대한 유전성 대사질환 : 제 1 권 제 1 호, pp28~29, 2001

Sudden Infant Death in the Second Case of Korean Girl with Very Long Chain Acyl CoA Dehydrogenase (VLCAD) Deficiency

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The very long chain acyl CoA dehydrogenase (VLCAD) is a mitochondrial membrane bound enzyme catalyzing the dehydrogenation of long-chain fatty acids in the first step of mitochondrial fatty acid (oxidation. Since the first description of a patient with very long chain acyl CoA dehydrogenase (VLCAD) deficiency (McKusick 201475) (Aoyama et al 1993), more than 20 patients have been reported to date. Among them, only a few cases were reported in connection with sudden infant death syndrome. Major phenotypic presentations are hypoketotic hypoglycemia, encephalopathy, hepatomegaly, myopathy, hypertropic cardiomyopathy and elevated plasma creatine phosphokinase (CPK) level. Though prolonged fasting and infections are the most common precipitants of acute metabolic decompensations in patients with VLCAD deficiency, unexplained cardiorespiratory arrest and sudden death are also known to occur.

We report the second Korean patient with VLCAD deficiency who expired with cardiac failure and arrhythmias and whose two previous siblings succumbed to tachypnea and sudden death during their neonatal period, at first and 3rd day after birth, respectively.

A girl weighing 2560 g was born to a healthy 36-year-old woman at the 38th week of gestation from an unrelated parent. The infant initially received a special care due to notable tachypnea and moaning sound in NICU for 2 weeks. Results of a workup for sepsis were negative, and she showed improvement with intravenous administration of glucose. Then she was well until 5 months of age when she presented with severe diarrhea and vomiting with tachypnea for 3 days, followed by respiratory difficulty, hypotonia and lethargy. On admission, she was critically ill with tachycardia. Her electrocardiographic findings suggested paroxysmal supraventricular tachycardia. Her liver was apparently abnormal with hepatomegaly, fatty liver suspected by sonography, and elevation of serum aspartate aminotransferase (239 IU/L, NL; <40) and alanine aminotransferase (304 IU/L, NL; <40). Her chest x-ray showed marked cardiomegaly without pulmonary congestion. A two-dimensional echocardiogram revealed marked concentric biventricular hypertrophy, increased echogenecity, and a moderate amount of pericardial effusion.

Blood chemistries revealed a compensated metabolic acidosis with an increased anion gap. Serum ammonia (119 μmol/L), CPK (1271 U/L, NL; <180) and lactate dehydrogenase (LDH) (4767 1U/L, NL; <550) increased with slightly low glucose (55 mg/dL) at the time of presentation. Her urine organic acid profile showed extremely tiny amount of excretion of C6-C10 dicarboxylic acids with 3-hydroxy C6-C12 dicarboxylic acids, which

is not diagnostic since these findings could be seen in peroxisosomal disorder or by acetaminophen or valproate administration. Her plasma amino acid profile was normal. Total carnitine [26.4 (mol/L (NL; 38-68)], free carnitine [18.2 (mol/L (NL; 27-49)] and acylcarnitine [8.2 (mol/L (normal, 7-9)] were slightly decreased with the normal ratio [0.45 (NL; 0.2-0.5)] of acylcarnitine to free carnitine.

Administration of carnitine, multiviatamin with 10% dextrose was iniiated without clinical improvement. Amiodarone and adenosisne were infused to normalize cardiac rate. However, the patient died on the 16th day of hospitalization.

Mutational analysis was undertaken in all 20 exons of the *VLCAD* gene, using genomic DNA isolated from peripheral leukocytes, by single strand conformation polymorphism and DNA sequence analysis. She turned out to be a compound heterozygote individual for mutations in the *VLCAD* gene. One allele carries a 3-bp deletion in exon 6 at nt 385-7, deleting a glutamic acid in codon 130 (E130 del), which is the same mutation identified in a Korean patient previously reported (Hahn et al 1999). The other allele contains an insertion of a T at nt 997 (997insT). This novel frame shift mutation leads to a premature termination at amino acid residue 318, near the end of exon 10. Such premature termination mutations are rarely expressed at the mRNA level, as the precursor mRNA is rapidly degraded.

Although the phenotype and genotype of this case share common features with the previously reported, this patient has unique features as follows; firstly, as an Asian ethnic background, this patient is only the third reported to our knowledge. Secondly, this case presented with cardiac manifestations such as dysrhythmia (paroxysmal supraventricular tachycardia) and pericardial effusion, leading to sudden death. Thirdly, this patient turned out to be a compound heterozygoete for a novel mutation(997insT) in the VLCAD gene. This indicates that although the VLCAD deficiency is rare, this disease is varying in clinical manifestations as well as genetically heterogeneous.

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