

Clinical profile of cystic fibrosis

Atypical presentation

Abdelhamid S. Najada, MRCP, FRCP, Muna M. Dababreh, MD, MRCPCH.

ABSTRACT

الأهداف: وصف التشخيص غير العادي بين المرضى الذين يعانون من التليف الكيسي .

الطريقة: أجريت دراسة استيعابية على جميع الأطفال (عدد 90) تم تشخيصهم بالتليف الكيسي الكلاسيكي عيادة الأمراض الصدرية للأطفال - مدينة الحسين الطبية - عمان - الأردن خلال الفترة من يناير 2002 حتى ديسمبر 2008م. اشتملت الدراسة الأطفال الذين تتراوح أعمارهم ما بين يوم حتى 14 عام. تمت مراجعة ملفات الحالات الغير عادية. جمعت معلومات العمر عند التشخيص و المعالجة و الفحص السريري وتاريخ المرض عند العائلة. كما تم استعراض النتائج المخبرية ذات الصلة، وقرارات كلوريد العرق، و اشتملت كذلك على نتائج الاختبارات الجينية.

النتائج: اشتمل البحث على 57% (51) طفل من الذكور، و 43% (39) أنثى مصابين بالتليف الكيسي الكلاسيكي. كانت الأعراض السريرية الأكثر شيوعاً صغير الصدر (24%) و الأقل شيوعاً الاضفرار المباشر 3%. كانت 7 حالة 8% غير عادية من حيث الأعراض السريرية والتي تمثل في ارتفاع ضغط الدم الرئوي في وقت مبكر 3 مريض، استسقاء الكلية اليسرى مع قلووية الأيض، معزولة واحدة للقلوية الأيضية، نقص الحديد الشديد، مع قصر القامة، والعثور على الآفات الجلدية. كان هنالك تاريخ عائلي إيجابي للتليف الكيسي في 3 مريض. كما توفي 2 مريض يعانون من ارتفاع ضغط الدم الرئوي. وكان العدد الإجمالي للوفيات 4%.

خاتمة: هنالك تنوع في الفحوصات السريرية التي تنطوي على الصورة السريرية للتليف الكيسي. إن إدخال برامج فحص المواليد على المستوى الوطني يمكن أن يقلل من عبء المرض على العائلات و المرضى.

Objectives: To describe the unusual presentation among patients with confirmed cystic fibrosis.

Methods: A retrospective review was carried out on all children (n=90) with the diagnosis of classical cystic

fibrosis who attended the Respiratory Pediatric Clinic at King Hussein Medical Center, Amman, Jordan from January 2002 - December 2008. All children from one day old to 14 years of age were included. Files of those with unusual presentation were reviewed. Age at presentation and diagnosis, clinical presentation, and family history were collected. Relevant laboratory results, sweat chloride readings, and radiological features were also reviewed.

Results: Ninety children (males 51 [57%] and females 39 [43%]) with classic cystic fibrosis were included. The most common initial classical presenting manifestation was recurrent wheezy chest (24%). The least common presentation was direct hyperbilirubinemia (3%). Seven cases (8%) had unusual clinical presentations: early pulmonary hypertension, non-obstructive left hydronephrosis with metabolic alkalosis, single isolated episode of metabolic alkalosis, severe iron deficiency anemia with short stature, and the finding of ichthyotic skin lesions. Three of these patients had a positive family history of cystic fibrosis. Two patients with pulmonary hypertension died. The overall mortality rate was 4%.

Conclusion: The wide variability of clinical presentations reflects the diversity of clinical picture of cystic fibrosis as a disease. Neonatal screening programs at a national level can decrease the burden of the disease.

Saudi Med J 2010; Vol. 31 (2): 185-188

From the Department of Pediatrics, King Hussein Medical Center, Amman, Jordan.

Received 12th June 2009. Accepted 12th January 2010.

Address correspondence and reprint request to: Dr. Abdelhamid S. Najada, Department of Pediatrics, King Hussein Medical Center, PO Box 855019, Amman 11855, Jordan. Tel. +962 (77) 7413034. E-mail: a_najada@hotmail.com

Cystic fibrosis (CF) is the most common lethal autosomal recessive disease in the Caucasian population.^{1,2} The usual presenting signs and symptoms involve recurrent and persistent pulmonary infections, and pancreatic insufficiency with elevated sweat chloride readings.³ Patients are diagnosed with various modes of presentations at different ages from birth to adulthood; however, few children can have atypical presentations which may have an impact on the delay of diagnosis and prognosis.⁴ This is especially important in countries where newborn screening for CF is not performed and the awareness of the disease is still lacking. We aimed at highlighting these cases among our cohort of increasing CF patients who attended the respiratory clinic at King Hussein Medical Center.

Methods. We conducted a retrospective chart review of all (n=90) children with classical CF from January 2002 to December 2008 at the Respiratory Pediatric Clinic, King Hussein Medical Center, Amman, Jordan. The Ethical Committee at King Hussein Medical Center, Amman, Jordan approved the study. All children between day one to 14 years of age were included. Only those with the confirmed diagnosis of CF were included. The diagnosis of classical CF is based on sweat chloride readings of >60 mmol/l in 2 separate occasions plus classical clinical features. Patients with borderline sweat chloride tests between 40-60 mmol/L, or unconfirmed diagnosis were excluded. Sweat testing was carried out in our laboratory using the Wescor Macroduct system (Wescor Inc., Utah, USA). Files of those with unusual presentation were recorded and highlighted. Data collected included: age at presentation and diagnosis, clinical presentation, and family history. Relevant laboratory results sweat chloride readings, and radiological features were reviewed. We also included the results of polymerase chain reaction (PCR) genetic

testing (PDR kit, Innogenetics, Ghent, Belgium). We performed the genetic testing for 36 mutations.

Results. There were 51 males and 39 females with a ratio of 1.3:1. The initial classic presenting features were recurrent wheezy chest (24%), recurrent chest infections (14%), and chronic diarrhea (14%). Less common presentations included syndrome of anemia and hypoalbuminemia (10%), hypotonic dehydration (9%), poor weight gain (8%), hepatosplenomegaly (6%), meconium ileus (4%) and direct hyperbilirubinemia (3%). Seven cases (8%) had unusual clinical presentations. As shown in Table 1, 3 patients presented with moderate to severe pulmonary hypertension. They were all referred from the cardiology clinic; 2 of them at approximately 6 months of age and the third was 2.5 years. Of the patients with recurrent hypotonic dehydration, one child had an isolated episode that manifested in infancy and never recurred. Another child had suffered persistent attacks of alkalosis with left hydronephrosis and was misdiagnosed as Bartter syndrome. When he manifested recurrent chest infections after 4 years of age, he was referred to our clinic. In one child, a severe iron deficiency anemia and short stature was manifested at the age of 12 years. We had one child who presented at 15 months of age with an ichthyotic skin rash associated with anemia and hypoproteinemia.

Discussion. Most patients with CF have classic pulmonary and/or gastrointestinal symptoms.² However, there is some clinical variability in terms of onset, progression, measure severity, and clinical features.^{2,3} Some children have unusual presentations.³ This is important especially in countries like ours, when no routine screening is performed; therefore, we highlight this in order to facilitate early diagnosis. The most common cause of death is related to pulmonary involvement and its complications.⁴ Pulmonary hypertension is a late complication of CF lung disease; such patients commonly have generalized bronchiectasis and usually die within one year.⁵ Pulmonary hypertension has not been reported yet to be seen in CF patients during infancy. We believe that our cases 1 and 2 are unique in their early presentation. In both cases, no other cause was found to explain the pulmonary hypertension other than CF. High resolution chest CT scans were performed, and one of them showed patchy consolidation of the left lower lobe with hyperinflation, while only hyperinflation was seen in the other 2 cases. Genetic testing was unrevealing in case one, as we only test for 36 mutations and we do not have the facility to carry out a full sequence genetic analysis for our population. Infants with CF

Table 1 - Sweat chloride readings in patients with atypical cystic fibrosis (CF).

Case	Presentation	Sweat CL readings (mmol/L)
Case1	Pulmonary hypertension	87, 84
Case 2	Pulmonary hypertension	66, 67
Case 3	Pulmonary hypertension	77, 76
Case 4	Isolated hypotonic dehydration	110, 100
Case 5	Hydronephrosis and hypotonic dehydration	120, 115
Case 6	Iron deficiency anemia and short stature	100, 120
Case 7	Ichthyosis	80, 99

are prone to develop recurrent attacks of hyponatremic; hypochloremic dehydration with metabolic alkalosis. This commonly present during hot weather , and sometimes with failure to thrive.⁶ Nine percent of our cohort had recurrent episodes of dehydration. Only one child presented with an isolated episode of dehydration that resolved with proper management. His genetic testing showed homozygous mutation for 2789 + 5G →A. Currently, he is 5-years-old and remained in no treatment and sustained appropriate growth centile for his age and gender. His younger sibling, 6-months-old, was recently diagnosed with CF. He carries the same gene mutation. The prevalence of metabolic alkalosis with electrolytes depletion as the first presentation of CF is 16-20%.⁷ Predisposing conditions include infancy, severe pulmonary involvement, severe pancreatic insufficiency, genetic variation, and profuse sweating.^{7,8} However, metabolic alkalosis has been reported recently in different populations as the sole manifestation of CF without other classical symptoms, but tends to be recurrent.⁹ The mutation in our patient was not reported among the specific cystic fibrosis transmembrane conductance regulator (CFTR) mutations most commonly implicated for the mild CF phenotype of isolated hypotonic dehydration that includes T3381, D110E, and D110H.¹⁰ The Turkish infant reported by Weller et al¹¹ has D110 mutation and was given daily oral substitution of 1-2 grams of sodium chloride.¹¹ Salvatore et al¹² reported from southern Italy, a novel mutation of D57G in a 10-month-old infant that presented with metabolic alkalosis in the absence of other CF manifestations. The child with persistent metabolic alkalosis and a left-sided hydronephrosis, was misdiagnosed as Bartter syndrome for 5 years. This persistence differs from the classical episodic pattern of hypokalemic hyponatremic dehydration commonly seen in CF patients. His genetic testing for CF gene mutation showed homozygous M.G85E. Renal manifestations are usually a complication of CF management, particularly aminoglycoside therapy.¹³ The hydronephrosis in our case could not be attributed to CF per se. However, hydronephrosis has been reported in conditions where polyuria is a prominent manifestation such as diabetes insipidus and Bartter syndrome.¹⁴ In our case, the hydronephrosis might be speculated to be related to the Pseudo-Barter manifestation and its accompanying polyuria. We did not study the prevalence of iron deficiency (ID) among our cohort yet the unusual manifestation of ID with short stature was a striking presentation in our case. Severe iron deficiency is a rare manifestation of CF and more commonly seen in adults than children.¹⁵ The ID has been reported in 32% of a

pediatric CF population and in more than 60% of adult cases.¹⁶ Possible causes of ID in CF include chronic inflammation, dietary deficiency, gastrointestinal blood loss, impairment of oral absorption by pancreatic enzyme supplement, and iron loss through the airways.^{15,16} Mild anemia and functional deficiency are usually associated with severe lung involvement and pseudomonas colonization.^{17,18} This was not the case in our child who had normal pulmonary function with no evidence of bronchiectasis on chest CT scan and no pseudomonas colonization. Iron deficiency in CF is not related to the severity of pancreatic insufficiency or the degree of pancreatic enzyme supplement.¹⁸ Other causes for ID were excluded in this case. Still we need to investigate the significance of early ID and its relation to the subsequent disease course. Cutaneous manifestations as a presenting feature in CF are rare and the cases reported usually develop the eruption between 3 and 7 months of age.¹⁹ The initial skin eruptions in CF patients include erythematous papules that progress over months to extensive desquamative plaques, sparing the mucous membranes and nails.^{19,20} Recently, *Acrodermatitis enteropathica* eruption has been reported as presenting feature of CF in a 7-month-old female infant.²⁰ Ichthyotic skin eruption in CF patients is not reported as a presentation. In our case all investigations for malabsorption were negative; yet she manifested progressive respiratory symptoms and had *Pseudomonas aeruginosa* colonization. Syndrome of anemia hypoproteinemia and edema was seen in 10% of our cohort. It is a well recognized association in infancy. Male gender, breast-milk feeding, and presence of severe CFTR mutations are predisposing factors.²¹ Such cases usually improve with proper nutritional support and treatment.²¹ There are over 1500 gene mutations responsible for CF disease.²² We only test for 36 mutations and have 30% positivity. The Kit is originally related for testing Caucasian population. This may indicate the need for whole DNA analysis to find the specific mutations for our population. Of the 7 cases, 4 patients with the atypical presentation had positive gene mutation. Mortality in our CF cohort is 3 patients (4%). Two of them had severe pulmonary hypertension that presented in infancy and died within months of referral.

In conclusion, we believe that highlighting the atypical rare presentations of CF might draw the attention of the researcher for new aspects of CF. Different genetic mutations play a role in disease expression, yet gene modifiers have a greater role in different populations. Cystic fibrosis neonatal screening programs might help in eliminating delayed and questionable cases.

References

- De Boeck K, Wilschanski M, Castellani C, Taylor C, Cuppens H, Dodge J, et al. Cystic fibrosis: terminology and diagnostic algorithms. *Thorax* 2006; 61: 627-635.
- Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr* 2008; 153: S4-S14.
- Doull IJ. Recent advances in cystic fibrosis. *Arch Dis Child* 2001; 85: 62-66.
- Chernick V, Boat T, Wilmott R, Bush A. Kindig's Disorders of Respiratory Tract in Children. Amsterdam (HOL): Saunders Elsevier; 2006.
- Podolska E, Pogorzelski A, Woś H. [Echocardiographic assessment of cor pulmonale in patients with cystic fibrosis]. *Wiad Lek* 2006; 59: 208-213. Polish
- Aranzamendi RJ, Breitman E, Ascitutto C, Delgado N, Castaños C. [Dehydration and metabolic alkalosis: an unusual presentation of cystic fibrosis in an infant]. *Arch Argent Pediatr* 2008; 106: 443-446. Spanish
- Yalçın E, Kiper N, Doğru D, Özçelik U, Aslan AT. Clinical features and treatment approaches in cystic fibrosis with pseudo-Bartter syndrome. *Ann Trop Paediatr* 2005; 25: 119-124.
- Ballesteros Y, Hernandez MI, Rojo P, Manzanares J, Nebreda V, Carbojosa H, et al. Hyponatremic Dehydration as a Presentation of Cystic Fibrosis. *Pediatr Emerg Care* 2006; 22: 725-727.
- Kose M, Pekcan S, Ozcelik U, Cobanoglu N, Yalcin E, Dogru D, et al. An Epidemic of Pseudo-Bartter syndrome in Cystic fibrosis. *Eur J Pediatr* 2007; 167: 115-116.
- Sojo A, Rodriguez-Soriano J, Vitoria JC, Vazquez C, Ariceta G, Villate A. Chloride deficiency as a presentation or complication of cystic fibrosis. *Eur J Pediatr* 1994; 153: 825-828.
- Weller F, Wiebicke W, Tümmler B. [Turkish infant with hyoelectrolytemia and metabolic alkalosis as the sole manifestations of a mild form of cystic fibrosis (mutation D110H)]. *Klin Padiatr* 2000; 212: 41-43. German
- Salvatore D, Tomaiuolo R, Abate R, Vanacore B, Manieri S, Mirauda MP, et al. Cystic fibrosis presenting as metabolic alkalosis in a boy with the rare D579G mutation. *J Cyst Fibros* 2004; 3: 135-136.
- Tai A. Renal impairment following Aminoglycoside therapy in cystic fibrosis. *Thorax* 2008; 63: 532-535.
- Jin XD, Chen ZD, Cai SL, Chen SW. Nephrogenic diabetes insipidus with dilatation of bilateral renal pelvis, ureter and bladder. *Scand J Urol Nephrol* 2009; 43: 73-75.
- von Drygalski A, Biller J. Anemia in cystic fibrosis: incidence, mechanisms, and association with pulmonary function and vitamin deficiency. *Nutr Clin Pract* 2008; 23: 557-563.
- Fischer R, Simmerlein R, Huber RM, Schiffl H, Lang SM. Lung disease severity, chronic inflammation, iron deficiency, and erythropoietin response in adults with cystic fibrosis. *Pediatr Pulmonol* 2007; 42: 1193-1197.
- Reid DW, Withers NJ, Francis L, Wilson JW, Kotsimbos TC. Iron deficiency in cystic fibrosis: relationship to lung disease severity and chronic Pseudomonas aeruginosa infection. *Chest* 2002; 121: 48-54.
- Grossman S, Grossman LC. Pathophysiology of cystic fibrosis: implications for critical care nurses. *Crit Care Nurse* 2005; 25: 46-51.
- Lovett A, Kokta V, Maari C. Diffuse dermatitis: An unexpected initial presentation of cystic fibrosis. *J Am Acad Dermatol* 2008; 58 (2 Suppl): S1-S4.
- Zedek D, Morrell DS, Graham M, Goodman D, Groben P. Acrodermatitis enteropathica-like eruption and failure to thrive as presenting signs of cystic fibrosis. *J Am Acad Dermatol* 2008; 58 (2 Suppl): S5-S8.
- McCloskey M, Redmond AO, Hill A, Elborn JS. Clinical features associated with a delayed diagnosis of cystic fibrosis. *Respiration* 2000; 67: 402-407.
- Ratjen F. Recent advances In Cystic fibrosis. *Paediatr Respir Rev* 2008; 9: 144-148.

Copyright

Whenever a manuscript contains material (tables, figures, etc.) which is protected by copyright (previously published), it is the obligation of the author to obtain written permission from the holder of the copyright (usually the publisher) to reproduce the material in Saudi Medical Journal. This also applies if the material is the authors own work. Please submit copies of the material from the source in which it was first published.