A Novel Frameshift Mutation of the ALDOB Gene in a Korean Girl Presenting with Recurrent Hepatitis Diagnosed as Hereditary Fructose Intolerance

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Hereditary fructose intolerance is an autosomal recessive disorder that is caused by a deficiency in fructose-1-phosphate aldolase (Aldolase B). Children can present with hypoglycemia, jaundice, elevated liver enzymes and hepatomegaly after intake of dietary fructose. Long-term intake of fructose in undiagnosed patients can result in hepatic failure or renal failure. We experienced a case of hereditary fructose intolerance presenting as recurrent hepatitis-like episodes. Detailed evaluation of her dietary habits revealed her avoidance of sweetened foods and fruits. Genetic analysis of ALDOB revealed that she is a homozygote for a novel frameshifting mutation c[758_759insT]+[758_759insT] (p.[val253fsX24]+[val253fsX24]). This report is the first of a Korean patient diagnosed with hereditary fructose intolerance using only molecular testing without undergoing intravenous fructose tolerance test or enzyme assay. (Gut Liver 2012;6:126-128)

Key Words: Fructose intolerance; Aldolase B; Hepatitis; Hypoglycemia; Gene

INTRODUCTION

Hereditary fructose intolerance (HFI, OMIM# 229600) is an autosomal recessive disorder, caused by a deficiency in fructose-1-phosphate aldolase (Aldolase B) which exists in the liver, kidney, and intestines.1 Deficiency of this enzyme causes an accumulation of fructose-1-phosphate after fructose intake, which results in toxic symptoms like vomiting, hypoglycemia, jaundice, elevated liver enzymes and hepatomegaly.2 HFI was diagnosed traditionally by biochemical tests such as intravenous fructose tolerance test or enzyme assay. A novel frameshifting mutation of the ALDOB gene was identified in this Korean girl, which was confirmed by molecular testing.
DISCUSSION

Deficiency of fructose-1-phosphate aldolase (aldolase B) causes accumulation of fructose-1-phosphate in the liver, kidneys, small intestines which leads to symptoms like abdominal bloating, vomiting and elevated liver enzymes. Deficiency of this enzyme also causes inhibition of other enzymes such as fructose-1,6-bisphosphate aldolase and fructokinase, resulting in impaired glycogenolysis and gluconeogenesis which can lead to fatal hypoglycemia. Chronic ingestion of fructose of sucrose results in failure to thrive and repeated episodes of hypoglycemia eventually leads to fatal hepatic or renal failure. Our patient presented with typical features of HFI such as vomiting, elevated liver enzymes, and hepatomegaly. Other symptoms of HFI include lethargy, convulsions, proximal tubular dysfunction which our patient didn’t present. However, these manifestations can also be found in other metabolic liver diseases including galactosemia. For making the diagnosis of HFI, detailed history taking, especially for the dietary habit, is important as noted in our patient who avoided sweetened foods and fruits. Many pa-
patients with HFI develop these unpleasant symptoms and hepatic dysfunctions after ingesting fructose of sugar. Therefore, treatment of HFI mainly consists of complete elimination of fructose and sucrose from the patient’s diet.

Although diagnosis of HFI was made traditionally by biochemical tests such as intravenous fructose tolerance test or by enzyme assay of Aldolase B activity through liver or small intestine biopsy, the risks of such procedures can be avoided by recent advance in molecular genetic testing. The ALDOB gene is located on chromosome 9q22.3.13 More than 50 mutations causing HFI have been reported to date, in which missense mutations are most common [http://www.hgmd.cf.ac.uk]. p.A149 is the most common genotype identified along with p.A174D, p.N334K.11-13 Three mutations account for 68% of HFI alleles worldwide but they are common mostly in northern European populations.14 The American population shows uniquely high prevalence of two nonsense mutations, p.ΔE4 and p.R590p.15 Spain also shows high prevalence of ΔE4 surpassing p.A174D, p.N334K. New Zealand, India, Japan did not have enough published reports to define HFI alleles, indicating the existence of variability in the incidence and mutation spectrum of HFI among ethnic groups.15 In Korea, one case of HFI has been reported in 2002, which was diagnosed by enzyme assay through intestine and liver biopsy, but not by genetic testing. Therefore, our patient is the first Korean case with HFI confirmed by genetic testing. p.val253fsX24 identified in our patient is a novel mutation. This frame-shifting mutation leads to premature truncated proteins, and is expected to result in functional deterioration of the mutant protein.

The relationship between genotype and symptoms is yet uncertain.16 Although earlier studies suggested that patients with null alleles presented with more severe phenotypes and higher incidence of death,17 current reports show no difference in the severity of the symptoms between null alleles and other missense mutations.3,18

In conclusion, to identify more Korean patients with HFI, detailed evaluation of the dietary habit is needed when a patient is experiencing recurrent hepatitis-like episodes. The genetic testing for ALDOB is a valuable as well accurate method for confirming the diagnosis of HFI.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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