A CASE OF NEONATAL DIABETES DUE TO NEWLY DEFINED MUTATION IN THE GLIS 3 GENE

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INTRODUCTION: GLIS3 is a member of the GLI-similar zinc finger protein family encoding for a nuclear protein that maps to chromosome 9p24.3-p23. Mutations in GLIS3 have been reported in association with Neonatal diabetes mellitus and hypothyroidism syndrome. GLIS3 is expressed in early embryogenesis and plays a critical role as both a repressor and activator of transcription by interacting with a specific nucleotide sequence, known as the Gli response element (GLI-RE) in the promoter region of target genes. Glis proteins contain a DNA binding domain consisting of five C2H2-type zinc finger motifs that are critical for nuclear localization. Two major GLIS3 transcripts from the 11 exon gene have previously been described—7.5 kb and smaller (0.8– 2.0 kb); the 7.5-kb transcript is strongly expressed in pancreas, thyroid, and kidney with smaller transcripts predominantly expressed in liver, kidney, eye, heart, and skeletal muscle. The cardinal feature of mutations in GLIS3 is the concomitant presentation of neonatal diabetes and congenital hypothyroidism although recently a patient with a compound heterozygous mutation in GLIS3 who did not develop hypothyroidism was reported. We aimed to present a case of congenital diabetes mellitus congenital hypothyroidism associated with a newly identified mutation in the GLIS-3 gene.

CASE REPORT: A seven day old female patient was referred to our outpatient clinic because of elevated TSH level in the newborn screening program. Laboratory examination revealed hyperglycemia and hypothyroidism. There was no consanguineous marriage between the parents. In her physical examination, her general condition was moderate to good, her skin had mild icteric and turgor decreased, she had anterior fontanel 4x3 cm, posterior fontanel 0.5x0.5 cm, no pathologic reflex and no skeletal deformity. In laboratory examination, blood glucose was 702 mg/dL, insulin 2 Uu/mL, C-peptide 0.01 ng/mL, Anti-GAD 2.5 IU/mL, islet cell antibody (-), Hemoglobin A1c 7.2%, TSH 28 uIU/mL, fT4 was 0.5 ng/dl. There was no acidosis in blood gases. Regular insulin was initiated as an infusion of 0.05 U/kg/h. Subsequently, NPH insulin was administered subcutaneously in 3 doses. Daily insulin dose was up to 2-3 u/kg. Blood glucose was partially regulated. At the age of two, she was followed up in our outpatient clinic, and her daily insulin requirement was approximately 1-2 U/kg. Due to the inability to regulate blood sugar, an infusion pump was considered but her family did not give consent. For hypothyroidism use 50 mcg / day levothyroxine. Two different homozygous c (1783A>C); and 1835G>C mutations were identified in the GLIS3 gene in their genetic analysis.

DISCUSSION

Infants with neonatal diabetes are usually born at term and with low birth weight. Due to its effect on growth in the intrauterine period, insulin deficiency in these cases results in IUGR. It is known that more than half of the cases are transient and the lesser part results in permanent DM. Mutations in the GLIS3 gene are very rare and are known to cause NDM. Gene product protein embryogenesis, especially pancreatic β cells, eye, liver and kidney development, as well as the heart, skeletal muscle, stomach, brain and bone development takes place. Congenital hypothyroidism, congenital glaucoma, hepatic fibrosis and polycystic kidneys are previously described concomitant anomalies. Eye examination, hearing test, skeletal radiographs and abdominal ultrasound of our patient were normal and there was no additional finding except congenital hypothyroidism.

58ESPE P2-099

Diabetes and insulin

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Poster presented at: ESPE 2019 VIENNA

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