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A case of cystic fibrosis presented with meconium ileus in a female neonate

In-Ok Hwang, M.D. and Eun-Sil Lee, M.D.

Department of Pediatrics, College of Medicine, Yeungnam University, Daegu, Korea

Meconium ileus (MI) is the earliest clinical manifestation of cystic fibrosis (CF) in infants. It arises from the intraluminal accumulation of highly viscid, protein-rich meconium, typically present in the terminal ileum as a neonatal intestinal obstruction. Therefore, the clinical symptoms include abdominal distension, bilious vomiting and delayed passage of meconium. CF is caused by mutations in the transmembrane conductance regulator gene (CFTR) located in the long arm of chromosome 7. CF is common in Caucacians, but is a rare disorder in Asian countries, including Korea. We experienced a case of CF combined with MI. Compared with the previous reports of CF in Korea which presented respiratory problems, this is the first case genetically diagnosed as CF with MI during the newborn period. **(Korean J Pediatr 2007;50:1252-1256)**

Key Words : Cystic fibrosis, Meconium ileus

Introduction

Meconium ileus (MI) is the earliest clinical manifestation of cystic fibrosis (CF) and occurs in 10 to 20% of infants with the condition[1]. Clinical presentation included abdominal distension, bilious vomiting and the delayed passage of meconium. MI arises from the intraluminal accumulation of highly viscid, protein-rich meconium, which typically obstructs the terminal ileum. The result is a neonatal intestinal obstruction with abdominal distension at birth.

CF is a life threatening disorder with severe consequences, including lung damage, nutritional deficiencies, intestinal obstruction secondary to MI, jejunoileal atresia, and meconium plug syndrome. CF is inherited as an autosomal recessive trait and caused by mutations in the transmembrane conductance regulator gene (CFTR) located on the long arm of chromosome 7[2]. This gene consists of exons and encodes for an integral membrane protein composed of 1,480 amino acids. There are currently 1,536 mutations listed in the CFTR mutation database[3]. Although common among Caucasians, it is a rare disorder in Asians, and also rare in Korea. Only a few cases of CF have been reported in Korea [4-6].

Recently, we experienced a case with intestinal obstruction secondary to MI, later proved to be CF by the genetic analysis. Our report is the first native Korean CF with MI.

Case Report

A two day-old girl was admitted to our hospital due to abdominal distension. At 5 hours of age, she was given glucose water. Soon after, she developed abdominal distension and vomiting. She was first taken to a regional clinic and checked with a simple X-ray of the abdomen, which showed distended loops of the bowel.

On her arrival into the nursery, she was grunting, breathing was hard and rapid, and her abdomen was severely distended.

Her body weight, length and head circumference were 2,900 g (25-50 percentile), 49 cm (50-75 percentile) and 32 cm (10-25 percentile), respectively.

Vital signs were 140 beats/min, 66 breaths/min, and 37℃ body temperature.

The patient looked acutely ill and was alert. Both chest walls expanded symmetrically but with subcostal retraction. The patient had clear breathing sounds at both lung fields, and a regular heart beat without murmur. Her abdomen showed intensive distension and increased bowel sound. No

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책임저자 : 이은실, 영남대학교 의과대학 소아과학교실
Correspondence : Eun-Sil Lee, M.D.
Tel : 053)620-3530 Fax : 053)629-2252
E-mail : les2055@ynu.ac.kr

pitting edema was shown on the extremities. The external genitalia were normal and there were no specific findings upon neurologic examination.

The infant was born via vaginal delivery at 38 weeks of gestation. At 25 weeks, polyhydramnios was noted, and amniocentesis, which showed normal results, was done. Her birth weight was 2.9 kg, and family history was negative for CF.

The laboratory finding were as follows : the white blood cell count was 17,040/mm^3, hemoglobin 13.5 g/dL, platelet count 301,000/mm^3, C-reactive protein 0.098 mg/dL, sodium 135 mEq/L, potassium 5.1 mEq/L, glucose 73 mg/dL, calcium 9.3 mg/dL, phospate 5.9 mg/dL, magnesium 2.7 mg/dL.

An abdomen roenterogram showed markedly distended bowel loops (Fig. 1). A barium enema at 3 days of age showed a large amount of meconium in the cecum and a functional microcolon with a normal rectum (Fig. 2).

An emergency operation was done on the same day. A right hemicolectomy with ileostomy was done. During the operation, the small bowel was edematous and severely dilated (Fig. 3). Meconium irrigation was done to the ileocecal valve area 50 cm proximal from the ascending colon.

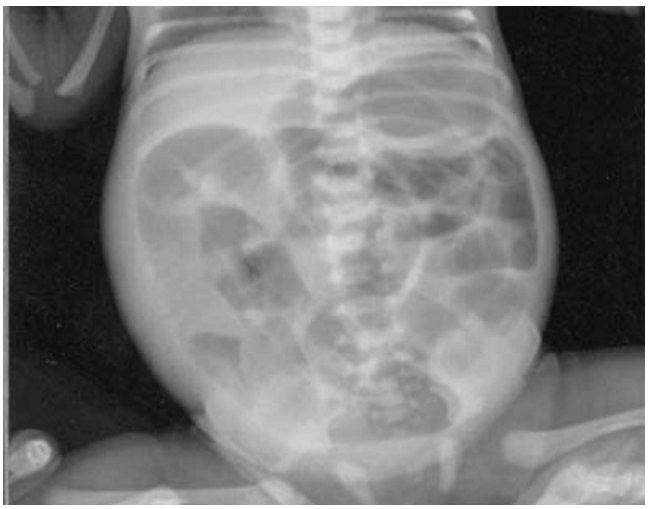

Fig. 1. Abdomen radiograph at 2 day of age. It shows markedly distended bowel loop.

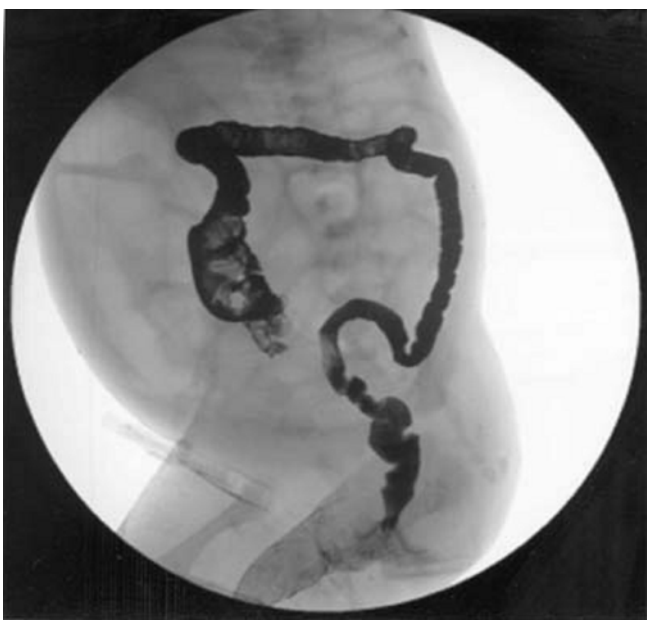

Fig. 2. Barium enema at 3 days of age shows a large amount of meconium in the cecum and a functional microcolon with a normal rectum. Diffused small bowel distension is also seen.

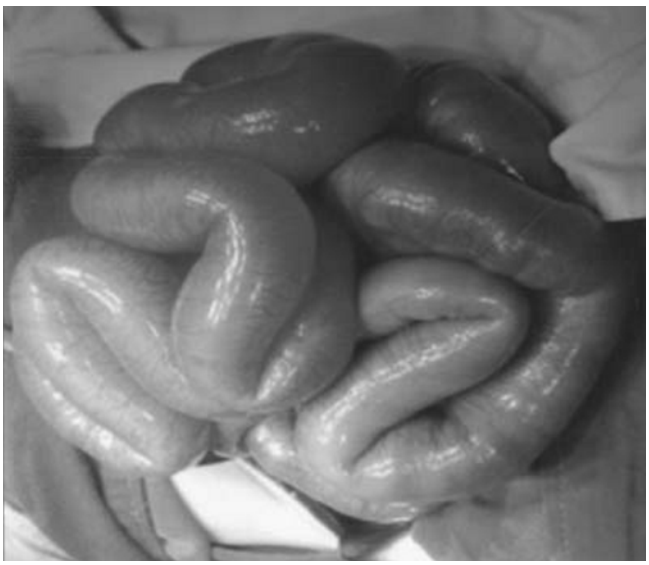

Fig. 3. The operative field shows that small bowel was edematous and severely dilatated. Plugged meconium was seen in inner space of loop.

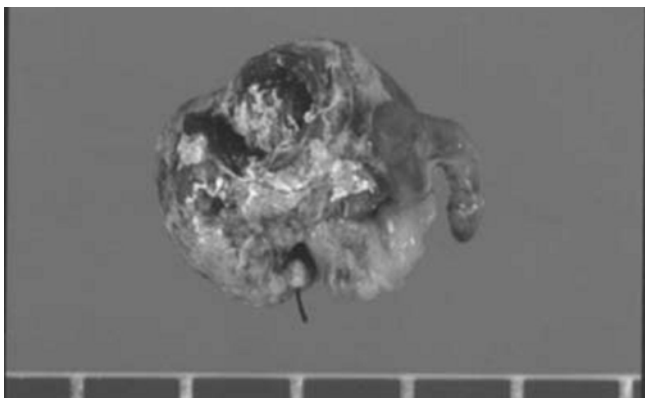

Fig. 4. Gross finding: resected cecum and appendix was seen in this figure. Impacted meconium and microperforation was also seen.

Resection was done at the area (Fig. 4). The colectomy site was designated from the distal ileum (about 10 cm proximal from the ileocecal junction) to the midtransverse colon, with a sufficient resection margin. Microperforation was noted 2 cm proximal of the cecum. On the 8th hospital day, cardiac murmur was heard, and an echocardiogram was done. Findings were consistent with patent ductus arteriosus (4 mm) and atrial septal defect (4 mm). On the 13th hospital day, tachypnea persisted, chest X-ray showed 62% cardiothoracic ratio, and B-type natriuretic peptide was 1,040 pg/mL. Digoxin and diuretics were used. On the 20th hospital day, she was discharged with tolerable feeding status.

In the gene analysis, the eleven mutation/polymorphism loci of the CFTR gene previously found in the Korean population and the ten most common disease-associated loci in Caucasians were screened using the SNaPShot method as previously detailed[7]. In addition, denaturing gradient gel electrophoresis and subsequent nucleotide sequencing were performed to find unknown CFTR mutations. Two disease-related mutations were identified in this patient (Q98R and Q1352H), and two mutations were located in different alleles (Fig. 5, Table 1). The results of genetic analysis of the patient's family members showed that Q98R was from her father and the Q1352H was from her mother.

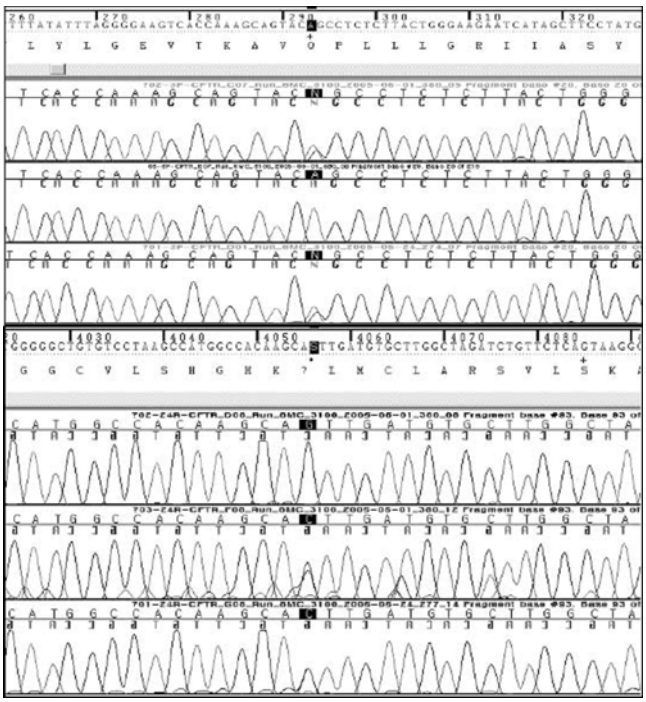

Fig. 5. Two disease-related mutations were identified by direct sequencing analysis. It showed that heterozygous A to G transition in 293 nucleotide (upper) and heterozygous G to C transition in 4056 nucleotide (lower) in this patient.

Discussion

CF is the most common autosomal recessive disease with a fatal outcome in Caucasians with a frequency of 1 in 2,500 life births. It is caused by the mutation of a single gene on the long arm of chromosome 7 encoding a protein called the CF transmembrane regulator (CFTR)[7]. The defect in the CFTR leads to pathological changes in all organs containing mucus secretory glands, such as the airway, pancreas, gut, biliary tract, vas deferens and sweat glands. CFTR functions as a chloride channel at the cell surface, and when CFTR is missing or malfunctioning, the result is impaired ion transport[2]. Consequently, water and volume depletion, followed by thickening of the mucus membranes leads to secondary problems in all the affected organs. The main symptoms are caused by an impaired mucociliary clearance in the airway that leads to chronic bacterial colonization, airway inflammation, and finally, lung destruction. Obstruction of the pancreatic duct followed by pancreatic fibrosis leads to pancreatic insufficiency, which leads to malabsorption and maldigestion. With increasing age, impaired glucose tolerance becomes a relevant clinical problem affecting more than half of the adult patients, with about 25% them being insulin dependent[8]. CFTR also affects the bile ducts, leading to chronic inflammation and periportal fibrosis in about one-third of patients, and very few results of liver cirrhosis[7]. Obliteration of the vas deferens is the cause of infertility in 98% of the male patients[9]. Female fertility seems to be nearly normal, although the cervical mucosa can be dehydrated and sperm activation can be impaired by the lack of HCO_3[9]. Main symptoms in infancy are gastrointestinal, secondary to the

Table 1. Identified Mutations in the Transmembrane Conductance Regulator Gene

Exon	Nucleotide	Base change	Codon	Amino acid change	Designation	Homo/Hetero	Effect
3	293	A→G	98	Gln→ Arg	Q98R	Hetero	Mutation
14	2562	T→G	854	-	T854T	Hetero	Polymorphism
24	4056	G→C	1,352	Gln→ His	Q1352H	Hetero	Mutation

pancreatic insufficiency. These children, despite good appetite, show abdominal distension, massive fatty stools and failure to thrive. The earliest manifestation of CF is MI, which occurs in 10-15% of the patients. It can occur from the eighteenth week of gestation resulting in bowel dilatation with thickened intestinal walls, intestinal atresia, perforation and peritonitis. These features are usually detected by a prenatal ultrasound[7].

The median age at diagnosis is 6 months[10]. Neonatal screening programs have been introduced in many countries, but whether early diagnosis affects long term outcome or not continues to be a controversy[11]. A positive family history can be informative. Concentration of sweat chloride greater than 60 mmol/L on repeated analysis is diagnostic for CF, but about 5% of cases are false negative[12]. Diagnosis can be confirmed by genotyping of mutations which can have regional variation.

Since the sweat electrolyte abnormalities in CF patients were first described by di Sant' Agnese[13], the sweat test is considered as the most valuable diagnostic procedure. Despite its importance in the correct diagnosis of CF, false positive sweat test results can be caused by several factors such as unreliable methods, technical errors in evaporation, contamination, instrument calibration and interpretation[14]. Therefore, a quantitative pilocarpine iontophoresis sweat test has been widely accepted as a reliable standard method. CF is diagnosed by an increased chloride concentration greater than 60 mmol/L on two or more repeated occasions. Although it is a reliable standard method according to the 'Guidelines for the performance of the sweat test'[15], the sweat test can be performed after 2 weeks of age in infants greater than 3 kg of weight who have been adequately hydrated and without significant systemic illness. The test should be avoided with subjects who are either dehydrated, underweight, unwell, or have a cutaneous rash affecting the potential stimulation site. Our case didn't have typical respiratory symptoms, other than meconium ileus. Of the CF cases reported in Korea, the most young patient was at the age of four months[4], complaining of recurrent wheezing. Since gene analysis was not available back then, diagnosis was made only with sweat chloride test. Few similar cases were reported, all of them with respiratory symptoms. In our case, diagnosis was made only by the CFTR mutation analysis because she was newborn and had congenital heart defects. Since this case is a newborn and had left-to- right shunt due to PDA, sweat chloride test could not be performed. And genetic analysis is also a useful diagnostic tool because the identification of the CFTR mutation is highly specific despite its low sensitivity.

In East Asia, only 15 cases were identified with CFTR mutation among more than 80 CF patients documented so far[16]. A recent analysis of the CFTR gene revealed that a significant number of genetics variations existed in a population of 192 Koreans, and that the sequences were quite different from those of Caucasians. For example, Q1352H mutation which was previously founded by Lee et al[17]. The 1,352nd amino acid residue coded by a trinucleotide in exon 24 of the CFTR gene, and is located in the second ATP binding domain. Thus, it is speculated that alteration of the codon for glutamine to histidine would cause decreased efficiency in activation of the CFTR chloride channel. And the other mutation, identified in this case is Q98R mutation. It is a missense mutation which was previously founded. The 98th amino acid residue that is coded by a trinucleotide in exon 3 of the CFTR gene, and it is located in the third ATP binding domain. Thus it is alteration of the codon for glutamin to arginine (Fig. 5)[18].

CF still remains a life-limiting disorder. As for the management of CF, the treatment plan should be comprehensive and individualized. Early diagnosis, institution of physical therapy and nutritional counseling, vigorous antibiotic therapy and careful follow-up are important aspects of the comprehensive regional CF treatment programs.

Diagnosis of CF requires a clinical suspicion. The majority of children with classic findings; MI at birth, a history of progressive obstructive pulmonary disease, chronic steatorrhea and malnutrition, and a family history of CF. By reporting this case, we hope to bring attention to the occurrence of CF in the Korean population and thus increases the awareness for the diagnosis.

In summary, this is the first documented CF case in Korea without respiratory symptoms, diagnosed in the newborn period. The significance of this case lies with the proof of already documented CFTR gene mutation, although the Sweat test could not be performed since the newborn had PDA. With advances in patient care, survival of CF patients has been prolonged, thus early diagnosis is more crucial. In addition, an expected increase in international marriages among Koreans may cause future rise in CF incidence. Therefore, for every patient with MI during newborn period, CF must be ruled out even without the presence of respiratory symptoms.

한 글 요 약

신생아에서 발생한 태변장폐색증에 동반된 낭성섬유증 1례

영남대학교 의과대학 소아과학교실

황 인 옥 · 이 은 실

태변장폐색증은 낭성섬유증에서 가장 초기에 나타나는 임상 증상으로 태변이 장관내 축적되어 회장말단의 폐색을 일으키고 복부팽만, 담즙성 구토, 태변 배출 지연이 동반된다. 낭성섬유증은 7번 염색체 장완에 위치한 막전도조절유전자의 돌연변이로 야기되며 한국인에서는 드문 질환이다. 지금까지 대한민국에서 보고된 호흡기 질환에 동반된 낭성섬유증과 달리, 저자들은 태변장폐색증에 동반된 낭성섬유증이 유전자 검사로 진단된 1례를 경험하였기에 보고하는 바이다.

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