Two Siblings with Congenital Hyperinsulinism - Homozygote and Heterozygote Mutation

Nursel Muratoğlu Şahin, Sibel Tulgar Kınık

Başkent University Faculty of Medicine, Department of Pediatric Endocrinology, Ankara, Turkey

A 3-day-old baby with resistant convulsion was admitted to our hospital. Patient's v history revealed that the parents were paternal cousins. Father and two nephews/nieces had a convulsion story when they were infants, and there was not any hypoglycemic event in the family. In physical examination, general status was bad; the baby was intubated with no reflexes. Laboratory results were as follows: glucose level 25 mg/dL, ketone (-), insulin 400 µU/mL, C-peptide 26.5 ng/mL (1.1-5), ammonia 53 µmol/L (18-72), tandem mass normal. The patient who was diagnosed with congenital hyperinsulism (CHI) received a diazoxide (20 mg/kg/day) therapy, but there was no response to this therapy. Then, the therapy was changed to octreotide (15 µg/kg/day) and nifedipine (0.5/mg/kg/day) to provide the normoglycemia. The patient at 4 months died at home. It was found that the patient had homozygote *ABCC8* gene mutation and his parents had a heterozygote *Q392H* mutation. The *Q392H* mutation was on exon 7's 3' end and it was a novel missense mutation which could affect the splicing. The patient was diagnosed with autosomal recessive CHI. In the second pregnancy, the family wanted a chorionic villus biopsy which later showed a + mutation. It was thought that the baby would be a carrier for this gene. After the birth, the baby had resistant hypoglycemia and the laboratory results were consistent with CHI. He responded better to octreotide than to diazoxide. At age 1 year, he did not need any therapy and in repeated mutation analysis, it was confirmed that he had a paternal heterozygote mutation.

The presence of homozygote and heterozygote patients in the same family was unexpected, so the condition was investigated deeply. The first possibility was that the mutation was inherited in an autosomal dominant (AD) way. In the literature, it was reported that people with AD *ABCC8* mutations could have spontaneous recoveries and mutant allele's expression ratio could be variable. The second child's symptoms being totally cured and his parents being asymptomatic were consistent with AD inheritance, however, the first child having homozygote mutation and its very severe course made us think that it might be inherited in androgen receptor (AR) way, so there was no need to do the functional analysis. Although rare, there are diffuse CHI cases which have heterozygote mutation but proved to be AR by functional analysis. The second possibility is of case being a focal CHI. We could not perform a PET. However, focal CHI is sporadic. For the fetus with paternal AR *ABCC8* mutation, focal CGI's probability of occurrence is approximately 1/270 and there was not any focal lesion in the heterozygote relatives of diffuse CHI cases with AR mutations until today.

Key words: Congenital hyperinsulinism, diffuse, focal, heterozygote, homozygote