

Georgian Cohort Study on Allergic Bronchopulmonary Aspergillosis in Children with Cystic Fibrosis

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ABSTRACT

Background: Cystic fibrosis (CF) is a rare genetic disease that affects the lungs, pancreas, and other organs, leading to thick mucus, repeated infections, and long-term health problems. As treatments improve and children with CF live longer, allergic conditions like allergic bronchopulmonary aspergillosis (ABPA), caused by the fungus *Aspergillus fumigatus*, need early detection. The Georgian National CF program does not include specific tests for detecting ABPA, making it more challenging to diagnose and manage this condition promptly.

Objectives: This study aimed to determine the prevalence of elevated IgE and/or *Aspergillus* sensitization in the pediatric CF population and evaluate their association with allergic or infectious complications, including suspected ABPA.

Methods: In this study, we followed 63 Georgian children with cystic fibrosis (CF) between 2022 and 2024, measuring total IgE and *Aspergillus*-specific IgG levels to assess for allergic sensitization and possible allergic bronchopulmonary aspergillosis (ABPA). Several children showed elevated levels, including one confirmed case of ABPA that was successfully treated.

Results: During the study, 63 out of 86 children with CF had at least one total IgE and *Aspergillus*-specific IgG test.

Conclusions: Our findings indicate that CF care in Georgia would benefit from incorporating regular ABPA testing, ensuring timely treatments are available, and providing more comprehensive support for children and their families.

Keywords: Allergic bronchopulmonary aspergillosis; *Aspergillus fumigatus*; cystic fibrosis.

BACKGROUND

Cystic fibrosis (CF) is a chronic, autosomal-recessive disease caused by mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene.¹ The CFTR protein functions as a chloride channel in the apical membrane of epithelial cells. It plays a significant role in electrolyte and fluid secretion and absorption, helping to maintain a balance of salt and water on many epithelial surfaces, including the airway lining.² When defective or absent CFTR, this ionic dysregulation produces abnormally thick, viscous secretions that impair mucociliary clearance and lead to multisystem complications such as recurrent respiratory tract infections, pancreatic insufficiency, malabsorption, infertility, etc.¹

With better ways to diagnose and treat cystic fibrosis (CF), people with CF now live much longer than before. As a result, allergic and immune-related problems — often overlooked in the past — are now becoming increasingly critical. One of these is allergic bronchopulmonary aspergillosis (ABPA), a complex allergic reaction to the fungus *Aspergillus fumigatus*, which grows in the airways. If ABPA is not noticed or treated, it can worsen lung function and cause permanent damage, such as bronchiectasis.^{3,4}

Eighty-six children with CF are registered in the National Monitoring Program of Rare Diseases (Georgia), managed by the Medical Genetics and Laboratory Diagnostics Center, Ltd. This program tracks 33 rare diseases in children under 18 and provides comprehensive care, including multiple laboratory tests and imaging studies.

However, the monitoring program for CF only includes some basic tests, such as abdominal ultrasound, kidney and liver function tests, complete blood count (CBC), sputum culture, and blood electrolyte levels. Many other essential tests — such as detailed immune system checks, fungal blood tests, and allergen-specific tests — are not included. This means families often have to pay for these extra.^{5,6}

To address this issue, we conducted a prospective observational study between 2022 and 2024, measuring total immunoglobulin E (IgE) and *Aspergillus*-specific immunoglobulin G (IgG) levels in Georgian children with cystic fibrosis (CF). These tests are essential for detecting allergic bronchopulmonary aspergillosis (ABPA) and other fungal complications, which are common but often missed in CF care.⁷⁻⁹

In the present study, we aimed to generate evidence supporting the development of targeted, evidence-based recommendations for improving ABPA screening, diagnosis, and monitoring practices within Georgia's national cystic fibrosis (CF) program.

METHODS

Our study included pediatric patients with cystic fibrosis (CF), defined as individuals under 18 years of age who were officially registered in the National Monitoring Program for Rare Diseases, managed by the Medical Genetics and Laboratory Diagnostics Center, Ltd. (Tbilisi, Georgia). The study was conducted between January 2022 and December 2024. Ethical



approval was obtained from the institutional review board, and written informed consent was obtained from parents or legal guardians before participation in accordance with national and international ethical standards.

Blood samples were collected during outpatient visits at the CF clinic. After venipuncture, 3 mL of blood was drawn into EDTA tubes for further analysis. Samples were collected and stored, and they were analyzed every four months. Serum total immunoglobulin E (IgE) and Aspergillus-specific immunoglobulin G (IgG) levels were measured using the ELISA immunofluorescence method, following the reagent manufacturer's instructions and the national reference laboratory's validated protocols. We followed quality control steps to ensure the test results were reliable and consistent.

Patients who permanently left the country were considered lost to follow-up and excluded from repeated testing and longitudinal analysis. Clinical and demographic data, including age, sex, prior microbiological findings, and relevant medical history, were extracted from patient records to support the interpretation of immunologic test results. All data were anonymized and securely stored to maintain patient confidentiality throughout the study.

Immunologic testing and reference ranges

Total serum immunoglobulin E (IgE) and Aspergillus fumigatus-specific immunoglobulin G (IgG) levels were measured in all participating patients as a part of our project. These tests are not included in Georgia's National Program of Rare Diseases.

Age-specific reference ranges were used to interpret results. For Aspergillus fumigatus-specific IgG pediatric reference limits were used to improve sensitivity. The age-specific upper limits for Aspergillus-specific IgG (IU/ml) are as follows: <1.6 IU/ml for newborns, <2.4 IU/ml for 0–8 months, <2.7 IU/ml for 8 months–3 years, and <4.9 IU/ml for children older than 3 years (Tab.1).

TABLE 1. Aspergillus-specific IgG levels, pediatric reference limits

Age group	Upper limit (IU/ml)
Newborn	< 1.6
0-8 months	< 2.4
8 months-3 years	< 2.7
>3 years	<4.9

The age-specific upper limits for total IgE (IU/ml) are as follows: <12 IU/ml for 0–6 months, <30 IU/ml for 6–12 months, <45 IU/ml for 1–3 years, <70 IU/ml for 4–6 years, <90 IU/ml for 7–9 years, <120 IU/ml for 10–15 years, and <130 IU/ml for individuals older than 15 years (Tab.2).

We monitored IgE dynamics in patients with repeated measurements and reviewed allergen test results and clinical records for patients with highly elevated IgE (>500 IU/mL) or positive Aspergillus-specific IgG. Treatment decisions were

made according to the Brompton Hospital-based CF management guidelines.⁵ Antifungal and/or corticosteroid therapy was prescribed for patients with clinically suspected allergic bronchopulmonary aspergillosis (ABPA).

TABLE 2. Total IgE levels, pediatric reference levels

Age group	Upper limit (IU/ml)
0-6 months	< 12
6-12 months	< 30
1-3 years	< 45
4-6 years	<70
7-9 years	< 90
10-15 years	< 120
>15 years	< 130
1-3 years	< 45
4-6 years	<70

RESULTS

During the study, 63 out of 86 children with CF had at least one total IgE and Aspergillus-specific IgG test.

A 7-month-old infant showed elevated Aspergillus-specific IgG (2.96 IU/mL) and total IgE (87.8 IU/mL), along with increased tissue transglutaminase (20.6 U/mL); however, further evaluation was not completed because the family emigrated.

In two patients, total IgE was persistently elevated across two measurements:

- A 14-year-old boy (with a CF sibling with normal IgE) initially recorded total IgE levels of 399.4 IU/mL, which later decreased to 154.6 IU/mL;
- A 2-year-old boy initially showed 103.3 IU/mL levels and 149.5 IU/mL on follow-up. Unfortunately, no additional allergen workup was performed in these cases due to financial issues.

Additional cases with elevated total IgE included: 99.7 IU/mL (2-year-old), 150.7 IU/mL (16-year-old), 60.4 IU/mL (1-year-old), 193.2 IU/mL (5-year-old), 57.1 IU/mL (11-month-old), 58.2 IU/mL (9-month-old).

Notably, one patient with total IgE levels 207.7 IU/mL — diagnosed at 12 years of age with CF (missed by newborn screening), undergoing growth hormone replacement therapy, and found to be allergic to dust and tree pollen based on allergen testing — was also included.

Another critical case involved a 14-year-old girl with a total IgE level of 1,500 IU/mL and an Aspergillus-specific IgG level of 5.5 IU/mL. She underwent extensive allergen testing (ALEX2 multiplex assay), which confirmed sensitization to tree pollen,

weed pollen, fungal spores, bee venom, ant venom, wasp venom, and *Aspergillus fumigatus*.

After the diagnosis of allergic bronchopulmonary aspergillosis (ABPA), treatment was started based on Brompton Hospital-based guidelines, using oral prednisolone (beginning at 2 mg/kg/day, maximum 40 mg) tapered over 4–8 weeks, alongside oral itraconazole (due to the unavailability of posaconazole in Georgia). Antifungal therapy typically continued for 2–4 weeks after steroid completion, with prolonged antifungal use required in some patients due to recurrent ABPA.

DISCUSSION

Our study highlights key aspects of CF care in Georgia and provides valuable insights into *Aspergillus* allergies and IgE levels in children with CF in Georgia.

First, the high number of patients with elevated total IgE suggests that allergic problems, including possible allergic bronchopulmonary aspergillosis (ABPA), may often be overlooked or inadequately treated in this group. While high total IgE alone is not enough for diagnosis, consistently elevated levels mean that further testing is needed, such as specific IgE or IgG tests, skin prick tests, or advanced allergy diagnostics.⁵ These tests are often financially inaccessible for families in Georgia, as the national rare diseases program does not cover them and requires direct payment by parents. This financial barrier highlights a critical gap in the healthcare system, which may result in missed or delayed diagnoses.

Second, the case of the 14-year-old girl with ABPA shows that Georgia needs clear, practical care plans made for local CF patients. While the Brompton Hospital guidelines are helpful, they must be adjusted for Georgia due to the unavailability of certain medicines (such as posaconazole) and limited healthcare resources. Good care requires a team effort, with lung doctors, allergy doctors, infection specialists, and pharmacists working together to give the best treatment for ABPA.⁶

Regularly monitoring patients is essential, rather than relying solely on a single test. ABPA is considered in remission when the patient is stable and total IgE levels stay the same or decrease (with less than a 50% increase from the starting level) for at least six months after stopping steroid and antifungal treatment. Regular follow-up — ideally every three months in the first year and every six months thereafter — should include a comprehensive clinical check-up, lung function tests (spirometry), repeat total IgE blood tests, and chest scans as needed. It is also important to note that antifungal medications are not currently recommended for prevention,

as they carry potential side effects and have not been proven to offer a benefit.

In addition, factors such as patient age, underlying bacterial lung colonization, genetic background, and individual immune status influence the risk of *Aspergillus* sensitization in CF patients. Our findings support earlier studies showing that CF patients, especially those with allergies, are more likely to develop sensitivities to fungi and mold. However, the interactions between CF, allergies, and the immune system remain incompletely understood. Larger studies, including genetic and microbiome data, are needed to clarify these connections and improve patient care.

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REFERENCES

- Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the Cystic Fibrosis Foundation. *J Pediatr*. 2017;181S:S4–S15.e1.
- Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. *N Engl J Med*. 2005;352(19):1992–2001.
- Stevens DA, Moss RB, Kurup VP, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis—state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis*. 2003;37(Suppl 3):S225–S264.
- Smith R, Patel K, Jones M, et al. Health system challenges in cystic fibrosis care: a global perspective. *J Cyst Fibros*. 2021;20(5):654–662.
- Georgian Ministry of Health. Annual Report on National Rare Disorder Programs. Tbilisi, Georgia; 2023.
- Stevens DA, Moss RB, Kurup VP, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis: state of the art. *Med Mycol*. 2016;54(6):580–587.
- Baatenburg de Jong A, Braunstahl GJ, Rijkers GT, et al. Serologic markers for allergic bronchopulmonary aspergillosis in cystic fibrosis patients. *Clin Exp Allergy*. 2020;50(3):334–343.
- Elborn JS. Cystic fibrosis. *Lancet*. 2016;388(10059):2519–2531.
- Greenberger PA. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol*. 2002;110(5):685–692.