Case Report

Cystic Fibrosis in Three Northeast Thai Infants Is CF Really a Rare Disease in the Thai Population?

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The authors report on three infants with cystic fibrosis (CF), with different genotypes, presenting with different clinical manifestations, but having similar abnormal serum electrolytes (i.e. hyponatremia, severe hypochloremia and metabolic alkalosis). Despite the diagnostic investigations, the child who presents with severe electrolyte imbalance especially persistent hypochloremia and a family history of early infant death with respiratory or gastrointestinal problems should point to a diagnosis of CF. Early identification and treatment remain critical to effective management. The diagnostic tool used, especially the sweat test, is needed for diagnostic investigations in Thailand.

Keywords: *Child, Cystic fibrosis. Thailand*

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Cystic fibrosis (CF) is an autosomal, recessive, genetically transmitted disease, which manifests as a chronic, multi-system, life-shortening disorder. It is the result of defective epithelial ion transport caused by mutations in the 230-kb gene on chromosome 7 - named the cystic fibrosis transmembrane regulator (CFTR).

Over 1 000 mutant alleles have been identified and among these DF508 is the most common. The prevalence of the disease varies among different ethnic groups, with the highest prevalence among Caucasians (1:2,000-3,000 live births)[1] and much less common among African Americans and Orientals (1:9,500-350,000)[2,3] Indeed, there have been very few case reports of the disease in the Asian population.

Diagnosis should be based on laboratory evidence of the CFTR abnormality, including an elevated concentration of the sweat chloride, identification of two CFTR mutations, or evidence of the characteristic patterns of ion transport across the nasal epithelia[4]. Sweat chloride levels between 60 and 165 mEq/L are considered diagnostic for CF.[5] However, not all of these investigative tools are available in Thailand, which may explain the lack of case reports from Thailand. The authors encountered three Northeast Thai infants with this rare disease and present the findings.

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Case Report

Case 1

A 4-month-old, Thai boy was admitted to this hospital (April 9, 2002) after suffering fever and watery diarrhea for 2 days. He had a history of wheezing, chronic cough and dyspnea since he was 3 months old.

He was the fourth child with a birth weight of 3,460 g. After birth, he was jaundiced with a weakly positive indirect Coombs' test and was placed under phototherapy for two days. He was breastfed and asymptomatic until 3 months of age.

His first brother died at the age of 7 months with a history of recurrent pneumonia from 2 months of age. The second brother died at 3 months of age because of sepsis and biliary atresia. The 2-year old third brother was healthy. There was no history of consanguineous marriage in the family. (Fig. 1A) His parents live in Muang District, Khon Kaen Province, Thailand.

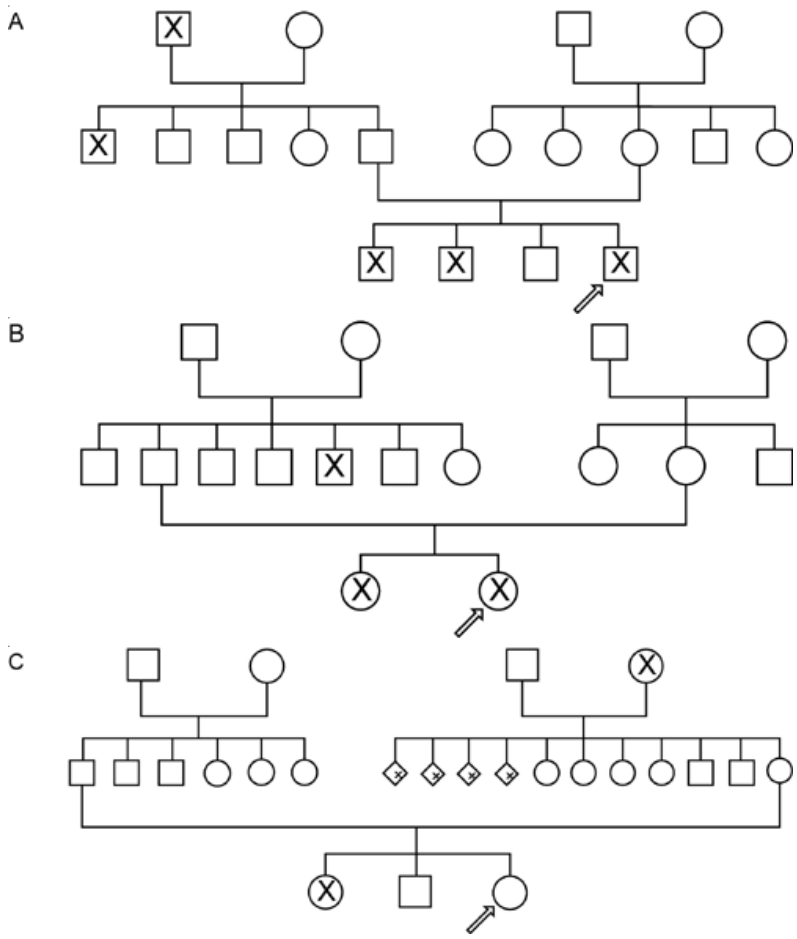


Fig. 1 The family pedigree of the patients

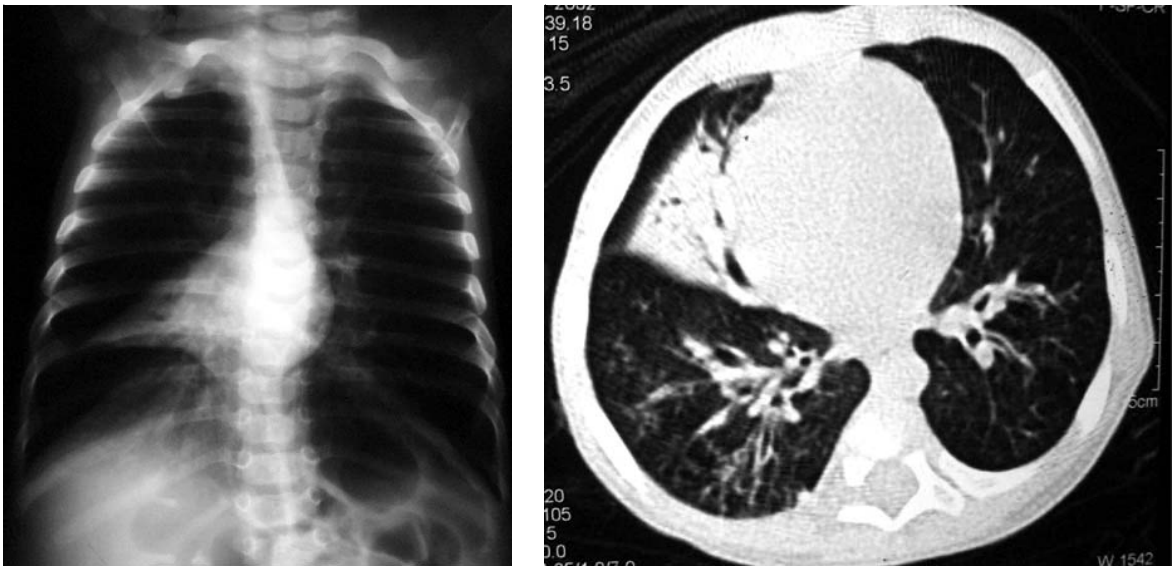
Physical examinations of the presented patient revealed a low-grade fever, lethargy, 140/min pulse, 40/min respiration, 4,400 g body weight, suprasternal and subcostal retraction and no heart murmur. Coarse crepitation and sonorous rhonchi were heard over the chest. The liver was firm upon palpation with a span of 8 cm while the spleen was impalpable.

Completed blood counts revealed Hb12 gm%, Hct 37%, WBC 18,100 cells/mm^3 with 86% polymorphonuclear cells. Urine analysis showed only trace albuminuria. The stool was loose, greenish-colored with 2-3 pus cells/high-power field. The initial serum electrolytes revealed sodium 106 mEq/L, potassium 1.9 mEq/L, bicarbonate 32.9 mEq/L and chloride 56 mEq/L. Total protein was 6 g/dL with albumin 3.7 g/dL.

After initial intravenous fluid administration, the general symptoms quickly improved, but the serum electrolyte imbalance showed persistent hypochloremic, hyponatremic, metabolic alkalosis.

The chest radiograph showed generalized hyperaeration with right middle lobe atelectasis (Fig. 2A). Computerized tomography of the chest was performed and showed complete atelectasis of the right middle lobe and mild tubular bronchiectasis, intralobular septal thickening was noted at the posterior basal segment of the right lower lobe (Fig. 2B). The diagnosis of cystic fibrosis was suspected even though it is rare in Thailand.

The sweat chloride test was not available at this hospital, so a modified sweat chloride test was created to support the diagnosis. The patient was placed under a heater to induce sweating. The skin was cleaned and covered with sterile gauze occluded with a transparent adhesive to prevent evaporation. The gauze was squeezed and the sweat collected in a capillary tube and sent for immediate laboratory analysis. The serum and sweat electrolytes obtained at the same time are presented in Table 1.



A B

Fig. 2 The chest X-ray and computerized tomography of the chest of Case No. 1
The chest radiograph reveals marked hyperearation both lungs with atelectasis of the right middle lobe (A). The axial CT scan of chest through lower lobes of the lung shows completely atelectasis of the right middle lobe and mild tubular bronchiectasis and intralobular septal thickening are noted at posterior basal segment of the right lower lobe (B)

During hospitalization, the child developed *Pseudomonas aeruginosa* septicemia and respiratory failure. He was intubated and placed on a mechanical ventilator and treated with antibiotics. He was later discharged with a tracheostomy tube and needed home-oxygen therapy after 3 months of admission. Five months later, he was re-admitted because of fever and respiratory distress. He died on the 4th day of re-admission due to a recurrence of *Pseudomonas aeruginosa* septicemia. A DNA analysis revealed deletion of delta F508 homozygous confirming the diagnosis of CF.

Case 2

A 2-month-old, Thai girl presented to the OPD on June 10, 2002, after suffering abdominal distension and vomiting for 2 weeks. She was a full-term baby with a birth weight of 3,500 g, born normally from a G2P1 mother whose first child died at 3 months of age due to severe pneumonia and ARDS (Fig. 1B). Her parents live in Wapeephatum District, Maha Sarakham Province, Thailand.

The physical examination revealed a drowsy baby, with a body weight of 3,400 g, moderate dehydration, no fever, mild chest retraction, while the rest of the examination was unremarkable. The initial serum electrolytes showed the sodium, potassium, bicarbonate and chloride were 130, 3.4, 33.7 and 66 mEq/L. The urine electrolytes for sodium, potassium and chloride, for the same period, were 15, 7.6 and 15 mEq/L, respectively. After intravenous fluid re-hydration, her serum electrolytes rose to normal levels.

Table 1. The serum and sweat and urine electrolytes of the first child

	Serum April 9, 02	Serum June 5, 02	Sweat June 5, 02	Serum June 7, 02	Sweat June 7, 02	Urine June 7, 02
Sodium, mEq/L	106	140	153	140	170	38
Potassium, mEq/L	1.9	4.0	30	3.2	28.1	10.9
Bicarbonate, mEq/L	32.9	35	-	22.5	-	-
Chloride, mEq/L	56	83	201	101	182	15

The radiological study of the chest and gastrointestinal tract were unremarkable. She was discharged from hospital within 10 days of admission with a diagnosis of gastroesophageal reflux.

Her second admission was on July 22, 2002, because of severe vomiting. Her serum electrolytes - sodium, potassium, bicarbonate and chloride - were 126, 3.1, 30.1 and 82 mEq/L, respectively. Her stool examination showed numerous fat cells. The chest X-ray revealed normal findings. She was suspected of having cystic fibrosis similar to our first case that was still admitted at the same time.

After symptomatic and supportive treatment, her parents asked to have her referred to a hospital in Bangkok; unfortunately, she died from respiratory failure and severe sepsis (at four months of age) at that hospital. DNA analysis revealed a novel homozygous nonsense mutation in exon 6a (738G>A, W202X).

Case 3

The third baby came to the authors' attention ten months after the first case (February 26, 2003). This 6-month-old, Thai girl was referred from a provincial hospital because of recurrent respiratory distress. She was born normally with a birth weight of 3,150 g, and had a good Apgar score. The first episode of respiratory distress, together with diarrhea, occurred at the age of 45 days. She was first diagnosed with pneumonia and treated in hospital for three weeks. After discharge, her mother noticed steatorrhea and tachypnea but the infant continued to feed well. At the age of four months, she suffered from pneumonia again and spent two weeks in hospital. The third admission occurred one week prior with a history of fever, cough and dyspnea. She was treated with parenteral antibiotics without improvement. Therefore, she was referred to this hospital for further evaluation.

She was the third child of the family. Her oldest sister died at the age of three months due to pneumonia and intestinal obstruction. Her second brother was healthy. There was no consanguineous marriage in the family. Her mother was the youngest child of her family and had four siblings who died of unknown causes within four months of age (Fig. 1C). Her parents live in Ranunakhon District, Nakhon Phanom Province, Thailand.

The physical examination revealed a temperature of 38.8 C, a respiration rate of 54/minute, a pulse of 144/minute, a body weight of 3 800 g, and mild suprasternal and subcostal retraction. Sonorous rhonchi were heard all over the chest with normal heart sounds. The liver was palpated 3 cm below the right subcostal margin and had a soft consistency and a smooth surface. The rest of the physical examinations were within normal limits.

The initial complete blood examination revealed: hemoglobin 10.4 gm%, hematocrit 28.2%, total white blood cells 8 700 cells/mm^3 with 47% polymorphonuclear cell, 45% lymphocytes, and normal platelet count.

The initial serum electrolytes revealed sodium, potassium, bicarbonate and chloride of 124, 2.6, 41 and 63 mEq/L, respectively. The concurrent urine electrolytes showed sodium, potassium and chloride of 18, 23.4 and 42 mEq/L. The serum total protein and albumin were 5.8 and 3.3 g/dL. The repeated serum electrolytes revealed persistent hypochloremic, hyponatremic, metabolic alkalosis despite intravenous fluid administration.

The stool examination was positive for fat globule. The chest radiograph showed generalized hyperaeration, no infiltration, and a normal cardiac shadow. An attempted sweat collection failed in this case.

Symptoms improved after the child was fed a special formula and underwent salt replacement. Her DNA analysis showed a heterozygous A455E point mutation, the other allele mutation could not be identified. She was referred back to be followed-up at the provincial hospital, where she has had 4 more hospitalization with recurrent pneumonia. The last admission was 1 years prior. Now she is 3 years old and has been well since then.

The parents of all 3 children were native-born in the Northeast, Thailand, and at least the last three generations of their ancestors were Thai.

Discussion

The authors report three children with cystic fibrosis of different genotypes, presenting with different clinical manifestations, but having similar abnormal serum electrolytes; namely, hyponatremic, severe hypochloremic and metabolic alkalosis.

The clinical manifestations of this disease vary greatly between affected individuals as related to the genotype for CFTR protein production and function[6,7]. There are few case reports of this disease from South East Asian Countries, particularly describing the genotype mutation. The common presentations are pulmonary (*i.e.* coughing, wheezing, recurrent pneumonia) and gastrointestinal symptoms (*i.e.* frequent loose, foul smelling and greasy stools due to pancreatic insufficiency).

Many other common diseases in children may cause similar presenting symptoms. Moreover, CF is rare in Asia and, therefore, left to the last or even omitted in the differential diagnosis. The diagnosis of CF is through a sweat chloride test, which (unfortunately) is not available for routine investigations in Thailand. The literature review revealed only three case reports of CF from Thailand diagnosed by: 1) autopsy (1 case)[8], 2) a modified sweat test and confirmed by autopsy (1)[9], and 3) DNA analysis (1).[10]

The authors' first case presented with typical manifestations of CF (chronic respiratory distress due to bronchiectasis, recurrent diarrhea, failure to thrive, and persistent hypochloremia), thereby leading us to a correct diagnosis of this relatively rare disease in Thailand. His genotype analysis showed homozygous DF508 and although the 2nd and 3rd cases presented to us a few months later with different manifestations, their serum electrolytes showed the same abnormality. Because of the unavailability of the sweat chloride test in this hospital, the authors tried to create a modified sweat collection protocol; the results showed very high chloride levels compared to a control, although the high level might be an artifact - due to evaporation during collection. The authors unfortunately failed to collect the sweat from the other two patients.

All of the presented patients had had a family history of death among older siblings due to severe pneumonia or sepsis during infancy, suggesting there may be more infants dying without definite diagnosis leading to unreported cases. Therefore, these three histories provide important clues for diagnosing CF in infants presenting with chronic respiratory or gastrointestinal symptoms, failure to gain weight and unexplained severe hypochloremia.

All of the presented patients were confirmed by genotype analysis showing different mutations among them: homozygous DF508; 738G > A, W202X and A455E point mutation, heterozygous, respectively. The presented patients had different genotype mutations than the previous Thai report[10].

ΔF508 is the most common mutation, accounting for 70% of CF chromosomes in patients from North America,[11] while the A455E mutation accounts for 0.1% of the CF chromosomes, but has a higher rate among patients of French-Canadian origin[12,13]. Patients with a homozygosity for ΔF508 have more severe disease than those heterozygous for ΔF508 and those with non-DF508 alleles[14-16].

Patients with compound heterozygosity for A455E mutations have milder pancreatic and lung diseases[17]. The presented patients sharing DF508 allele either homozygous or heterozygous presented with severe diseases and high mortality. Only the patient with an A455E mutation had mild pulmonary and pancreatic insufficiencies. From the history, they and their ancestors were native-born and living in the Northeast Thailand; although the authors could not trace their lineage. The third case (an A455E mutation) lived in Nakorn Panom province located near the border with Laos.

Conclusion

The prevalence of CF in our population may rise in the future because of the increasing trend among Thai women to marry Caucasians. Then the incidence of CF in Thailand may be underestimated due to the unavailability of diagnostic tests. Since early identification and treatment are critical to effective management and the unavailability of diagnostic tools, clinical manifestations, severe electrolyte imbalance especially persistent hypochloremia and a family history of early infant death with respiratory or gastrointestinal problems should be recognized as major pointers for a diagnosis of CF. The diagnostic tools, especially the sweat test, should be made available to aid diagnostic investigations and ensure timely treatment in Thailand.

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รายงานผู้ป่วยเด็กโรคซีสติกไฟโบรสิสจากภาคตะวันออกเฉียงเหนือจำนวน 3 ราย โรคนี้พบน้อยในประชากรไทยจริงหรือ

จามรี ธีรตกุลพิศาล, เพ็ญศรี โควสุวรรณ, จิราภรณ์ ศรีนัครินทร์, ชาญชัย พานทองวิริยกุล, สุมิตร สุตรา

รายงานผู้ป่วยทารก จำนวน 3 ราย ที่ได้รับการวินิจฉัยเป็นโรคซีสติค ไฟโบรสิก โดยการตรวจพบจีนที่มีความผิดปกติที่แตกต่างกัน ผู้ป่วยทั้งสามรายมาพบแพทย์ด้วยอาการสำคัญที่แตกต่างกัน แต่ตรวจพบความผิดปกติของระบบแร่ธาตุและดุลกรดด่างในเลือดเช่นเดียวกัน คือ มีค่าซีรัมโซเดียมต่ำและคลอไรด์ต่ำมาก รวมทั้งมีภาวะเลือดเป็นด่าง แม้ว่าโรคนี้จะมีรายงานผู้ป่วยพบน้อยมากในประเทศไทย ทั้งนี้อาจจะเนื่องจากขาดเครื่องมือในการตรวจวินิจฉัย โดยเฉพาะการตรวจหาค่าคลอไรด์จากเหงื่อ หากผู้ป่วยโดยเฉพาะเด็กทารกที่ตรวจพบความผิดปกติของระบบแร่ธาตุ โดยเฉพาะซีรัมคลอไรด์ต่ำมาก ร่วมกับมีประวัติการเสียชีวิตของพี่น้องในครอบครัว ด้วยปัญหาความผิดปกติของระบบหายใจหรือระบบทางเดินอาหารตั้งแต่เล็ก ๆ แพทย์ควรวินิจฉัยแยกโรคนี้ด้วย

ควรจะมีเครื่องมือ การตรวจวินิจฉัยโรคนี้ โดยเฉพาะการตรวจเหงื่อ ให้มีขึ้นในโรงพยาบาล ระดับใหญ่ในประเทศไทย เพื่อให้แพทย์สามารถให้การวินิจฉัยโรคนี้ได้ตั้งแต่เริ่มต้น