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Case Report

Late Diagnosis of Cystic Fibrosis in a Child with a Negative Neonatal Screening Test

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Abstract

Cystic fibrosis (CF) is an autosomal recessive genetic disease in which dysfunction of the CFTR gene (cystic fibrosis transmembrane conductance regulator), related to transmembrane chlorine drive [1]. This leads to the production of thicker secretions that occlude light from the structures involved, causing inflammation and compromising the function of the affected organs. The respiratory and digestive systems are the main affected by this pathology, generating growth deficits, chronic respiratory infections, progressive damage to lung tissue. As it is a multisystemic disease, early treatment aided by the screening test showed a better outcome when compared to a treatment initiated after late diagnosis [2-4]. The various neonatal screening tests (TTN) for cystic fibrosis present high sensitivity and specificity, but false-positive and false-negative may occur [5]. In this case report, we describe a preschool that had a negative neonatal screening test and its diagnosis occurred after 2 years of age in the investigation of a hepatomegaly. However, the child had pulmonary symptoms from the first days of life that were being treated as bronchial hyperresponsiveness and later, as asthma. In the diagnostic investigation, the first dosage of chlorine in sweat has already demonstrated an important elevation. Enzymatic treatment was initiated, as well as support for the respiratory condition, with slow and progressive improvement of respiratory symptoms, being discharged for outpatient follow-up. Thus, although the neonatal screening test for cystic fibrosis has high sensitivity, it does not replace the chlorine dosage in sweat in children with very suggestive symptoms.

Keywords: *Cystic Fibrosis; Neonatal Screening; Hepatomegaly; Lung Disease*

Introduction

Cystic fibrosis is an autosomal recessive disorder with involvement of several organs [1]. Although lung disease is the main responsible for morbidity and mortality, some children have gastrointestinal tract involvement (GiT). The manifestations of GiT are mainly due to pancreatic and hepatobiliary involvement (5.7%) and are related to impacts on weight growth [1]. Thus, early diagnosis can improve the prognosis and quality of life for these children [2]. Strong evidence has demonstrated the benefits of including the screening test for cystic fibrosis in the neonatal period, enabling immediate interventions that minimize the effects of malabsorption on weight gain and growth of these children [2]. In addition, children submitted to the screening test seem to have a decrease in pulmonary complications [2,3]. The long-term benefits after the identification of CF at an early stage of the disease are already well established, especially in reducing nutritional improvement, reducing morbidity and mitigating the impact of treatment on the patient [3,4].

Case Report

Female child, 2 years and 7 months, referred to the specialist for investigation of hepatomegaly associated with alterations of liver enzymes. It also reported softened bowel movements to liquids since birth and, more recently, hair loss and increased abdominal volume. On examination, she was malnourished, with dry skin, thin and brittle hair, disheartened, globose abdomen with palpable liver at the level of the umbilical scar and digital drumming. In pulmonary auscultation, wheezing was audible without stethoscope, with subcostal retraction and runs. In the previous history, she reported persistent wheezing from 8 months of age, with several going to the emergency room. Wheezing crises were accompanied by cough, dyspnea and peripheral cyanosis requiring rescue medications and sometimes systemic corticosteroids. Under the guidance of the pediatric pulmonologist, she used a long-term corticosteroid since 16 months of life, with progressively higher dose needs. Mother reports 4 episodes of pneumonia since birth, the last being 2 years and 6 months. The neonatal screening test was not altered. In the diagnostic investigation, she presented an increase in liver enzymes, especially the costs of PGT, hypoalbuminemia and ultrasonography with hepatomegaly and increased hepatic echogenicity (Figure 1). In addition to hepatobiliary involvement, the child showed signs of pancreatic insufficiency with altered glycemic control. Three chlorine dosages were performed in sweat all above 60 (the first with a value of 156). In view of the diagnosis of cystic fibrosis, enzymatique and supportive treatment for wheezing was initiated. Chest X-ray (Figure 2) showed the presence of peribronchial thickening and weft augmented. The culture of bronchial washes showed colonization by *Pseudomonas aeruginosa* sensitive to ciprofloxacin. Durante hospitalization was necessary to use antibiotic therapy to treat pulmonary infection and nutritional support measures. She remained hospitalized for more than 10 days to control symptoms, being discharged for outpatient follow-up.

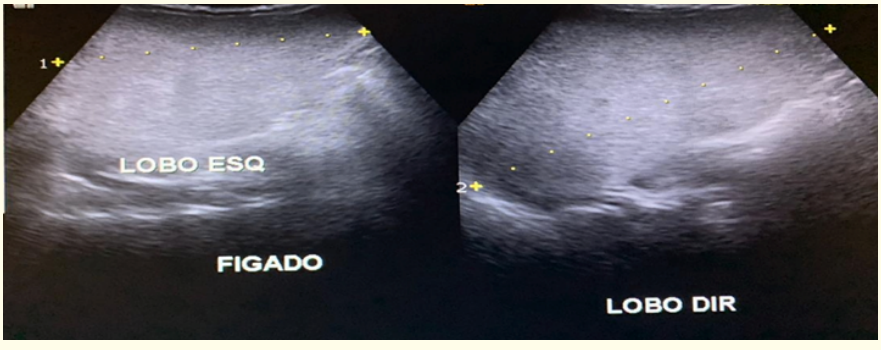

Figure 1: *Abdominal ultrasound with increased hepatic echogenicity.*

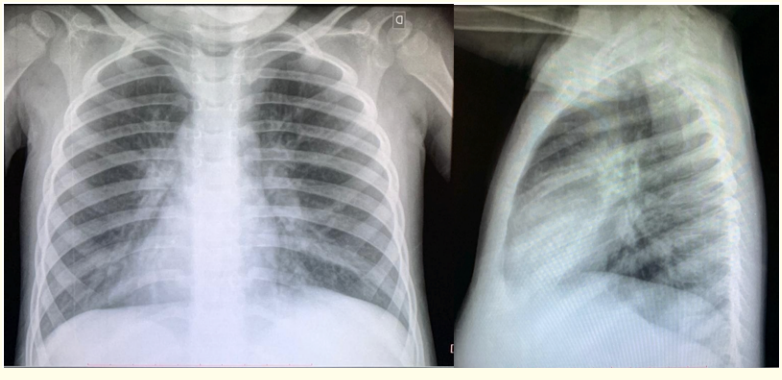

Figure 2: *Chest X-ray AP and profile with plot alteration.*

Discussion

More than 2000 mutations are associated with CF. These molecular differences, associated with individual and environmental-related factors, result in varied phenotypes, making diagnosis difficult [1]. Currently, most children have cf diagnosis in the neonatal period, still in the asymptomatic phase, through the neonatal screening test [2,4,5]. A study conducted in American children showed that neonatal screening was responsible for the diagnosis of CF in 62% of children [6]. However, some individuals are diagnosed already in the symptomatic phase, perhaps because they have not undergone screening or because they have presented a false-negative test. Therefore, in children who have 1 or more CF symptoms, they should be suspected of the disease and monitored, regardless of age and the result of the screening test [2,5].

Diagnosis should include chlorine sweat dosage and genetic testing to identify associated mutations. The evidence demonstrates benefit in early identification by the screening test, with improvement in weight-height growth [2,5]. In addition, they show a decrease in pulmonary complications, although the results are limited in relation to changes in the natural course of the disease. On the other hand, children with late diagnosis, who may have received a false-negative screening test, have worse pulmonary function with frequent *Pseudomonas aeruginosa* infections and increased hospital admissions [6]. Studies show that molecular, cellular, tissue and organic abnormalities occur from the first months of life and the progression of both respiratory and gastrointestinal tract disease has been demonstrated in children younger than 6 months [6]. Pulmonary involvement is the most common clinical form, and it represents about 92% of cases [6]. Studies suggest that airway changes in CF affect the pulmonary periphery more extensively than in asthma.

Pancreatic insufficiency is the second most frequent manifestation and is present in about 90% of children and manifests with a syndrome of mal absorption with stenatherher and impaired weight gain [7]. Hepatic involvement, although not as frequent, represents the third leading cause of death. Hepatomegaly and elevation of liver enzymes can occur in more than 20% of patients. Hepatic steatosis and cholelithiasis can also be observed and may compromise liver function [6,7]. In the case reported, the child presented a phenotype with pulmonary and pancreatic involvement, including hepatic involvement.

The development of complications in younger children including respiratory infections at higher risk for colonization by *Pseudomonas aeruginosa* and irreversible deleterious effects on the pulmonary tree may occur around 2 years of age [8]. Many studies show that infants and preschoolers represent a critical period in which structural changes in the pulmonary parenchyma by CF can initiate [8]. The structural damage is due to injuries caused by inflammatory and infectious processes in the first years of life. On the other hand, there is no evidence that the early identification of these structural alterations, such as bronchiectasis, may change the prognosis of these patients [8].

In relation to digestive manifestations, between 59 and 71% of children are doomed to present pancreatic insufficiency at birth [7]. In those born with normal pancreatic function, 16 to 20% will have pancreatic impairment until around 6 months [1]. A study conducted in Brazil in 55 children diagnosed with CF, the mean age of diagnosis in the group with the hepatobiliary disease was 7 months, much earlier than in the group without hepatobiliary involvement, and occurred as an initial clinical manifestation in 55.6% of patients [9]. In the case described, the child was symptomatic from the first months of life, with episodes of diarrhea and, later, pulmonary symptoms with progressive worsening from 8 months of life [1,6]. And, at 2 years of age, at the time of diagnosis, she already demonstrated advanced lung disease with limitation of expiratory function and pancreatic insufficiency with hyperglycemia, as reported in the literature. Thus, early diagnosis and initiation of treatment between 4 and 13 months of life are associated with a better prognosis of the disease [1,6].

Conclusion

In conclusion, the pulmonary phenotype is the most common, although extrapulmonary manifestations also occur and are clinically relevant. In children, weight growth and quality of life are compromised, with an increased need for hospital admissions. Neonatal scree-

ning tests significantly reduced the mean age of CF diagnosis and allowed early treatment, reducing hospitalizations and morbidity and mortality. However, the diagnosis should be remembered in all symptomatic children with suggestive pulmonary and/or extrapulmonary manifestations, even with normal neonatal screening test. Early and rapid access to health care by a multi-discipline team allows immediate interventions in younger children with impacts on the evolution of the disease at older ages, although it is insufficient to prevent anatomical and functional impairment of the respiratory system over time.

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