Case Report

Rare F311L CFTR Gene Mutation in a Child Presented with Recurrent Electrolyte Abnormalities and Metabolic Alkalosis: Case Report

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Delta F508 mutation is recognized as the most common genotype of cystic fibrosis (CF) however, there are small numbers of CF patients having Delta F508/F311L. In the present study, the authors report a 2 year-old Thai boy, originating from North India, presenting with recurrent episodes of febrile illness, hyponatremia, hypokalemia, and metabolic alkalosis since 4 months of age. He was transferred to our hospital for further investigation. Blood chemistry revealed the following serum electrolytes, sodium 122, potassium 3.69, chloride 79.7, and bicarbonate 33.8 mEq/L, and the following urine electrolytes, sodium < 10, potassium 45.7 and chloride < 10 mEq/L. After intravenous fluid administration, hyponatremia and metabolic alkalosis improved. DNA sequencing analysis of his blood demonstrates compound mutation for Delta F508 and F311L in CFTR gene. In conclusion, the authors report a rare case of CF with Delta F508/ F311L genotype presented with recurrent hyponatremia and metabolic alkalosis. Awareness of electrolyte abnormalities during febrile illness, proper genetic counseling, and long-term follow up are necessary in this patient.

Keywords: *Alkalosis, Cystic fibrosis, Cystic fibrosis transmembrane conductance regulator, Hyponatremia, Mutation*

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Cystic fibrosis (CF) is characterized by mutations in single gene on chromosome 7 that encodes CFTR protein[1]. So far, there are 1604 mutations reported in CF. Delta F508 has been recognized as a common site of mutation[2,3]. The usual presenting symptom and sign are persistent pulmonary infection, pancreatic insufficiency and elevated sweat chloride level, however, electrolyte imbalance and acid base disorder may be the initial presenting symptom[4-7].

Case Report

A 2 year-old boy was evaluated in our center because of recurrent hyponatremia, hypokalemia, and metabolic alkalosis since he was 4 months old. He was the first child to be born and grow up in Thailand. His parents originated from North India without any history of chronic illness or consanguineous marriage in the family. He had recurrent episodes of electrolyte disturbance and metabolic alkalosis at the age of 4 months, 16 months, and 18 months (Table 1). Each episode was precipitated by high-grade fever, vomiting, and poor appetite. Pseudomonas aeruginosa pneumonia developed at the first and third admission in a hospital. Urine electrolyte was collected after intravenous fluid administration and demonstrated chloriuresis. All electrolyte abnormalities and metabolic alkalosis resolved after rehydration, sodium, and potassium supplement. The diagnosis of Bartter syndrome was suspected and he was transferred to our hospital for further investigation. At our hospital, he was doing well without dehydration. His body weight and height were in the 50th centile. Blood pressure was 90/60 mmHg. Serum electrolytes and renal function were normal. One month later, he was admitted to the hospital again due to high-grade fever and poor appetite. He was severely dehydrated. Lab investigation revealed serum Na 122, K 3.69, Cl 79.7, and CO_2 33.8 mEq/L, calcium 10.9 mg/dL,

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Table 1. Clinical manifestation, serum and urine electrolytes before transferred to our center

	4-month old	1 year and 4-month old	1 year and 6-month old
Clinical manifestation	Fever, poor appetite, pneumonia	Fever and vomiting	Fever, poor appetite, seizure
Serum electrolytes (mEq/L)			
Sodium	137.00	115.00	106.00
Potassium	2.43	2.40	1.00
Chloride	92.00	66.00	50.00
Bicarbonate	40.30	36.00	62.00
Urine electrolytes (mEq/L)			
Sodium	16.00	20.00	not done
Potassium	19.10	29.00	not done
Chloride	36.00	40.00	not done

* All urine electrolytes were collected after rehydration

phosphorus 4.8 mg/dL, magnesium 2.2 mg/dL, BUN 43 mg/dl, and serum creatinine 0.4 mg/dL. Urine electrolytes before rehydration revealed Na <10, K 45.65, Cl < 15 mEq/L. His clinical symptoms improved after fluid bolus and correction of hyponatremia. Because CF was the possible cause of metabolic alkalosis in this case and sweat chloride test was not available in our center, blood sample was transferred overseas to Quest Diagnostics Nichols Institute, California, USA for further investigation. The DNA sequencing analysis of the entire coding region and splice-site of CFTR gene revealed compound mutation for DeltaF508 and F311L, DeltaF508/F311L genotype (Fig. 1). T to G transversion at nucleotide 2694 in exon 14a at position 854 and G to A transversion at nucleotide 4521 in exon 24 at position 1463 were also demonstrated, but there were no alteration of amino acid encoding genes, threonine, and glutamine.

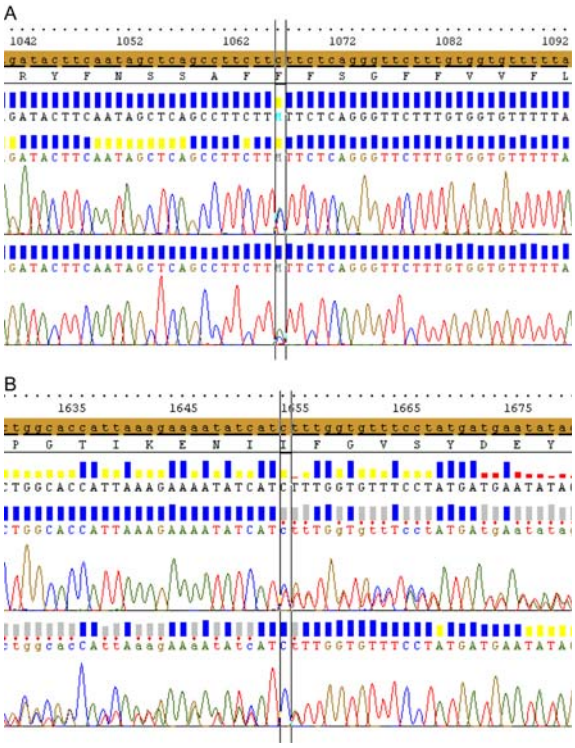

Fig. 1 Genetic sequencing analysis of CFTR gene
A) mutation of cytosine (C) at nucleotide 1065 in exon 7, B) deletion of 3 base pairs between nucleotide 1652 and 1655 in exon 10

Discussion

The incidence of cystic fibrosis in Caucasians is 1: 2000-4000 live births however, the disease is rare in Asian population[7,8]. McCormick J, et al reported an incidence of 1: 10,000-12,000 for CF in Asian migrants in the United Kingdom[9-11]. In the Indian population, prevalence of CF is 1: 5000 live births and more than 81% originated from North India[12]. Common symptoms of Indian patients are recurrent or persistent pneumonia, failure to thrive, and malabsorption. There are few reports about CF in Thailand. Pacharee P reported fibrocystic change of the pancreas in an infant[13]. Teeratakulpisarn J, et al reported three cases of CF, aged 4-6 months, presenting with pneumonia, gastro-intestinal tract malabsorption, electrolyte, and acid-base disturbances[14]. Prevalence of the DeltaF508 mutation is approximately 70% in Caucasian and 50% in Indian population while F311L is demonstrated only 0.2% in Brittany, France, 0.0% in Basse-Bretagne and 0.7% in Haute-Bretagne[3,15,16]. Mutation of DeltaF508 is caused by deletion of three base pairs between nucleotide 1652 and 1655 in exon 10 of the CFTR gene.

The consequence is the deletion of a phenylalanine at position 508. For mutation of F311L, the cause is a cytosine (C) to guanine (G) transversion at nucleotide 1065 in exon 7 of the CFTR gene. This single nucleotide substitution leads to the replacement of a normal phenylalanine by a leucine at position 311 of the translated CF protein[17]. A study from the European Epidemiologic Registry of Cystic fibrosis revealed that patients with defective conductance of CFTR gene such as F311L alleles have milder symptoms of pancreatic insufficiency, diabetes mellitus, and liver disease[18]. F□rec et al reported two French origin patients with F311L mutation. One is G551D/F311L genotype with pancreatic insufficiency and mild respiratory symptoms, and the other is DeltaF508/F311L genotype with pancreatic insufficiency[17]. Scotet V, et al demonstrated a neonate with N1303K/F311L mutation in Britanny, France who had false negative neonatal screening test[19]. The major clinical manifestation in the presented patient was hyponatremia, hypokalemia and metabolic alkalosis while pneumonia and pancreatic insufficiency were mild. Hyponatremia, hypokalemia and metabolic alkalosis have been described as initial presentation in CF between 16.2-28.3% and presented during neonatal and infantile period[4-7,20]. However, CF may be detected in previously healthy adolescents[21]. Most of them have only mild pulmonary symptoms. Predisposing factors of severe hypoelectrolytemia and metabolic alkalosis are early infant age, breast-feeding, delayed CF diagnosis, and heat exhaustion[6]. The common clinical findings are signs of dehydration, vomiting, fever, anorexia, irritability, and failure to thrive. However, hypoelectrolytemia and metabolic alkalosis may be observed in mild dehydrated infants due to chronic electrolyte loss and volume depletion related to hot climates[4,6]. Fustik S, et al demonstrated genotypes of CF patients with manifestations of metabolic alkalosis and hypoelectrolytemia that 64.7% were homo mutation of DeltaF508, 17.6% were DeltaF508/G542, 5.9% were G542X/N1303K, 5.9% were DeltaF508/unknown, and 5.9% were CFTR del 21 Kb/unknown[6]. Low urine specific gravity may be observed in CF infants due to temporary loss of renal concentrating ability from severe hypokalemia[4]. Hyponatremia and hypochloremia in CF patients are caused by excessive sodium and chloride loss in sweat without sufficient salt supplement. Infants with CF may lose more than 80 mEq/L of sodium, 100 mEq/L of chloride, and 40 mEq/L of potassium per day[22]. Chloride may also lose from diarrhea in CF infants[23]. Activation of renin-angiotensin-aldosterone system is responsible for increasing sodium reabsorption, potassium excretion, and hydrogen excretion causing hypokalemia and metabolic alkalosis, so-called pseudo Bartter's syndrome in CF[24]. Urine chloride is hallmark for differentiation of CF and Bartter's syndrome. Usually, urine chloride is less than 20 mEq/L in CF and more in Bartter's syndrome. Urine chloride should be performed before fluid administration since volume expansion will increase sodium and chloride excretion. In our hospital, serum and urine electrolytes were collected at the same time before fluid management and revealed low urine sodium and chloride[25]. Vomiting is the contributory factor that aggravates electrolyte depletion and metabolic alkalosis. Although there is no history of CF in his family, some family members may carry this mutation. Family study may be indicated and genetic counseling is important.

In conclusion, the authors report a rare case of DeltaF508/F311L mutation presented with recurrent hypoelectrolytemia and metabolic alkalosis. Awareness of excessive salt loss and increased salt intake during febrile illness and hot climate, proper genetic counseling, and long-term follow up are necessary.

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รายงานความผิดปกติทางพันธุกรรม F311L ของ CFTR gene ในผู้ป่วยเด็กที่มีความผิดปกติของเกลือแร่และเลือดเป็นด่าง

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การเปลี่ยนแปลงทางพันธุกรรมของ Delta F508 เป็นตำแหน่งที่พบบ่อยที่ทำให้เกิดโรค cystic fibrosis อย่างไรก็ตามการเปลี่ยนแปลงทางพันธุกรรมของ Delta F508/ F311L พบได้ไม่บ่อยนัก ในการศึกษา ครั้งนี้ได้นำเสนอผู้ป่วยเด็กอายุ 2 ปีมีอาการไข้ ระดับโซเดียมและโปแตสเซียมในเลือดต่ำเป็น ๆ หาย ๆ ตั้งแต่อายุ 4 เดือน โดยพบซีรัมโซเดียม 122 โปแตสเซียม 3.69 คลอไรด์ 79.7 และไบคาร์บอเนต 33.8 มิลลิอิควิวาเลนต์/ลิตร จากการตรวจปัสสาวะพบโซเดียม < 10 โปแตสเซียม 45.7 คลอไรด์ < 10 มิลลิอิควิวาเลนต์/ลิตร ภาวะดังกล่าวสามารถแก้ไขได้ด้วยการให้สารน้ำแก่ผู้ป่วยจากการตรวจทางพันธุกรรม พบการเปลี่ยนแปลงทางพันธุกรรมของ Delta F508 และ F311L ของยีน CFTR จากการศึกษาครั้งนี้ผู้วิจัยได้นำเสนอผู้ป่วยโรค cystic fibrosis ที่เกิดจากการเปลี่ยนแปลงทางพันธุกรรมของ Delta F508 และ F311L ซึ่งมีอาการนำคือระดับซีรัมโซเดียม ในเลือดต่ำและมีภาวะเลือดเป็นด่าง การให้การป้องกันและแก้ไขความผิดปกติของเกลือแร่ การให้คำปรึกษาทางพันธุกรรมตลอดจนการดูแลผู้ป่วยอย่างต่อเนื่องมีความจำเป็นสำหรับผู้ป่วยรายนี้