Genetic Syndromes & Gene Therapy

Genel et al., J Genet Syndr Gene Ther 2014, 5:3
http://dx.doi.org/10.4172/2157-7412.1000224

Case Report Open Access

Cystic Fibrosis - An Open Book that must be Always Updated

Sur Genel[1,2]*, Floca Emanuela[1], Sur M Lucia[1], Sur Daniel[1] and Miclos M Corina[1]

[1]*University of Medicine and Pharmacy, IuliuHatieganu, Cluj-Napoca, Romania*

[2]*Emergency Clinical Hospital for Children, Cluj-Napoca, Romania*

***Corresponding author:** Sur Genel, University of Medicine and Pharmacy, IuliuHatieganu, Cluj-Napoca, Romania, Tel: 0040746095835; E-mail: surgenel@yahoo.com*

Received: March 05, 2014; **Accepted:** March 29, 2014; **Published:** March 31, 2014

Copyright: ©2014 Genel S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Cystic fibrosis (CF) is the most common autosomal recessive disease in Caucasians. The dysfunction of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) causes the disease by disrupting epithelial salt and water transport. Characteristic manifestations of the disease such as chronic respiratory infections, pancreatic enzyme insufficiency, and infertility are caused by the accumulation of mucus in the ducts. Nowadays nearly 2000 CFTR mutatioans are known. The most common mutation is F508del. F508del/F508del mutation is not always accompanied by severe manifestations. The clinical expression is different among patients, taking into account the mutations and another factor, among them, enviromental and modifier genes. In the case of rare mutations symptoms vary from patient to patient being influenced by environmental factors and modifier genes. We present a case with a less common combination of mutations and an atypical clinical presentation.

Keywords: Cystic fibrosis; Rare mutation; Child

Introduction

Cystic fibrosis (CF) is a systemic, recessively inherited disease affecting the exocrine glands. CF occurs most commonly among Caucasians of Northern European descent and an estimated 1 in 2500 Caucasian births are affected. It is the most common lethal hereditary disorder in the European population and it is the major cause of chronic debilitating pulmonary disease and pancreatic exocrine deficiency during the first three decades of life [1].

The severity and symptoms of the disease vary considerably due to different mutations of the gene (sometimes patients may experience few symptoms: infertility, other times the symptoms may become more severe: pancreatic/respiratory insufficiency) [2-4].

Exocrine abnormalities are reflected by electrolyte imbalance, changes in mucus (thick, sticky mucus, difficult to eliminate), obstructive lesions with cystic dilation and destruction of the mucous glands. Impairment of bronchial, pancreatic and bile epithelium is responsible for the manifestations of pulmonary and pancreatic-biliary disease [5,6].

The generalized exocrinopathy is responsible for the classic triad of symptoms that associate progressive obstructive lung disease, exocrine pancreatic insufficiency and a high sweat chloride level (the Sweat test measures chloride level in sweat and is the standard method for diagnosing CF [7-9].

Mutations in a single gene - the Cystic Fibrosis Transmembrane Regulator (CFTR) gene - causes CF. CFTR gene is mostly expressed in epithelial cells, where CFTR exerts its multiple functions, including the chlorine channel and regulator of ion channels function (resulting an adequate surface hydration). Nowadays nearly 2000 CFTR mutations are known, but few of them have a frequency higher than 1%. One in 20 people is an unaffected carrier of the CF mutation [10,11].

The most common mutation, F508del is a deletion of three nucleotides that result in a loss of the amino acid phenylalanine at the 508th position on the protein. F508del mutation accounts for 70% of CF cases worldwide [10].

There are some rare mutations, carriers of these mutations presenting an atypical symptomatology. R1070 mutation has different clinical presentation. R1070P and R1070Q mutation have been associated with severe pancreatic insufficiency. R1070W mutation has been associated with mild pancreatic insufficiency and obstructive azoospermia. There are 140 cases in the world with the R1070W mutation [4,6,12,13].

Case Report

We report the case of a boy who at the age of 6 months was hospitalized for weight loss, vomiting, eating disorders, and drowsiness.

From family history mention that mother is diagnosed with asthma. He was born full term, following a normal pregnancy; birth weight was 2950 g, Apgar score 8 and he was exclusively breast fed to 6 months. In the first two weeks of life he had omphalitis; at the age of 3 months suffered a craniocerebral trauma. A Computerized Tomography exam revealed a long linear fracture running across the temporo-parietal bone and an extracerebral hematoma in the left temporoparietal region.

Initial clinical examination revealed: fair general state of health, afebrile, but lethargic, dark circles under the eyes, pale skin, dry lips and slightly long capillary refill time, but without signs of shock; generalized micro-papular rash.

Clinical neurologic examination revealed: psychomotor agitation and iritability, with no abnormalities in tone, strength and coordination and normal fontanelle (0.5–1cm).

External genitals examination revealed phimosis.

After 24 hours of spitalization a diagnosis of vomiting syndrome, moderate dehydratation syndrome and phimosis was made.

Laboratory results revealed metabolic alkalosis (pH=7.56), hyponatremia (130 mmol/L), hypopotasemia (3.2 mmol/L), hypocalcemia (1.12 mmol/L), hypochloremia (84 mmol/L) and high levels of lactic acid (30 Mg/mL). Also it revealed leukocytosis (23000/μL) with lymphocytosis (12700/μL) and thrombocytosis (749000/μL), with normal C-reactive protein (0.1 Mg/dL).

Liver function enzymes were normal, also creatinine, uric acide and alkaline phosphatase levels. Cortizol levels were lower than normal (29.9 mol/L); normal urine test with undetectable urine sodium levels, negative stool test for fat and meat fibers; normal transfontanellar ultrasound scan.

The neurological examination revealed general hypotonia and lethargy. Electroencephalogram recording showed no abnormal activity. Magnetic resonance imaging of the brain revealed a small subdural fluid collection adjacent to the left frontal lobe (2 mm diameter and 18 mm length).

Abdominal ultrasound revealed: normal located kidneys, with normal shape, hyperechoic cortex (which appears similar to the echogenicity of the liver), good corticomedullary differentiation. Sonography of the urinary bladder showed: thin bladder wall and transonic content.

Ophtalmologic examinations revealed normal findings.

Additional neurological examination showed mild psychomotor retardation. The patient had a history of traumatic brain injury. He received Pyritanolum and was recommended neuromotorial recovery.

Neurosurgical examination showed that subdural hematoma didn't require any medical surveillance.

After 72 hours of hospitalization, a diagnosis of hypochloremic alkalosis, mild psychomotor retardation, traumatic subdural hematoma and phimosis was made.

We have taken into consideration the following differential diagnoses: Bartter syndrome, Gitelman syndrome, Seegmiller-Kelley syndrome, encephalitis, aminoacidopathies, salt wasting syndrome, and CF.

Sweat tests were negative on three separate occasiones, with measured sweat chloride of: 59 mmol/L, 68 mmol/L, and 58 mmol/L (normal value = 0–60). Serum amino acids levels and creatine phosphokinase were normal.

Genetic analysis showed that the child was positive for F508del heterozygote mutation, and for c.3208C >T familial mutation in heterozygote form (which has been localized to chromosome 17b, band CFTR (R1070W)). Mother was found to be carrier of c.3208C>T familial mutation in heterozygote form. Father was found to be carrier of F508del heterozygote mutation. The patient's brother was diagnosed with Hirschprung disease. Patient's brother was not diagnosed with CF.

- After all laboratory investigations patient is diagnosed with CF.
- The head trauma of the patient has not any rellationship with
- CF symptoms

The child had several hospital stays for acute dehydratation. In January 2012 he was hospitalized for acute pancreatitis, he received pancreatic enzyme therapy (Kreon 10000 UI), and evolution was favorable. In April 2012 he was tested for genetic mutation PRSS1 (cationic trypsinogen gene) R122C, R122H, N291, A16V, SPINK1, N345- NEGATIVE (which are most frequently associated with idiopatic chronic pancreatitis).

At age of 3 and 8 month year this boy has presented with vomiting cough and modified stool. Symptomatology appeared a week ago, when the patient had presented an episode of upper respiratory tract infection and received symptomatic treatment at home. Four days prior to hospitalization the patient presented stool modification (constipation), and two days before, he suffered two episodes of vomiting.

On this last admission his weight was 16.5kg (p50), height 106cm (p90) and BMI=14.7 kg/m2 (p25 – p10). He was afebril, but his general state of health was fair. He presented signs of mild dehydratation, neck with laterocervicaladenophaty, but normal coloured throat and palatglossal arch. The abdomen was tender to touch in the epigastric area; without organomegalia.

Laboratory results revealed elevated levels of serum and urine amylase (162 U/L, 1680 U/L), elevated lipase levels (120 U/L), C-reactive protein negative (0.6 Mg/dL), normal bilirubin values (total bilirubin = 0.35 Mg/mL, direct bilirubin = 0.16 Mg/mL), elevated liver enzymes (aspartate aminotransferase= 50 U/L), normal urea, normal white blood cells, platelets and creatinine. The patient had metabolic alkalosis (pH=7.48, HCO3=26.1 mmol/L) and anemia (haemoglobin=10.9 g/dL). The day after admission analyses were repeated. Laboratory results revealed high serum amilasis (155 U/L), anemia (Haemoglobin=10.9 g/dL), and other values were within normal limits. Abdominal ultrasound was performed with normal results.

A diagnosis of CF, acute pancreatitis, moderate dehydratation syndrome, acute angina and microcytic hypochromic anemia was made. He received therapy with intravenous fluids for electrolyte and acid-base rebalancing, antitussive syrup, probiotic, NaCl aerosol and evolution was favorable. He was discharged from the hospital with following treatment: NaCl aerosol, oral rehydratation salts and vitamins A, D, and E. A nasopharyngeal swab was performed periodically, also fecal pancreatic elastase, urinary and serum amylase levels, and biochemical dosages of vitamins A, D, E. Analysis of pancreatic elastase in feces revealed values higher than 500 μg/ g (which allow exclusion of acute pancreatitis).

Short-term and long term prognosis is good, but in long term mild pancreatic insufficiency and infertility may occur.

Particularities of the case

Genetic testing detected a rare combination of CFTR mutations.

Symptomatology is atypical for the diagnosed disease.

We cannot appreciate the role of each mutation in the appearance of symptoms; clinical manifestations are caused by mutations combination.

References

1. Rachel Williams, Helen Barker (2010) Cystic Fibrosis. InnovAiT 3: 743-752.
2. Ooi CY, Dupuis A, Ellis L, Jarvi K, Martin S, et al. (2012) Comparing the American and European diagnostic guidelines for cystic fibrosis: same disease, different language? Thorax 67: 618-624.

3. Dequeker E, Stuhrmann M, Morris MA, Casals T, Castellani C (2009) Best practice guidelines for molecular genetic diagnosis of cystic fibrosis and CFTR-related disorders - updated European recommendations. Eur J Hum Genet 17: 51-65.
4. Havasi V, Rowe SM, Kolettis PN, Dayangac D, Sahin A, et al. (2010) Association of cystic fibrosis genetic modifiers with congenital bilateral absence of the vas deferens. Fertil Steril 94: 2122-2127.
5. Flume PA, Mogayzel PJ Jr, Robinson KA, Goss CH, Rosenblatt RL, et al. (2009) Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. Am J Respir Crit Care Med 180: 802-808.
6. Ooi CY, Dorfman R, Cipolli M, Gonska T, Castellani C, et al. (2011) Type of CFTR mutation determines risk of pancreatitis in patients with cystic fibrosis. Gastroenterology 140: 153-161.
7. Legrys VA, McColley SA, Li Z, Farrell PM (2010) The need for quality improvement in sweat testing infants after newborn screening for cystic fibrosis. J Pediatr 157: 1035-1037.
8. Goubau C, Wilschanski M, Skalická V, Lebecque P, Southern KW, et al. (2009) Phenotypic characterisation of patients with intermediate sweat chloride values: towards validation of the European diagnostic algorithm for cystic fibrosis. Thorax 64: 683-691.
9. Cotton SW, Bender LM, Willis MS (2012) Multiple Positive Sweat Chloride Tests in an Infant Asymptomatic for Cystic Fibrosis. Lab Medicine 43: 1-5.
10. Cystic Fibrosis Genetic Analysis Consortium. Cystic fibrosis mutation database-. CFMDB Statistics.
11. Thibodeau PH, Richardson JM, Wang W, Millen L, Watson J, et al. (2010) The Cystic Fibrosis-causing Mutation F508del Affects Multiple Steps in Cystic Fibrosis transmembrane Conductance Regulator Biogenesis. J Biol Chem 285: 35825-35835.
12. Spicuzza L, Sciuto C, Di Dio L, Mattina T, Leonardi S, et al. (2012) Mild cystic fibrosis in patients with the rare P5L CFTR mutation. J Cyst Fibros 11: 30-33.
13. de Prada Merino A, Bütschi FN, Bouchardy I, Beckmann JS, Morris MA, et al. (2010) [R74W;R1070W;D1270N]: a new complex allele responsible for cystic fibrosis. J Cyst Fibros 9: 447-449.