

## Case Report

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# Later Diagnosis of Cystic Fibrosis with Negative Newborn Screen: Importance of the Clinical Picture

Batoczki B<sup>1</sup>, Galvis AE<sup>1,2,3\*</sup>, Pecson IS<sup>2</sup>, Meyers J<sup>1</sup>, Nakamura C<sup>1,2</sup>

<sup>1</sup>University of Nevada Las Vegas School of Medicine, Department of Pediatrics, Las Vegas, Nevada, USA

<sup>2</sup>Children's Lung Specialists, Las Vegas, Nevada, USA

<sup>3</sup>Children's Hospital of Orange County Department of Infectious Disease, Orange, California, USA

\***Corresponding Author:** Dr. Alvaro Galvis, Children's Hospital of Orange County, Department of Infectious Disease 1201 W. La Veta Ave. Orange, CA 92868, USA, E-mail: [draegalvis@gmail.com](mailto:draegalvis@gmail.com)

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## Abstract

Cystic fibrosis (CF) is the most common inherited life-limiting disorder among Caucasians. The implementation of CF newborn screening has enabled early diagnosis and prompt treatment onset. However, several factors may affect circulating levels of immunoreactive trypsinogen leading to a normal CF newborn screen. This case aims to highlight the importance of taking clinical manifestations as a strong factor for the diagnosis of CF even in the presence of a negative newborn screen. This may allow early referral to a specialized CF center where the onset of appropriate treatment can be implemented, thereby positively impacting the course of the disease.

**Keywords:** Cystic fibrosis; Newborn screen

## 1. Introduction

Cystic fibrosis (CF) is an autosomal recessive inherited disease and the most common life-limiting disorder among Caucasians. It affects nearly 30,000 children in the United States and almost 70,000 individuals worldwide [1, 2]. CF is characterized by mutations in the CF transmembrane regulator (CFTR) gene, which encodes a membrane chloride channel, causing dysregulation of ion and water exchange. This results in decrease of airway surface liquid and an increase in abnormally thick mucus, which is consequential in a wide range of clinical manifestations including sinopulmonary, gastrointestinal, and reproductive [2, 3].

Alongside with advances in CF therapies, an improvement in survival of patients affected by CF has evolved. Currently, the median survival outcome approaches the age of 40 years old. In addition, new mutation-specific medications directed at the defective CFTR protein have generated an important shift in the current management of

CF as well as its morbidity and mortality rates [2]. At present, newborn screening is frequently implemented for CF diagnosis, which allow for an early identification of the disease even before the onset of symptoms [4]. In this report, we present the case of a 3-year-old patient whose newborn screening failed to diagnose CF, resulting in the delay of referral to a CF-specialized center for appropriate treatment initiation.

## **2. Case Report**

A 3-year-old Caucasian female was brought to the pulmonology clinic for evaluation of asthma following hospitalization. This was the patient's second hospital visit within one month. In her previous hospitalization, she was observed for 3 days due to cough, desaturations, wheezing, and labored breathing. A chest X-ray showed bilateral air space infiltrate. She was started on a course of antibiotics and given breathing treatments. O<sub>2</sub> saturation was 87% on room air. She was put on oxygen and eventually discharged on prednisolone and albuterol. However, she continued to show low O<sub>2</sub> saturation and therefore, resulted in her readmission 5 days later. At the time of admission, the physical exam was remarkable for bilateral wheezing and abdominal distension.

Laboratory workup showed a total WBC count of  $37 \times 10^3/\text{mcL}$ , ALP 188 units/L, ALT 108 units/L, AST 51 units/L. In addition, her fecal occult blood test was positive. The results of the celiac panel, stool culture, ova and parasite, WBC and Rotavirus antigen tests came back negative. The patient was kept on room air and started on albuterol every 3 hours, which was transitioned to every 4 hours. Her O<sub>2</sub> saturation increased to 95% and she was discharged on an inhaled corticosteroid BID, albuterol PRN and a short tapering course of oral corticosteroids.

The patient was born at 37 weeks with meconium-stained fluid; a first newborn screen reported an IRT level of 101 ng/mL 2 days after birth (normal < 90 ng/mL). The repeat IRT reported 80.2 ng/mL and no further action was taken at that time. Past medical history was significant for allergic rhinitis and asthma, hyponatremic dehydration, gastroesophageal reflux, cholelithiasis, and idiopathic acute pancreatitis during infancy. She had a history of loose, oily and foul-smelling stools. On physical examination, her weight and height were 14.42 kg (58th percentile) and 90.17 cm (13th percentile), while the rest of the exam appeared unremarkable. A sweat chloride test was ordered and was positive at 102 mmol/l. The CF DNA analysis was homozygous for delta F508 mutation.

## **3. Discussion**

CF-related lung disease often has an early onset even before the appearance of clinical manifestations. It is characterized by impaired mucociliary clearance and chronic neutrophilic inflammation leading to a vicious cycle of obstruction, inflammation, and infection that consequently results in the development of bronchiectasis, respiratory failure and death [2, 4-6]. Meconium ileus, bleeding due to vitamin K deficiency, and prolonged jaundice may be present during the neonatal period. During infancy, hyponatremic and hypochloremic alkalotic dehydration can occur in some cases as a result of salt loss through sweat [7]. Many patients with CF have pancreatic exocrine insufficiency, resulting in malabsorption of fat, protein and fat-soluble vitamins. In addition, they may experience constipation, distal intestinal obstruction syndrome, rectal prolapse, and hepatobiliary disease and gallstones [7, 8].

The postnatal diagnosis of CF must be based on the presence of one or more characteristic clinical features, the history of a sibling with CF, or a positive newborn screening test as well as laboratory evidence of an abnormality in the CFTR gene, such as biological evidence of channel dysfunction (sweat test) or identification of a CF disease-causing mutation on each chromosome [3]. The measurement of immunoreactive trypsinogen is used as the primary screening tool for CF. After the identification of an abnormal IRT, a DNA testing (IRT/DNA) or a repeat IRT measurement, obtaining a second blood sample after 2 weeks (IRT/IRT) should take place; nonetheless, several factors have shown to affect the circulating levels of IRT [3, 5]. A sweat chloride concentration > 60 mmol/L is considered abnormal [1]. When the sweat chloride value is in the intermediate range DNA analysis can be used to help establish a diagnosis of CF. The identification of two CF-causing mutations makes a diagnosis for CF, on the other hand, the presence of one or no CF-causing mutation plus clinical manifestations of CFTR dysfunction will place the individual at risk of CF and the sweat chloride test should be repeated in infants by age 2-6 months and immediately in older individuals. If sweat chloride remains in the intermediate range the patient should be referred to a CF care center for further evaluation where ancillary testing can clarify the diagnosis, being clinical signs and symptoms of CF, laboratory evidence of pancreatic insufficiency or a positive culture for a CF associated pathogen such as *P. aeruginosa* strongly indicative for CF [3].

Early onset of treatment in CF patients should be implemented as evidence has shown the presence of structural and functional abnormalities even before symptoms appear [4]. Current treatments for CF consist of a multidisciplinary approach—integration of airway clearance techniques, physical activity and nutritional support to help maintain pulmonary health, use of drug therapy including mucolytics (dornase alpha), hydration therapy, antibiotics, CFTR modulator therapy, and psychosocial assistance. Transplantation is an established therapy for end-stage lung and liver disease in CF patients [9].

#### 4. Conclusion

Our case has aimed to highlight the importance of taking clinical manifestations as a strong factor for the diagnosis of CF even in the presence of a negative initial test. This will be of great assistance as the patients can be immediately referred to a specialized CF center, whereby the onset of appropriate treatment can be done that would positively impact the course of the disease.

#### Conflict of Interest

None

#### References

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