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CASE REPORT

Late diagnosis of cystic fibrosis in child with negative neonatal screening test

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Abstract

Cystic fibrosis (CF) is an autosomal recessive genetic disease in which CFTR (cystic fibrosis transmembrane conductance regulator) gene dysfunction, related to the transmembrane chlorine movement. This leads to the production of thicker secretions that occlude the light of the involved structures, 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 the lung tissue. Because it is a multisystem disease, early treatment aided by the screening test showed a better outcome when compared to treatment initiated after late diagnosis. The various neonatal screening tests (TTN) for cystic fibrosis have high sensitivity and specificity, but false positives and false negatives may occur. In this case report, we describe a preschooler who had a negative neonatal screening test and his diagnosis occurred after 2 years of age in the investigation of a hepatomegaly. However, the child presented 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 shown significant elevation. Enzymatic treatment was started with slow and progressive improvement of respiratory symptoms. And although the child responded to the start of treatment, it already had significant impairment of lung function. Thus, although TTN for cystic fibrosis has high sensitivity, it does not replace sweat chlorine dosage in children with very suggestive symptoms.

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INTRODUCTION

Cystic fibrosis is an autosomal recessive disorder with multi-organ involvement[1]. Although lung disease is primarily responsible for morbidity and mortality, some children have gastrointestinal (GI) tract involvement. The manifestations of GIT result mainly from pancreatic and hepatobiliary involvement (5.7%) and are related to impacts on weight and height growth[1]. Thus, early diagnosis can improve the prognosis and quality of life of 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 in these children[2]. In addition, children submitted to the screening test seem to show 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 relation to nutritional improvement, reduction of morbidity and an attenuation of the impact of treatment for the patient[3,4].

CASE REPORT

Female child, 2 years and 7 months old, referred to a specialist for investigation of hepatomegaly associated with changes in liver enzymes. She also reported soft to liquid stools since birth and, more recently, hair loss and increased abdominal volume. On examination, she was malnourished, with dry skin, thin and brittle hair, discolored, globular abdomen with a palpable liver at the level of the umbilical scar and digital clubbing. On pulmonary auscultation, wheezing was audible without a stethoscope, with subcostal retraction and retractions. In her previous history, she reported persistent wheezing since 8 months of age, with several visits to the emergency room. Wheezing attacks were accompanied by cough, dyspnea and peripheral cyanosis, requiring rescue medication and, sometimes, systemic corticosteroids . Under the guidance of the pediatric pulmonologist, he had been using long-term corticosteroids since 16 months of age, with progressively higher doses required. Mother reports 4 episodes of pneumonia since birth, the last one at 2 years and 6 months. The newborn screening test was not altered. In the diagnostic investigation, he presented an increase in liver enzymes, mainly at the expense of TGP, hypoalbuminemia and ultrasound with hepatomegaly and increased hepatic echogenicity (figure 1). In addition to hepatobiliary involvement, the child had signs of pancreatic insufficiency with altered glycemic control. Three measurements of chlorine in sweat were performed, all above 60 (the first with a value of 156). In view of the diagnosis of cystic fibrosis, enzymatic and

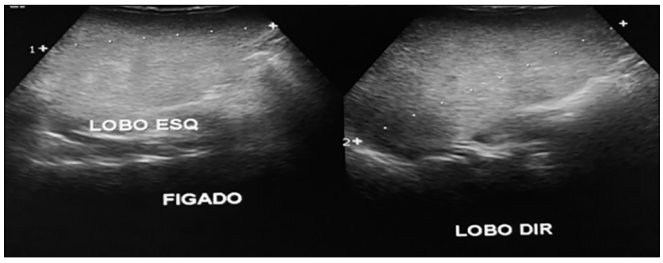


Figure 1. Abdominal ultrasound with increased hepatic echogenicity.

supportive treatment for the wheezing was initiated . A chest X-ray (Figure 2) showed the presence of peribronchial thickening and increased weft. Bronchial lavage culture showed colonization by ciprofloxacin sensitive *Pseudomonas Aeruginosa* . During hospitalization, antibiotic therapy was required to treat pulmonary infection and nutritional support measures. She remained hospitalized for more than 10 days for symptom control, being discharged for outpatient follow-up.

COMMENTS

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

Diagnosis should include sweat chloride measurement and genetic testing to identify associated mutations. Evidence shows benefit in early identification by screening test, with improvement in weight and 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 a worse evolution of lung function with frequent infections by *Pseudomonas Aeruginosa,* and an increase in 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 disease has been demonstrated in children younger than

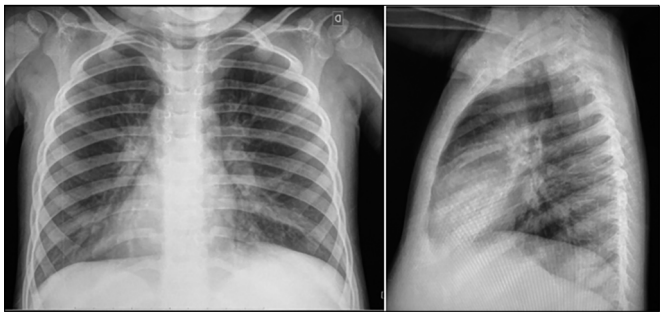


Figure 2. AP chest X-ray and profile with weft alteration.

6 months[6]. Pulmonary involvement is the most common clinical form, representing approximately 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 approximately 90% of children and manifests as a malabsorption syndrome with steatorrhea and impaired weight gain[7]. Liver involvement, although not as frequent, represents the third leading cause of death. Hepatomegaly and elevation of liver enzymes may 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 liver involvement.

The development of complications in younger children, including respiratory infections with a 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 have shown that infants and preschoolers represent a critical period in which structural changes in the lung parenchyma caused by CF can begin[8]. Structural damage results from injuries caused by inflammatory and infectious processes from the first years of life. On the other hand, there is no evidence that the early identification of these structural alterations, such as bronchiectasis, can change the prognosis of these patients[8].

Regarding 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 involvement by around 6 months[1]. In a study carried out in Brazil with 55 children diagnosed with CF, the mean age at diagnosis in the group with hepatobiliary disease was 7 months, much earlier than in the group without hepatobiliary involvement, and it occurred as an initial clinical manifestation in 55.6% of patients[9]. In the case described, the child was symptomatic since the first months of life, with episodes of diarrhea and, later, pulmonary symptoms with progressive worsening after 8 months of life[1,6]. And, at 2 years of age, at the time of diagnosis, he already showed 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 and height growth and quality of life are compromised, with an increase in the need for hospital admissions. Newborn screening tests significantly reduced the mean age at diagnosis of CF and allowed for 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 a normal newborn screening test. Early and rapid access to health care by a multidisciplinary 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.

REFERENCES

1. Santos ALM, Santos HM, Nogueira MB, Távora HTO, Cunha MLJP, Seixas RBPM, et al. Cystic fibrosis: clinical phenotypes in children and adolescents. Pediatr Gastroenterol Hepatol Nutr. 2018 Out;21(4):306-14.
2. Neemuchwala F, Taki M, Secord E, Nasr SZ. Newborn screening saves lives but cannot replace the need for clinical vigilance. Case Rep Pediatr. 2018 Jul;2018:7217326.
3. Course CW, Hanks R. Newborn screening for cystic fibrosis: Is there benefit for everyone. Paediatric Respir Rev. 2019 Ago;31:3-5.
4. Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N et al. Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. J Pediatr. 2017 Fev;181(Supl 1):S4-15.e1.
5. Rosenfeld M, Sontag MK, Ren CL. Cystic fibrosis diagnosis and newborn screening. Pediatr Clin North Am. 2016 Ago;63(4):599-615.
6. Coffey MJ, Whitaker V, Gentin N, Junek R, Shalhoub C, Nightingale S et al. Differences in outcomes between early and late diagnosis of cystic fibrosis in the newborn screening era. J Pediatr. 2016 Fev;181:137-45.e1.
7. Van Devanter DR, Kahle JS, O'Sulliva AK, Sikirica S, Hodgkins PS. Cystic fibrosis in young children: a review of disease manifestation, progression, and response to early treatment. J Cyst Fibros. 2016 Mar;15(2):147-57.

8. Ranganathan SC, Hall GL, Sly PD, Stick SM, Douglas TA. Early lung disease in infants and preschool children with cystic fibrosis. what have we learned and what should we do about it? Am J Respir Crit Care Med. 2017 Jun;195(12):1567-75.

9. Nascimento FS, Sena NA, Ferreira TA, Marques CDF, Silva LR, Souza EL. Hepatobiliary disease in children and adolescentes with cystic fibrosis. J Pediatr (Rio J). 2018 Set/Out;94(5):504-10.