A Novel Mutation in Deficiency of 11 β-Hydroxylase: A Possible Association with Disease Severity

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Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by the loss of one of five steroidogenic enzymes affecting cortisol synthesis. 11β-hydroxylase gene is located in the 8q21-q22 chromosome. When there is deficiency of 11β-hydroxylase, 11-deoxycortisol cannot be converted to cortisol, and deoxycorticosterone cannot be converted to corticosterone. We present our 11β(OH)D case that we follow due to medical-treatment-resistant hypopotasemia and hypertension and in whom we found a novel mutation.

Case: A 20-year-old male patient who has been on steroid replacement treatment for adrenal insufficiency for 18 years was admitted with spasm, dyspnea, and syncopal attacks. His potassium level was 1.4 meq/L, so potassium infusion treatment was started. The patient had a surgery due to ileus. Laboratory results were as follows: aspartate aminotransferase 358 U/L, alanine aminotransferase (ALT) 163 U/L, CK 12740 U/L, CKBM 117 U/L, creatinine 0.81 mg/dL, sodium 149 meq/L, potassium 1.4 meq/L, myoglobin >3000 ng/mL, adrenocorticotropic hormone 16.6 pg/mL, cortisol 5.14 µg/dL, free triiodothyronine 2.15 pg/mL, free thyroxine 1.40 ng/dL, thyroid-stimulating hormone 1.51 µU/mL, total testosterone 3.44 ng/mL, dehydroepiandrosterone sulfate 114.9 µg/dL, and 17-hydroxyprogesterone 9.4 ng/mL. 11β(OH)D-related CAH was suspected as the patient had adrenal insufficiency, hypertension, and hypokalemia. Aldactone treatment was started to the patient who had resistant hypokalemia despite potassium infusion. Potassium levels were back to normal in the follow-up. Hypokalemia-related rhabdomyolysis regressed. MRI showed longer and thicker adrenal cruris than in normal view. In the genetic examination of the patient, "pAla199pro and pArg448his compound heterozygous mutation" was detected in *CYP11B1* whole genome sequencing analysis.

Results: In *CYP11B1* whole genome sequencing analysis, pAla199pro and pArg448his compound heterozygous mutation was detected. pArg448his mutation was previously defined in the database and was associated with the disease; however, pAla199pro mutation was never defined before. The analysis conducted with modeling programs indicates that pAla199pro mutation could disrupt protein functioning and "splicing". Thus, these two compound heterozygous mutations were thought to be associated with the severity of the disease.

Key words: Congenital adrenal hyperplasia, 11β-hydroxylase, pAla199pro, pArg448his, whole genome sequencing analysis