Case Report
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A Korean Family with Cholesterol Ester Transfer Protein Deficiency

Seo Young Youn[1], Ik Soon Shin[1], Yong Hee Hong[2] and Dong Hwan Lee[1*]

[1]Department of Pediatrics, College of Medicine, Soonchunhyang University, Seoul, Korea
[2]Department of Pediatrics, Seoul Seong Ae Hospital, Seoul, Korea

A 32-year-old female patient and her sister show high levels of high density lipoprotein (HDL) cholesterol in regular health checkups, since female patient was 11 years old. The patient's serum total cholesterol was 285 mg/dL and HDL cholesterol was 113 mg/dL. Her sister's total cholesterol was 240 mg/dL and the HDL cholesterol measured to be 90 mg/dL. Lipoprotein pattern and cholesteryl ester transfer activity gene analysis were examined in these patients. We found c.1321+1G>A (IVS14+1G/A) hetero mutation in cholesteryl ester transfer protein (CETP) genes. Generally, CETP mediates transfer and exchange of triglycerides and cholesteryl ester between plasma lipoproteins. Also we investigated a key role of HDL-CE and Apo A-1 metabolism. Patients with low levels of CETP have increased serum HDL levels. We hereby report two Korean cases of CETP deficiency in a family. Brief literature review ensues with the cases.

Key Words: Cholesteryl ester transfer protein, High density lipoprotein, Hypercholesterolemia

Introduction

High density lipoprotein (HDL) extracts cholesterol from cells and transports the excessive cholesterol of atherosclerotic lesions. Therefore the serum HDL level is inversely proportional to atherosclerotic cardiovascular diseases.[1,2] It has been reported that 1 mg/dL increase of the serum HDL can reduce the risk of atherosclerotic cardiovascular diseases by 2-3%.[3,4] The plasma cholesterol ester transfer protein (CETP) mediates transporting as well as exchanging of cholesterol ester and triglyceride among the plasma lipoprotein, and plays an important role for metabolism of HDL-CE and apo A-1.[5]

Since Kurasaka et al. and Koizumi et al. had reported on CETP gene defect in 1985, CETP gene defect is known as the most common and important cause of HALP (Hyperalphalipoproteinemia) in Japanese population. HALP has been reported as being inherited as an autosomal dominant trait.[5-8] Since the CETP gene splicing defect was found in the Japanese pedigree for the first time c.1321+1G>A (IVS14+1G>A), CETP deficiency shows very high prevalence in the Japanese pedigree as shown from a study performed in the Japanese population that had reported CETP deficiency and nucleotide pleomorphism which were caused by mutation of D442G at the same site. 27% of population in Omagari region of Japan had shown c.1321+1G>A (IVS14+1G>A). Congenital CETP deficiency raises the blood HDL level and reduces the content of cholesterol ester in Very Low Density Lipoprotein (VLDL), intermediate density lipoprotein and chylomicron, consequently resulting in formation of a lipid

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*Corresponding author: Dong Hwan Lee
Department of Pediatrics, College of Medicine, Soonchunhyang University, 22, Deasagwan-gil, Yongsan-gu, Seoul 140-743, Korea
Tel: +82-2-709-9114, Fax: +82-2-709-9135, E-mail: ldh@schmc.ac.kr

profile with low likelihood of atherosclerosis in the human body overall.[2,5,9]

The author, hereby, makes an empirical report on diagnosing cases with CETP deficiency, by using the chromosome gene test in Korean sisters whose HDL were measured at high levels from a periodic health check up, together with report on the literature reviews.

Case Report

1. Case 1

- Patient: 32 years old, female
- Chief complaint: Elevation of the serum HDL level accidentally found from regular health check up
- Past history: No specific history
- Family history: No specific history
- Present illness: The patient has precise examination as she found her serum HDL level was elevated from the results of annual health check up since 11 years old
- Physical examination: BP was 110/70 mmHg, body temperature 36.8℃, pulse rate 70 per min, respiration 20 per min, and there was no specific findings in the medical examination on the skin and head/neck. In terms of thorax, the lung sound was clear, heart beat was regular. There was no palpable lumps and no enlargement of liver and spleen. Also there were no specific findings in neurological examination.
- Laboratory findings: The results of peripheral blood test performed: WBC was 11,100/μL, hemoglobin 12.0 g/dL, hematocrit 35.3% and platelet 299,000/μL. The biochemical assay results showed AST 19 IU/L, ALT 14 IU/L, BUN 8.1 mg/dL, Creatinine 0.7 mg/dL, Protein 7.5 g/dL, Albumin 4.7 g/dL, Total bilirubin 0.9 mg/dL and Inorganic phosphate 4.1 mg/dL The test results on overnight fasting lipid profiles included: Total cholesterol 285 mg/dL (Normal range 130-220), Triglyceride 73 mg/dL (Normal range 0-200), HDL-cholesterol 113 mg/dL (Normal range 49-74) and the electrolytes were Na 138 mmol/L, K 4.8 mmol/L and Cl 103 mmol/L. There was no abnormal results from the urine test. The blood lipoprotein electrophoresis test also had no abnormality in its results. But from the CETP gene test, c.1321+1G>A (IVS14+1G/A) hetero mutation was identified.
- Treatments and Prognosis: Based on abnormal findings from the blood test, a gene analysis was performed and diagnosis was made. The patient is currently under no specific treatment .

2. Case 2

- Patient: 28 years old, female
- Chief complaint: Elevation of the serum HDL level accidentally found from regular health check up
- Past history: No specific history
- Family history: All family members including 1 brother and 2 sisters had shown the elevation of the serum HDL level
- Present illness: The patient had visited our hospital to have a precise examination as she found her blood HDL level was elevated from the results of annual health check up since 9 years old
- Physical examination: Height was 162 cm, weight was 52 kg, and body mass index (BMI) was 19.8 kg/m^2. BP was 120/70 mmHg, body temperature 36.8℃, pulse rate 70 per min, respiration 20 per min, and there was no specific findings in the medical examination on the skin and head/neck. In terms of thorax, the lung sound was clear, heart beat was regular. There were no palpable lumps and no enlargement of liver and spleen found from abdominal examination. Also there was no specific finding in neurological examination.
- Laboratory findings: The results of peripheral blood test performed at the time of visit: WBC was 5,400/μL, hemoglobin 12.9g/dL, hematocrit 40.3% and platelet 295,000/μL. The biochemical assay results showed AST 13 IU/L, ALT 12 IU/L, BUN 12.0 mg/dL, Creatinine 0.7 mg/dL, Protein 6.4 g/dL, Albumin 4.0 g/dL, Total bilirubin 0.7 mg/dL and Inorganic phosphate 3.5 mg/dL while the test results on the blood lipid included: Total cholesterol 240 mg/dL (Normal range 130-220), Triglyceride 70 mg/dL (Normal range 0-200), HDL-cholesterol 90 mg/dL (Normal range 49-74) and the electrolytes were Na 139 mmol/L, K 4.0 mmol/L and Cl 103 mmol/L. There were no abnormal results from the urine test. The results of lipoprotein test had shown Apolipoprotein A as 204.06 mg/dL (Normal range 79-169), Apolipoprotein B was 104.94 mg/dL (Normal range 46-174) and ß-Lipoprotein was 446 mg/dL (Normal range 200-680) in its results. The CETP gene test, c.1321+1G>A (IVS14+1G>A) hetero mutation was identified.
- Treatments and Prognosis: Based on abnormal findings from the blood test, a gene analysis was performed and diagnosis was made. The patient is currently under no specific treatment.

Discussion

The serum lipoprotein is a complex as a carrier of lipid between the body fluids and tissues, and it is indispensable for absorptions of cholesterol and lipophilic vitamins. It transports triglyceride,

cholesterol and lipophilic vitamins between the liver and the peripheral tissues as well as inversely transports cholesterol from the peripheral tissues to the liver. The serum HDL is synthesized at the small intestines and the liver inside human body, and lipids and phospholipids degraded at peripheral parts are transported as HDL.[9,10]

The existence of highly concentrated HDL in the blood has been widely known as one of independent factors to prevent atherosclerotic coronary diseases from most studies. 2004 Revised Version of the Adult treatment Panel III had considered that when the serum HDL level is ≥60mg/dL, it becomes an advantageous factor for prevention of atherosclerotic coronary diseases.[4,11]

CETP, which has been known as an important factor with effects on the serum HDL level, consists of 476 amino acids and 4 of N-linked glycosylation as hydrophobic glycoprotein.[11] In case of the human CETP gene, it is composed of 16 exons, and is 25kbp in size. It is located at the chromosome 16q21 adjacent to the coordinate of lecithin cholesterol acyltransferase gene (16q22).[12] Ten mutation of the CETP gene has been demonstrated as cause of HALP. The splicing defect of intron 14 is the most common mutation. And single nucleotide polymorphisms such as C-631A, C-629A, Taq1B, A373P, 1405V and D4442G, R451Q are well known.[5,13,14]

It also plays an important role for CETP-induced HDL metabolism in primary or secondary hyperlipidemia as well as post-meal lipidemia. As cholesterol ester is carried in the form of VLDL or chylomicron, the transport of cholesterol ester in HDL is reduced and the cholesterol ester is pulled out of HDL particles reducing its size and presenting the serum HDL level being dropped. Based on the above results, it can also cause excessive amounts of cholesterol ester in the potential atherosclerotic substances such as VLDL or chylomicron.[9, 15]

Meanwhile, CETP gene deficiency induces dropping down of the serum CETP level which is led to the elevation of the serum CETP level. The relevance between CETP gene polymorphism, the serum lipoprotein concentrations and cardiovascular diseases can be presented in diversity depending on different races and frequency of gene polymorphism.[9,16]

Some authors said CETP gene deficiency is associated with long life as it increases the HDL level and then reduces atherosclerotic coronary diseases.[17-19] However, others had reported that CETP deficiency increases atherosclerotic coronary diseases in spite of HDL's elevation, due to retrograde cholesterol disorder.[6,10] Although CETP deficiency generates anti-atherogenic lipoprotein profile, the benefits of CETP deficiency still remain as controversial so far.[12,14,20,21]

In the cases presented by the authors, it was possible to diagnose CETP gene polymorphism by performing the chromosome gene analysis in two sisters from the same family who had visited our hospital due to persistent elevation of the blood HDL level from periodic health check-ups since 9 and 11 year old.

In summary, we make an empirical report on identification of gene mutation from the same site in Korean population by performing CETP gene analysis and the serum cholesterol distribution characteristics as shown in two sisters from one family who had shown persistently high HDL level from periodic health check-ups since 9 and 11 years old.

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