute eosinophil count
IgG	r	0.02	-0.19	0.15
	p	0.86	0.87	0.2
IgA	r	0.18	0.12	-0.19
	p	0.1	0.17	0.08
IgM	r	0.18	0.18	-0.1
	p	0.1	0.09	0.33

Ig: Immunoglobulin, CRP: C-reactive protein

Study Limitations

The main limitations of our study are the relatively small number of patients and its single-centre nature. The significance of some differences could provide a more accurate assessment in larger patient groups. Additionally, when studies are limited to children, ensuring homogeneity among groups becomes difficult. We believe that cohort studies will yield more accurate results. Since our study is prospective, it is difficult to evaluate the significance between acute *P. aeruginosa* infections and Ig levels. The effect of low Ig levels on the airways was not evaluated in our study. We were also unable to assess changes in IgG levels over time, due to our study's nature. We did not have the subtypes of IgG in our data, and therefore, could not evaluate correlations between subtypes of IgG and disease severity. Levels of other inflammatory markers, such as cytokines, were not available.

Conclusion

Elevated IgG levels in patients with CF may be an indirect indicator of deterioration in PFT. There was no significant difference between *P. aeruginosa* colonization and IgA and IgG elevation. We surmise that an increase in IgA may be an indicator of a deterioration in PFT. We recommend that the results of our study be supported by larger population and cohort studies.

Ethics

Ethics Committee Approval: Approval was obtained from the Dicle University Faculty of Medicine Non-Invasive Research Ethics Committee (number: 507, date: 15.12.2021).

Informed Consent: Informed consents were not required because the study was conducted retrospectively.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: V.Ş., A.K., Design: V.Ş., A.K., Data Collection and/or Processing: S.S., Writing: A.K., M.T.

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