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심포지움 2

Overview of citrin deficiency and its incidence in Asian region

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≡ Abstract ≡

Citrin deficiency[1-3] is an autosomal recessive disease discovered in Japan which shows at least two phenotypes: adult-onset type II citrullinemia (CTLN2; MIM#603471) and neonatal cholestatic hepatitis (NICCD; MIM#605814).

The most characteristic feature of CTLN2 is the late onset of serious and recurring hyperammonemia and neuropsychiatric symptoms including nocturnal delirium, aggression, irritability, hyperactivity, delusions, disorientation, restlessness, drowsiness, loss of memory, flapping tremor, convulsive seizures, and coma; death can result from brain edema. Onset is sudden and usually between the ages of 20-50 years. Many individuals with CTLN2 are fond of protein-/lipid-rich foods and have an aversion to carbohydrate-rich foods; symptoms are often provoked by alcohol intake, medication, and/or surgery. Pathological findings include fatty infiltration and mild fibrosis of the liver despite little or no liver

dysfunction. The prognosis is poor, but liver transplantation is remarkably effective. CTLN2 has been characterized by a liver-specific deficiency of argininosuccinate synthetase (ASS) which is a rate-limiting enzyme of the urea cycle. CTLN2 patients have been diagnosed on the basis of well-established criteria, including their symptoms and laboratory findings such as high blood ammonia, increased citrulline, arginine, ratio of threonine to serine and pancreatic secretory trypsin inhibitor (PSTI) levels, and decreased hepatic ASS activity/protein levels. However, there are no abnormalities in hepatic ASS mRNA and within the ASS gene locus, and the primary defect of CTLN2 has been unknown for a long time.

We have noted that 26 of 132 CTLN2 patients are apparently from consanguineous parents, suggesting that CTLN2 is an autosomal recessive disorder. By using homozygosity mapping and positional cloning, Kobayashi et al. (1999)[1] discovered that CTLN2 is caused by mutations of the SLC25A13 gene organized into 18 exons, which is localized on chromosome 7q21.3, mainly expresses in the liver and encodes a calcium-binding mitochondrial solute carrier protein with a molecular weight of 74 kDa (675 amino acids), designated citrin. Yasuda et al. (2000)[4]have detected no cross-reactive immune materials in the liver of CTLN2 patients by Western blot analysis with anti-human citrin antibody. From these findings, we found that CTLN2 is a citrin deficiency, although the mechanism of secondary ASS deficiency is still unknown. Later, Palmieri et al. (2001)[5] found that citrin is localized in the mitochondrial inner membrane and functions as a Ca^{2+}-stimulated aspartate-glutamate carrier (AGC).

Until recently, very little was known about clinical symptoms in the neonatal/infantile period of CTLN2 patients. DNA analyses have revealed that some neonatal/infantile patients with a type of hepatitis associated with galactosemia, multiple aminoacidemia including citrullinemia, hypoproteinemia and jaundice, were homozygotes or compound heterozygotes for the same SLC25A13 mutations as those found in CTLN2 patients[6-8]. Therefore, we designated them NICCD (neonatal intrahepatic cholestasis caused by citrin deficiency) as a neonatal/infantile phenotype[2,9]. NICCD patients show various and transient symptoms (such as intrahepatic cholestasis, diffuse fatty liver and parenchymal cellular infiltration associated with hepatic fibrosis, low birth weight, growth retardation, hypoproteinemia, decreased coagulation factors, hemolytic anemia, hepatomegaly, variable liver dysfunction, and/or hypoglycemia) and laboratory findings (such as increased plasma citrulline, arginine, threonine/serine ratio,methionine, tyrosine, galactose, total and direct bilirubin, total bile acids, and/or -fetoprotein with little or no increased blood ammonia). NICCD is generally not severe. Symptoms disappear by one year of age without or with fat-soluble vitamin supplementation and lactose-free formulas or formulas containing medium-chain triglycerides, and most NICCD patients become apparently healthy probably due to some sort of metabolic change, adaptation or compensation. Starting around 1.5-2 years of age, children show a peculiar fondness for protein-/lipid-rich foods and an aversion to sugar-/

carbohydrate-rich foods. One or more decades later, some of them suffer from CTLN2.

Citrin deficiency was thought to be restricted to Japan, however, several cases have been found in other countries, indicating a wide distribution of citrin deficiency. So far, we have identified twenty-eight SLC25A13 mutations [14 out of them have been published[1,4,9-12] others: Tabata et al. manuscript in preparation] and diagnosed the patients not only in Japan (152 CTLN2 and 182 NICCD) but also in many other countries. We have detected 3 CTLN2 Chinese[12-15], 25 NICCD Chinese including Taiwanese[12,13,16,17] (3 or 4 of 6 Taiwanese NICCD patients reported by Yeh et al.[18] may be involved in the patients we have diagnosed), 4 NICCD Vietnamese (in Australia[19], USA, Czech and France), 1 NICCD Malaysian Chinese and 1 NICCD Korean with the same mutations as Japanese. In Israel[10], USA[20], UK and Czech, we have detected 12 NICCD patients with mutations different from those found in Japanese.

The DNA diagnoses of 12 known SLC25A13 mutations found in Japanese patients revealed that the carrier frequency was high in control individuals from East Asia[12,13]. We noticed some regional specificity in mutation type in East Asia and regional difference in mutation frequency in China. Mutations 851del4 and 1638ins23 were found in all Asian countries tested, and 851del4 was especially frequent, suggesting that the distribution of these mutations may be due to the founder effect. IVS11+1G>A in Japanese and Korean, S225X in Japanese, and IVS6+5G>A in Chinese may have arisen after racial divergence. From haplotyping analysis of microsatellite marker D7S1812 located in intron 15 of SLC25A13 gene, it is reasonable to consider that 851del4 associated with 290-haplotype occurred in the south China, and IVS11+1G>A found in Japan and Korea associated with 281-haplotype occurred in north Mongolia or southeast Siberia. We found a remarkable difference in carrier rates in China (including Taiwan) between north (1/940) and south (61/2933=1/48) of the Yangtze River. We detected many carriers in Chinese (64/4169=1/65), Japanese (21/1372=1/65) and Korean populations (22/2455=1/112), suggesting that over 100,000 East Asians are homozygotes with two mutated SLC25A13 alleles.

In Japan, frequency of homozygote (1/17,000) is almost the same as NICCD incidence (1/17,000-34,000), but quite different from CTLN2 incidence (1/100,000-230,000). From our observation in Japanese patients, we consider that after NICCD symptoms (0-1 years) were ameliorated, the homozygotes may be partly diagnosed as CTLN2 (10-80 years), other diseases such as pancreatitis, hepatoma, hyperlipidemia or psychosis, and/or healthy. In order to avoid mis-diagnosis and mis-treatment of the patients with citrin deficiency, it is now important to find out patients with CTLN2 and NICCD, to treat them properly, and to prevent onset of severe CTLN2.

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