World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(CASE REPORT)

Check for updates

Atypical form of cystic fibrosis in early childhood

Mejborna Gjata *, Anisa Hysenllari and Banuela Rapos

Department of Pediatric, University Hospital Center of Tirana "Mother Teresa", Albania.

World Journal of Advanced Research and Reviews, 2023, 18(01), 769–775

Publication history: Received on 06 March 2023; revised on 14 April 2023; accepted on 17 April 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.18.1.0661

Abstract

Introduction: Cystic fibrosis (CF) is an autosomal recessive genetic disorder, more prevalent in the Caucasian population. The disease is the result of mutations in a gene that codifies a chloride channel called CFTR (cystic fibrosis transmembrane conductance regulator) at affects most critically the lungs, pancreas, sweat glands and wolffian ducts. The variety of mutations in the CFTR gene is in some way responsible for the clinical variations by having and presentation in its atypical forms. Other factors, such as environmental factors and other genetic modifiers, affect the clinical variability of the disease.

Aim: The purpose of the case presentation is to show that CF is also presented with unusual signs and symptoms of the disease, causing it to be diagnosed late in time.

Case report: An 8 years old child A.D. admitted to the University Hospital Center of Tirana with a history of hypertransaminasemia, hypergammaglobulinemia and hepatomegaly which were found after a routine check.

From the laboratory tests which were normal, causes such as: HIV, Viral Hepatitis, CMV infection, Toxoplasmosis and Rubeola are excluded as causes of increased transaminases and hepatomegaly. Antibodies for autoimmunity and liver-specific antibodies were normal, so autoimmune pathologies were excluded as their cause. Based on the history, the girl had repeated history of pulmonary infections, defecation with a heavy and greasy smell, poor weight gain, mother with a history of two spontaneous abortions, so the cystic fibrosis was suspected. Also, changes with an inflammatory aspect were found in chest radiography. Two sweat tests were performed, which were positive within a period of two weeks. The positive fecal elastase test confirmed pancreatic insufficiency. The child was started therapy with vitamine ADEK and ursodeoxycholic acid and an improvement was observed in the laboratory values of the examinations.

Conclusion: Continue neonatal screening for cystic fibrosis. Since we have cases with atypical clinical presentation that are diagnosed late in time when we have cases with hepatic manifestations and the child has a history of repeated respiratory infections, steatorrhea, poor weight gain according to age, a differential diagnosis of hepatic pathologies should be made with Cystic Fibrosis. Since hepatic involvement can be the first manifestation that leads to the diagnosis of cystic fibrosis in its atypical forms.

Keywords: Cystic fibrosis; Early screening; Diagnosis; Atypical clinic

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disease, most common in the Caucasian population. The important successes that have been achieved at the level of genetic have led to a better understanding of the disease and, as a consequence, to a better follow-up, greatly increasing their life expectancy and the hope for final recovery. From a completely pediatric disease, CF is now a disease of adults as well.

* Corresponding author: Mejborna Gjata

The disease is caused by mutations in the gene that codifies for the chloride channel protein known as CFTR (cystic fibrosis transmembrane conductance regulator) that is essential for regulating the movement of salt and water across the membrane 's cells (1, 2, 3). The consequence of this disorder will be thick secretions in organs such as the lungs and pancreas. In the respiratory tract, this impairs the clearance of microorganisms leading to recurrent infections, bronchial damage, bronchiectasis and eventually, as the disease progresses, death from respiratory failure. In the pancreas, the exocrine ducts are blocked and, furthermore, they may be severely damaged before birth. Many men with CF are sterile as a result of failure to develop the vas deferens, seminal vesicles, ejaculatory ducts, body and size of the epididymis. The variety of mutations in the CFTR gene is partly responsible for these clinical variations. However, this clinical variability of the disease is influenced by other factors, such as environmental factors and other genetic modifiers

Aim

The purpose of presenting this case is to show that CF is also presented with unusual signs and symptoms of the disease, causing it to be diagnosed late in time.

2. Case report

An 8 years old female with the initials A.D. admitted to the University Hospital Center of Tirana with a history of hypertransaminasemia, hypergammaglobulinemia and hepatomegaly which were found after a routine check.

On physical examination the child did not appear ill. From the analysis, transaminases and gamma-globulins were increased above 2 times the norm. She does not complain of abdominal pain or fever. Since the age of 2, the child has had episodes of frequent dry cough, in the morning and in the evening, which was preceded by a fever. Hospitalized several times for bronchopneumonia, she improved, but the cough persisted throughout her life. The child complains of frequent and foul-smelling defecation. Normal growth in height. Poor weight gain.

The couple's second child, the first healthy child. The mother refers to two spontaneous abortions after the second child.

Physical examination: Sclera were normal, no pharyngeal infection, no cervical lymphadenopathy was observed. Pulmonary and cardiovascular system were normal, no tachycardia, no tachypnea was observed. The abdomen was soft, not distended, bowl sounds were present. The spleen was not palpable while the liver was palpable 4 cm below the rib cage. No edema or rash on the skin were observed.

Laboratory investigations on admission are as below:

- Radiography of pulmons: Inflammatory changes perhilar bilateral.
- Abdominal ultrasound: The liver is heterogeneous with undulating contours, 12 cm. Cholecyst normal, free bile ducts. Portal vein 9mm. Homogeneous pancreas. Spleen normal. Kidney and bladder normal, mild flatulence. Minimal fluid in the pelvis.

Echocardiography: Foramen ovale apertum, with minimal flow.

Table 1 Viral, endocrine and autoimmune examinations

HIV 1 DHE 2 Ab, RDT		**Negative**	
HBsAg	0.30 S/CO	Negative	(N: <0.99)
Anti -HCV	0.24 S/CO	Negative	(N: <0.99)
HAV -Ab, IgM	0.15 S/CO	Negative	(N: <0.79)
HAV-Ab, IgG	0.12 S/CO	Negative	(N: <0.99)
Anti -HBs	2.18 IU/L	Negative	(N: <0.99)
Anti-HBc	0.07 S/CO	Negative	(N: <0.99)
Rubella IgM	0.14 S/CO	Negative	(N: <1.19)
Rubella IgG	16.1 IU/mL	Positive	(N: <4.9)
CMV IgM	0.50 Index	Negative	(N: <0.84)

CMV IgG	175.1 AU/mL	Positive	(N: <5.9)
Toxoplasmosis IgM	0.09 Index	Negative	(N: <0.49)
Toxoplasmosis IgG	0.10 IU/mL	Negative	(N: <1.59)
Reticulocyte	14 %	High ↑	(N: <5)
ANA	< 160	Negative	(N: <160)
AMA	<100	Negative	(N: <100)
MPO	1.8 RU/mL	Negative	(N: <20)
Anti tissueTransglutaminase antibodies, IgA	3.6 U/mL	Negative	(N: <20)
TSH	2.047 mU/L	Normal	(N: 0.7-4.17)
FT4	1.18 ng/dL	Normal	(N: 0.89-1.37)
Anti-TPO	< 3 IU/mL	Normal	(N: <5.5)
Ferritinemia	43 ng/mL	Normal	(N: 13.7-79.8)
PT 70% INR 1.27, a PTT 32.7 SEC		Normal	
Fibrinogen activity	405 mg/dL	High ↑	(N: 140-360)

Table 2 Protein electrophoresis

Albumin	**46.3 %**	**Low ↓**	**(N: 55.8-66)**
Alpha 1-globulins	5.4%	High ↑	(N: 2.9-4.9)
Alpha 2-globulins	11.1%		(N: 7.1-11.8)
Beta 1-globulins	5.8%		(N: 4.7-7.2)
Beta 2- globulins	4.7%		(N: 3.2-6.5)
Gamma -globulins	26.7%	High ↑	(N: 11.1-18.8)
A/G RATIO	0.86		(N:11.5-13.5)

Table 3 Hemogram

RBC	**5.25 X10^6/UL**	**(N: 4-5.3 x10^6)**
Hgb	12.5 g/dl	(N:11.5-13.5)
HCT	39.9%	(N: 33-43)
MCV	75 fL	(N: 76-90)
MCH	23.8 pg	(N: 25-31)
MCHC	31.3 g/dl	(N: 32-36)
RDW	15%	(N: 11.8-14)
WBC	7.1 K/uL	(N: 4.5-10)
Neutrophils	3.5 K/uL	(N: 0.65-4.8)
Lymphocytes	2.6 K/uL	(N: 2.3-9.12)
Monocyte	0.9 K/uL	(N: 0.15-1.32)
PLT	150 K/uL	(N: 150-400)

Table 4 Biochemical balance

Glicemia	**100 mg/dL**		**(N: 60-100)**
Bun	15.8 mg/ dL		(N: 15-36)
Creatinine	0.44 mg/dL		(N: 0.52-0.69)
Total bilirubin	0.76 mg/dL	High ↑	(N: <0.4)
Direct bilirubin	0.38 mg/dL	High ↑	(N: 0.1-0.2)
Total protein	9.0 g/dL	High ↑	(N: 6-8)
Albumin	4.6 g/dL		(N: 3.8-5.4)
Acid uric	4.7 mg/dL		(N: 1.8-4.9)
ALT	141 U/L	High ↑	(N: 9-25)
AST	86 U/L	High ↑	(N: 18-36)
GGT	67 U/L		(N: 9-36)
ALP	273 U/L		(N: 156-369)
LDH	195 U/L		(N: 192-321)
CK	39 U/L		(N: 29-168)
Amylase	167 U/L	High ↑	(N: 25-125)
Lipase	143 U/L	High ↑	(N: 4-39)
PCR	0.76 mg/dL		(N: <0.5)
Iron	25 ug/dL		(N: 16-128)
Calcium	9.5 mg/dL		(N: 8.8-10.8)
Magnesium	2.24 mg/dL		(N: 2.09-2.84)
Phosphorus	4.6 mg/dL		(N: 4.1-5.9)
Cholesterol	98 mg/dL		(N: <170)
Tryglicerides	33 mg/dL		(N: 44-97)
HDL-cholesterol	50 mg/dL		(N: 36-73)
LDL- cholesterol	38 mg/dL		(N: <110)
Natrium	137 mmol/L		(N: 138-145)
Kalium	4.4 mmol/L		(N: 3.4-4.7)
Chlor	103 mmol/L		(N: 98-107)
CEA	1.7 ng/mL		(N: 0-2.5)
AFP	< 2 ng/mL		(N: 0-40)
CA-125	24.6 U/mL		(N: 0-35)
Beta HCG	< 2.3 IU/L		(N: <5)
Cortisol	14 ug/dL		(N: 5-25)

Table 5 Imunoelectrophoresis

IgA	**175 mg/dl**		**(N: 33-298)**
IgM	160 mg/dl		(N: 26-174)
IgG	2833 mg/dl	High ↑	(N: 559-1439)
CERULOPLASMIN	0.38 g/L		(N: 02-0.6)

- Parasite stool test was Negative
- Culture of sputum for MDR Negative
- Hemoglobin electrophoresis Normal
- Coproculture Negative
- Sweat test 125 mmol/l Positive on first time and 127 mmol/l Positive on second time, after two weeks.
- Stool elastase 175.5 ugE/g Positive (N: >200)
- ASMA IgG 1:40 Negative (N: <1:40)
- Anti-LKM1 < 3 Negative (N: <12)
- Cytosolic hepatic Tip 1 IgG Anticorpe 1:20 Negative (N: <1:20)

The child, based on clinical, laboratory and imaging data and after consultation with a pulmonologist and geneticist, was given a genetic analysis and the child is being followed up with a pulmonologist for specific treatment.

3. Discussion

Cystic fibrosis is characterized by a variety of clinical manifestations ranging from significant lung disease at a young age to mild symptoms in adulthood. The first presentation of CF can be with common signs such as: chronic sinusitis, nasal polyps, bronchiectasis, chronic or recurrent lower respiratory tract infection, meconial ileus, distal intestinal obstruction syndrome, pancreatic insufficiency with steatorrhea, male infertility or obstructive azoospermia, hyponatremic dehydration, unusual signs such as: allergic bronchopulmonary aspergillosis or atypical mycobacterial infection, chronic obstructive pulmonary disease, rectal prolapse, elevated hepatic enzymes, cirrhosis, prolonged neonatal jaundice, edema, anemia , female infertility. The presentation with edema, anemia and hypoproteinemia, which is currently referred to in the guidelines as an unusual presentation, is referred to in the literature in a percentage of about 5% (4, 5) and is mainly found in breast-fed children. Based on the European CF registry, the typical form of the disease is diagnosed under the first year of life, while the atypical forms are usually diagnosed in adulthood.

Cystic fibrosis is a multisystemic disease that includes liver damage or, as it is called, hepatobiliary disease related to cystic fibrosis, the pathogenesis of which is not well known. It is associated with an abnormal expression of CFTR on the apical surface of the biliary epithelium (6, 7). Hepatic manifestations are rarer than involvement of the lungs or pancreas. Abnormal activity or absence of CFTR decreases bile fluidity and alkalinity causing accumulation and precipitation of hyperviscous bile secretions in the intrahepatic tree (8). Our case did not present clinical complaints. She is hospitalized to find out the origin of the hepatomegaly discovered by a follow-up visit. From the laboratory tests which were normal, causes such as: HIV, Viral Hepatitis, CMV infection, Toxoplasmosis and Rubeola are excluded as causes of increased transaminases and hepatomegaly. Autoimmunity antibodies and liver-specific antibodies were normal, so autoimmune pathologies were excluded. Based on the history where the girl had repeated history of pulmonary infections, foul-smelling and greasy stools, poor weight gain, the mother with a history of two miscarriages suspected Cystic Fibrosis. Two sweat tests were performed which were positive. A positive fecal elastase test confirmed pancreatic insufficiency.

Costa et al. (2011) observed the development of hepatic involvement in a patient at the age of 8 years while he had been diagnosed with cystic fibrosis since the age of 3 years.

The liver involvement is considered one of the primary complications of cystic fibrosis and can influence the survival rate and quality of life.

Due to the wide spread of neonatal screening for Cystic Fibrosis, today in the world in about 64% of cases the diagnosis is made before the signs of the disease appear, simply starting from the positive results of the neonatal screening. Today, screening for CF mutations and the possibility of information about their association with CFTR dysfunction has greatly increased, which usually helps to interpret the signs of the disease, a fact that has often added stress and made it difficult

in practice to make a decision about the correct diagnosis, since, two mutations have been detected in individuals with little or no signs of the disease. Many cases of the disease are detected with few symptoms and at a relatively old age in the population that has not undergone neonatal screening. All of this has made diagnosis nowadays quite challenging, given that the age of onset of the disease and the severity of symptoms can vary greatly depending on the level of CFTR dysfunction.

Due to all the new information and the difficulties that appear in practice in making the diagnosis, in order to have a harmonization of the diagnostic criteria and the terminology used, guidelines for the diagnosis of cystic fibrosis have been drawn up since 2008 and revised from time to time, most recently in 2017 (9). An individual is diagnosed with Cystic Fibrosis when they have both clinical signs of the disease and evidence of CFTR dysfunction. The tests for CFTR function in a hierarchical order to make the diagnosis of CF are: sweat test first, then genetic screening for CFTR mutations and then physiologic tests

The identification of two mutations in the CF gene is the absolute confirmation of the diagnosis. Likewise, the study of carriers in the entire family of the affected child can be offered, as well as prenatal diagnosis for future burdens. About 2,000 mutations of the CFTR gene have been discovered, but only 400 are disease-causing. (10, 11, 12).

F508del is the most frequent worldwide mutation, although some Middle Eastern and Jewish populations have other more frequent mutations (13). In Europe, this mutation is found in 82% of patients with CF (41% of cases in homozygosity and 41% in heterozygosity) (14).

Despite the problems mainly related to false positive and false negative test results, all the evidence is in favor of newborn screening for cystic fibrosis (15).

4. Conclusion

Hepatic involvement in children with cystic fibrosis is a rarer manifestation compared to pulmonary involvement and manifestations. It appears several years later from the moment of diagnosis, but it can also be the first manifestation that helps to suspect cystic fibrosis and deepen the diagnosis. In all cases when the presentation is in the form of a liver pathology but the child has steatorrhea, repeated infections of the respiratory tract and not gaining weight in accordance with age and gender, we should also think about cystic fibrosis as a differential diagnosis. Cystic fibrosis is also presented with an atypical clinic, which is diagnosed at older ages than the typical forms. Neonatal screening is an important examination for the earliest diagnosis of CF.

Compliance with ethical standards

Acknowledgments

We thank all the medical staff of the General Pediatric Ward for their constant support.

Disclosure of conflict of interest

The authors declare no conflicts of interest regarding the publication of this paper.

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans by any of the authors.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Romens JM, Jannuzzi MC, Kerem B, Drumm ML, MELMER g, Dean M, Rozmahel R, Cole JL, Kennedy D, Idaka N, et al. Identification of the cystic fibrosis gene: Chromosome Walking and Jumping. 1989;245: 1059- 1066

[2] Riordan JR, Romens JM, Kerem B, Alon N, Rozmahel R, Grzeczak Z, Zielenski J, Lok S, Plavsic N, Chou JL et al. Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA. Science 1989;245: 1066-1073

[3] Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravari A, Buchwald M, Tsui LC, Identification of the cystic fibrosis gene: genetic analysis. Science 1989;245: 1073-1080

[4] Skopnik H, Heiman G. Manifestation of intolerance to cow`s milk protein in mucoviscidosis with the symptom triad of hypoproteinemia, edema and anemia. Klin Pediatr. 1087 Nov-Derc; 199(6): 453-456

[5] Nielsen OH, Larsen BF. The incidence of Anemia, hypoproteinemia and edema in infants as presenting symptoms of Cystic fibrosis: a retrospective survey of the frequency of this symptom complex in 130 patients with cystic fibrosis. J Pediatr Gastroenterol Nutr.1982; 1 (3): 355-359.

[6] Cohn JA, Strong TV, Picciotto MR, Nairn AC, Collins FS, Fitz JG. Localization of the cystic fibrosis transmembrane conductance regulator in human bile duct epithelial cells. Gastroenterology. 1993; 105(6):1857-64.

[7] Kinnman N, Lindblad A, Housset C, Buentke E, Scheynius A, Strandvik B, et al. Expression of cystic fibrosis transmembrane conductance regulator in liver tissue from patients with cystic fibrosis. Hepatology. 2000; 32(2):334-40.

[8] Lindblad A, Glaumann H, Strandvik B. Natural history of liver disease in cystic fibrosis. Hepatology. 1999; 30(5):1151-8.

[9] Farrell PM1, White TB2, Ren CL3, Hempstead SE2, Accurso F4, Derichs N5, Howenstine M3, McColley SA6, Rock M1, Rosenfeld M7, Sermet-Gaudelus I8, Southern KW9, Marshall BC2, Sosnay PR10. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017 Feb; 181S:S4-S15.e1. doi: 10.1016/j.jpeds.2016.09.064.

[10] Castellani, H. Cuppens, M. Macek, Jr., J.J. Cassiman, E. Kerem, P. Durie, E. Tullis, B.M. Assael, C. Bombieri, A. Brown, T. Casals, M. Claustres, G.R. Cutting, E. Dequeker, J. Dodge, I. Doull, P. Farrell, C. Ferec, E. Girodon, M. Johannesson, B. Kerem, M. Knowles, A. Munck, P.F. Pignatti, D. Radojkovic, P. Rizzotti, M. Schwarz, M. Stuhrmann, M. Tzetis, J. Zielenski, J.S. ElbornConsensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practiceJ Cyst Fibros. 2008 May; 7(3): 179–196.

[11] Zelenski J Genotype and Phenotype in cystic fibrosis. Respiration.2000; 67:117-33CFTR231 August 2018. www.cftr2.org/mutation list

[12] Barben J1, Castellani C2, Dankert-Roelse J3, Gartner S4, Kashirskaya N5, Linnane B6, Mayell S7, Munck A8, Sands D9, Sommerburg O10, Pybus S11, Winters V11, Southern KW11.The expansion and performance of national newborn screening programmes for cystic fibrosis in Europe.J Cyst Fibros. 2017 Mar; 16(2):207-213.

[13] Bobadilla JL1, Macek M Jr, Fine JP, Farrell PM.Cystic fibrosis: a worldwide analysis of CFTR mutations--correlation with incidence data and application to screening. Hum Mutat. 2002 Jun; 19(6):575-606.

[14] ECFS. Patient Registry 2017. Annual Data Report. www.ecfs.eu/ecfspr.

[15] doi: 10.1016/j.jcf.2016.12.012. Epub 2016 Dec 30