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Cystic Fibrosis
— A Case Presented with Recurrent Bronchiolitis in Infancy in A Korean Male Infant—

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The aim of this case report is to draw the attention to the occurrence of cystic fibrosis (C.F.) in a Korean infant and thus increase the awareness for the diagnosis. The male infant was presented with a history of recurrent bronchiolitis manifested by severe cough, wheeze and dyspnea from three weeks of age, in whom the diagnosis of C.F. was clinically suspected and was confirmed by demonstration of two elevated sweat chloride levels (97 mEq/L and 99 mEq/L) in the patient. The diagnosis was delayed because the main manifestations of C.F. were the same as the main symptoms of common diseases such as cough, diarrhea and failure to thrive.

C.F. is probably underdiagnosed in Korean population both because the diagnosis is not considered since the disease is thought to be uncommon or even not to occur and because diagnostic facilities including the quantitative iontophoresis sweat test are lacking.

Key Words: *Recurrent bronchiolitis, Cystic fibrosis, Sweat test.*

INTRODUCTION

Cystic fibrosis (C.F.) is an autosomal recessive inherited, generalized disorder of exocrine gland function that results in abnormal mucus production. Chronic obstructive pulmonary disease, pancreatic insufficiency, and an abnormally high electrolyte concentration in sweat are the characteristics. C.F. is the most common lethal genetic disease in Caucasians, but there has been no report about C.F. in Korea.

We experienced a 4-month old infant with C.F., and so report him with review of literatures.

CASE REPORT

A four months old Korean male infant was admitted to the ward of Seoul National University Children's Hospital for the third time on May 24, 1986 because of severe cough and wheezing. He had been relatively doing well until about three weeks of age when cough and tachypnea developed and the symptoms persisted in spite of treatment at a private clinic. On February 19, 1986 at about five weeks of age, he was admitted to the Neonatal Intensive Care Unit of the Hospital for the first time because of cough and was managed under the impression of acute bronchiolitis. He was discharged with some improvement in condition on the thirteenth hospital day. He was readmitted to the Neonatal Intensive Care Unit four days later due to acute exacerbation of cough, sputum and dyspnea. With general supportive care and antibiotic therapy, his clinical status showed some improvement and he was discharged on the twentieth hospital day. However, after the discharge cough and wheezy respiratory sound persisted and the symptoms were aggravated with increasing respiratory embarrassment until this hospitalization for further diagnostic work-up and management.

He was delivered by Cesarean section at full term

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weighing 2.56 kg without any perinatal problems. He was vaccinated with PDT and TOPV once, and Hepavax twice. His mother was known HBsAg carrier. His elder brother who was only sibling had been suffering from cough, sputum, wheeze and dyspnea since one month of age and had been admitted to another University Hospital twice at three months and four months of age and succumbed to Pseudomonas pneumonia, respiratory failure and sepsis at five months of age.

On physical examination at admission, the temperature was 37.1° C, the heart rate, 136 and the respiratory rate, 66 per minute. The body weight was 7.0 kg; the height, 63.0 cm; the head circumference, 41.0 cm and the chest circumference, 43.0 cm. The patient was dyspneic without cyanosis. The head was normocephalic without scar. The pupils were isocoric and light reflex was prompt. The conjunctivae were not pale and the sclerae were not icteric. Neither palatine tonsillar hypertrophy nor pharyngeal injection was present. The neck was supple and venous engorgement was not noted. There was no lymph node eniargement. The chest was symmetrically expanded with subcostal retraction. The breathing sound was coarse with wheeze. The heart beat was regular without murmur. The abdomen was soft and flat. The liver, spleen and kidneys were not palpable. There was no CVA tenderness. No pitting edema was present on the extremities. The external genitalia was normal and no neurological abnormalities were elicited.

On admission, the patient was placed on general supportive respiratory care including bronchodilators and mucolytic agents.

The laboratory findings were as follows: the hemoglobin was 12.9 g per 100 ml; the hematocrit was 40.8 per cent. The white-cell count was 9,700, with 5 per cent segmented neutrophils, 88 per cent lymphocytes, 5 per cent monocytes and 2 per cent eosinophils. The platelet count was 162,000. ESR was 5 mm per hour. The findings of urine and stool were normal. The urea nitrogen was 10 mg, the creatinine 0.4 mg. The sodium was 139 mEq, the potassium 3.4 mEq, the chloride 96mEq. The glutamic oxaloacetic transaminase was 32 U, the glutamic pyruvate transaminase 41 U. CRP was non-reactive. Nitroblue tetrazolium dye reduction was found in 7 per cent of polymorphonuclear leukocytes in the patient, 15 per cent in the mother, and 17 per cent in the father. Serum levels of IgG/A/M/D were 555/42/145/2.0 mg/dL and IgE was 17 IU/ml. Serum α_1-antitrypsin was 260 mg/dL. The results of multi-cell mediated immunity (CMI) test and dinitrochlorobenzene (DNCB) test were normal. Sixty-three per cent T-lymphocytes (E rosette formation) and thirteen per cent B-lymphocytes (immunofluorescence identification) were present. Protein electrophoresis revealed normal pattern. An X-ray film of the chest revealed markedly emphysematous lungs. Qualitative analyses of stool fat revealed increase in size (50-90 um) and number of fatty acid and neutral fat. Dribbling of $AgNC_3$ on the patient's palms caused more extensive whitish precipitation compared to the normal control. Sweat specimens in amount of 2 to 3 gm collected by a similar method described by Di Sant'Agnese PA et al.(1953) were analysed for electrolyte concentrations. The results obtained were as shown in the following Table.

Table. Sweat electrolyte concentrations of the patient and control.

Electrolyte (mEq/L)	Patient	Control	Normal range *	Normal range **
Na	70 & 63	18	14.5±4.7	28.2±6.1
K	25 & 30	13	11.2±3.4	10.3±2.4
Cl	97 & 99	22	12.3±4.9	28.0±6.0

Normal data were cited from Hong, 1984 (*) and Shwachman et al., 1981 (**).

On the 12th hospital day, antibiotics were started to cover pneumonia. On the 14th hospital day, the patient became severely ill and respiratory arrest developed with generalized tonic-clonic seizure. He was transferred immediately to the Pediatric Intensive Care Unit for ventilatory support. In a specimen of arterial blood, the partial pressure of oxygen was 232 mmHg, the partial pressure of carbon dioxide 98 mmHg, pH 7.13 and HCO3 33 mEq/L. At the PICU, intensive air-way suction and physiotherapy were repeatedly instituted and his respiratory symptoms improved gradually. On the 48th hospital day, he could be returned to the ward. However, a few days later his respiration became dyspneic progressively. He was transferred again to the PICU on the 51th hospital day and was placed on ventilator care until the 64th hospital day when he was tolerable after weaning. On the 85th hospital day, he could be returned to the ward. Arterial blood gas analysis revealed the pH 7.33 the partial pressure of carbon dioxide 61 mmHg, the partial pressure of oxygen 110 mmHg, and HCO_3^- 31 mEq/L. On the 95th hospital day, he was discharged in tolerable respiratory status in guarded prognosis to be followed up at the out-patient clinic.

DISCUSSIONS

C.F. is the most common single-gene inherited

disease in North Europeans. The inheritance of C.F. is autosomal recessive (Danks et al., 1965), with an incidence of approximately 1 in 1600 in Caucasians and the incidence among the American blacks population is approximately 1:17000 (Kulczycki et al., 1974), among Orientals, 1:90000 (Wright et al., 1968). The incidence of the carrier state is therefore approximately 5% in the Caucasian population.

Until now, there is no available method for reliably detecting the heterozygote with C.F. in a random population (Qureshi et al., 1985). But isolation of the defective C.F. gene would provide a more definitive method of diagnosis, and by analysis of the base coding for the gene, might also improve our understanding of the underlying biochemical basis of the disease. Exclusion mapping of the genome using polymorphic protein and DNA marker showed that C.F. gene is on the long arm of human chromosome 7 (Tsui et al., 1985; Robert et al., 1985), and subsequently, the C.F. gene has been shown to be closely linked to two DNA probes (the met oncogene and J 3.11) which are situated in the region between 7q21 and 7q31 (Ray et al., 1985; Wainwright et al., 1985). And this information, combined with amniotic fluid enzyme assay, led to reliable prenatal diagnosis in selected patients.

Since the 1950's, demonstration of an elevated sweat chloride level has remained the principal method of confirming the diagnosis of C.F.. The quantitative pilocarpine iontophoresis sweat test, as described by Gibson and Cook in 1959, is currently the only uniformly acceptable method for the diagnosis of C.F. which was unavailable in this laboratory. In the presence of suggesting clinical features, a sweat chloride level greater than 60 mEq/L is consistent with the diagnosis of C.F..

Elevated sweat chloride levels have been reported in association with a number of other clinical entities such as unilateral adrenal insufficiency, glycogen storage disease type 1, fucosidosis, hypothyroidism, nephrogenic diabetes insipidus, ectodermal dysplasia, malnutrition, mucopolysaccharidosis, panhypopituitarism and all of these conditions are clinically distinct from C.F. (Stern, 1986). In recent years, several rapid sweat testing methods have become available, but these alternative methods of sweat testing should only be considered as screening procedures, and should not be relied upon for the definitive diagnosis of C.F. (Denning et al., 1980).

C.F. is characterized by a heterogeneous group of abnormalities in exocrine gland function, involving salivary, sweat, bronchial, pancreatic, and biliary gland dysfunction, as well as abnormalities in the vas deferens and uterine cervix (Maclusky et al., 1985). The major clinical sequelae arise from defective mucus gland function, production of hyperviscous secretions causing plugging of glandular ducts (Wood et al., 1976), with secondary histologic and functioning abnormalities.

The severity of pulmonary disease remains the major determinant of both the quality and duration of life in the majority of patients with C.F. surviving the neonatal period. Many children are presented in infancy with a history of bronchiolitis, recurrent respiratory tract infection, or overt pneumonia. With the introduction of treatment, these patients show substantial improvement in their clinical status, which is usually maintained until around puberty. However, at this stage, pulmonary status frequently declines, particulary in females. Progressive bronchiectasis leads to increasing cough, sputum production and reduced exercise tolerance. Finger clubbing usualy becomes prominent, and diffuse inspiratory crackles are usually heard on auscultation. Subsequently, patients frequently develop acute exacerbations of their lung disease with associated hypoxemia and deterioration in clinical condition.

Although hospitalization and intravenous antibiotic therapy produce improvement in the patient's condition, steady deterioration in pulmonary status occurs with increasing respiratory embarrassment, cardiac involvement (Stern et al., 1980), and eventually death from cardiorespiratory failure. In these advanced cases, assisted ventilation was rarely valuable since sufficient improvement rarely occurred to allow subsequent extubation (Davis et al., 1978).

The chest radiograph is characteristically normal at birth, though some individual with severe disease may present with rapidly progressive pulmonary disease in the neonatal period. In the early stages of the disease, the chest film typically shows hyperinflation with periobronchial thickening, and possibly patchy atelectasis. Subsequently, air trapping and frank bronchiectasis, initially more marked in the upper lobes, may become apparent. In advanced cases, apical bullae may occur with the potential to rupture and cause a spontaneous pneumothorax. Finally, thoracic deformity may become evident in the advanced stages of the disease. A number of radiologic scoring system have been devised for quantifying the severity of lung disease and are useful for follow up of patients (Shwachman et al., 1958; Brasfield et al., 1979; Coates et al., 1981).

Among the methods of pulmonary function testing, spirometric measurements, particularly mid-expiratory flow rate (FEF 25-75%), are the useful for following

the long-term course of the disease (Gurwitz et al., 1979; Maclusky et al., 1985).

Patients with C.F. characteristically become colonized by specific organism, the pattern of colonization changing with the age of the patient. When C.F. was originally described, Staphylococcus aureus was the principal pathogen isolated (Cohen, 1986). Subsequently, there has been a shift in bacterial spectrum, with Pseudomonas species now being the most common organism identified, particularly in the older patients (Mearns et al., 1972; Kulczycki et al., 1978; Marks, 1981; Corey et al., 1984; Vasil, 1986). Colonization with Pseudomonas aeruginosa is associated with more advanced lung disease (Pitcher-Wilmott et al., 1982), possibly due to tissue damage mediatd by immune-complex mechanisms (Church et al., 1981). And many other immunologic evidences have been reported to explain the pathogenesis of chronic and progressive Pseudomonas aeruginosa infection (Piedra et al., 1986). In recent years, Pseudomonas cepacia infection is increasing with some fatal cases (Isles et al., 1984; Goldmann et al., 1986; Thomassen et al., 1986.)

Since there is a clear relationship between nutritional status and severity of pulmonary disease (Gurwitz et al., 1979), various techniques have been attempted to improve calolic intake, such as by nasogastric feeding or parenteral nutrition. Some patients have shown significant weight gain and improvement in functional status with aggressive nutritional therapy. But lung function does not improve with nutritional supplementation (Editorial, 1986).

Gastro-intestinal manifestations of C.F. are pancreatic exocrine insufficiency, steatorrhea, malabsorption of protein and fat, growth retardation, meconium ileus (10-15%) (Park et al., 1981), and meconium ileus equivalent (Mullins et al., 1985). Biliary cirrhosis (2-3%) and steatosis are the hepatobiliary complications of C.F..Hyperglycemia and glycosuria are the results of pancreatic involvement (Handwerger et al., 1969; Park et al., 1981).

Males with C.F. are generally sterile (>95 %) due to failure of development of Wolffian duct structures (Taussing et al., 1972).

Sweat gland involvement may produce hyponatremic dehydration, hypokalemia, and hypochloremic metabolic alkalosis.

The diagnostic criteria for C.F. are positive sweat test {chloride conc. > 60mEq/L (Behrman et al., 1987) or > 80mEq/L (Stern et al., 1986)}and one or more findings among followings ; (1) positive family history, (2) progressive chronic obstructive pulmonary disease that does not have another obvious etiology, (3) pancreatic exocrine deficiency.

But first of all, diagnosis of C.F. requires clinical suspicion. The majority of children with C.F. present with classical findings ; meconium ileus at birth, a history of progressive obstructive pulmonary disease, chronic steatorrhea and malnutrition, and a family history of C.F. (present in 20% of cases). However, C.F. is an extremely pleomorphic disease, while the age of presentation may vary from infancy to adulthood. Thus, any one of a variety of different clinical findings requires investigation for C.F. In our case, the recurrent bronchiolitis with deterioration, a family history and the positive sweat test led us to the diagnosis of C.F.

C.F. still remains a life-limiting disorder, although survival has improved dramatically during the past 30yr (Shwachman et al., 1965). As for the management of C.F., the treatment plan should be comprehensive and individualized. Early diagnosis, institution of physical therapy (Desmond et al., 1983) and nutritional counseling, vigorous antibiotic therapy and careful follow-up are important aspects of the comprehensive regional C.F. treatment programs (Shwachman et al., 1970; Stern et al., 1976). Because immune mechanisms might contribute to detrimental pathogenesis in C.F. patients, some tried steroid and could reported that alternate day oral steroids might ameliorate the progression of lung disease (Auerbach et al., 1985). And immunization with Pseudomonas aeruginosa vaccines before the development of pulmonary colonization is currently being explored. Since the cause of death in 98% of patients beyond the perinatal period is cardiorespiratory failure, heart-lung transplantation may eventually benefit patients reaching the terminal stage of the disease.

After the diagnosis of this case, we were of the opinion that patients presented with early onset recurrent bronchiolitis had to undergo sweat test. By reporting this case, the authors aimed to draw the attention to the occurrence of C.F. in Korean population and thus increase the awareness for the diagnosis and stimulate to studies about the gene frequency in this population which remains quite unknown.

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