Severe Congenital Insulin Resistance Syndrome Due to a Compound Heterozygous c.836G>A & c.1268+2T>A Mutation in Insulin Receptor (*INSR*) Gene

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Aim: We aimed to report the clinical and laboratory characteristics of a patient with severe congenital insulin resistance syndrome due to a compound heterozygous c.836G>A & c.1268+2T>A mutation in *INSR* gene.

Case: A female patient presented with hyperglycemia at postnatal 36th day. She was born to non-consanguineous Turkish parents after a 39 week uneventful gestation via normal spontaneous vaginal delivery. Her birth weight was 2700 g. At presentation, she had coarse facies, abdominal distention, umbilical hernia, and macroglossia. Laboratory examination revealed blood glucose of 393 mg/dL, insulin >300 µIU/mL, and C-peptide >20 ng/mL (0.9-4). She was started on regular insulin and subsequently subcutaneous NPH-insulin. Insulin requirement was decreased gradually from 2.5 unit/kg/day to 0.5 unit/kg/day at the first month and stopped at 2.5 months. During follow up, she developed acanthosis nigricans and fasting hypoglycemia suggesting insulin resistance syndrome. Molecular genetic analysis: Sanger sequence analysis of the *KCNJ11, ABCC8* and *INS* genes did not identify a mutation. Analysis of all the coding regions and exon/intron boundaries of the monogenic diabetes genes by targeted next-generation sequencing revealed a compound heterozygous missense c.836G>A (p.R279H) variant in exon 3 and a splicing c.1268T>A variant in exon 5 of *INSR* gene.

Conclusion: Mutations in the *INSR* cause severe congenital insulin resistance syndromes which may lead to intrauterine and postnatal growth retardation, acanthosis nigricans, fasting hypoglycemia, and postprandial hyperglycemia. At neonatal period, patients may present with clinical findings of neonatal diabetes and develop the specific clinical findings of insulin resistance (e.g. acanthosis nigricans) during follow-up.

Key word: *INSR* gene

Different Genotypes in Prader-Willi Syndrome

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Prader-Willi syndrome (PWS), first described in 1956, is a common and complex disorder affecting multiple systems. PWS is due to absence of paternally expressed imprinted genes at 15q11.2-q13. DNA methylation analysis can detect >99% of individuals with PWS, but it is unable to distinguish between the molecular classes of the disease. This study's aim was to create a diagnostic algorithm for PWS by examining the genotype of patients seen in clinical practice. In this study, clinically suspected 7 PWS patients aged between 7 months and 17 years (4 female and 3 male) are discussed. Karyotype analysis revealed deletion in 2 cases (confirmed by FISH analysis). Deletion at 15q11.2-q13 was observed in 1 case, while in two cases, karyotyping and FISH analysis were normal and PWS was diagnosed by methylation analysis. In two cases, karyotyping and FISH analysis were normal; methylation analysis result is expected.

Key words: Prader-Willi, algorithm, DNA methylation, karyotyping, paternally