

Mutant Neurogenin-3 in Permanent Neonatal Diabetes and Congenital Malabsorptive Diarrhea

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Introduction

Neurogenin-3 is expressed in endocrine progenitor cells and is required for endocrine-cell development in the pancreas and intestine.

Case Report

A 20-month-old male patient was referred from another clinic due to hyperglycemia. He was born to consanguineous parents at 40 weeks of gestation with a birth weight of 2270 g and birth length of 41 cm. There was no history of diabetes in the parents or relatives. It was learned that he had suffered from non-progressive non-ketotic moderate hyperglycemia (110-250 mg/dL) from 45 days old until now and received subcutaneous insulin treatment irregularly because of severe hypoglycemia after insulin treatment. He had never developed diabetic ketoacidosis. Additionally, he had been investigated due to diarrhea and indirect hyperbilirubinemia by a gastroenterology clinic when he was 15 days old. Comprehensive evaluations for allergic, immunologic, infectious and metabolic causes of diarrhea were all negative. The pancreatic exocrine function was normal. Biopsy of liver revealed paucity of intrahepatic bile ducts and cholestasis; biopsy of intestine revealed immature

ganglion cells. He was started on ursodeoxycholic acid and sodium bicarbonate for cholestasis and hyperchloremic metabolic acidosis, respectively. Physical examination showed dysmorphic features. His growth and development were retarded. His height and weight were less than the 3rd percentile. Both testes were 0.5 cc sized within the scrotum and he had a glanular hypospadias. Other aspects of physical examination were normal. Laboratory investigations revealed acidosis (pH: 7.24, HCO₃: 19.8 mmol/L) and hyperglycemia (plasma glucose 510 mg/dL), but there was no ketonuria. His serum insulin was 4.37 uU/mL (N: 2-15), C-peptide was 1.32 ng/dL(N: 0.9-7.1), hemoglobin A1c (HbA1c) was 10.7% (N: 4-6%). Anti-glutamic acid decarboxylase, anti-insulin antibodies and islet cell antibodies were negative. Abdominal ultrasonography demonstrated a normal pancreas anatomy. Subcutaneous insulin was started. The patient is currently 3 years old and receiving insulin treatment regularly and his latest HbA1c is 9.6%. With all these findings, *RFX6* gene was sequenced but no mutations were detected. A homozygous stop codon mutation in neurogenin 3 (*NEUROG3*) gene was identified in the patient. Both father and mother were carriers of the same mutation in the heterozygous state.

Conclusion

Our study shows that a recessive null mutation in *NEUROG3* may cause a rare form of neonatal diabetes with congenital malabsorptive diarrhea. In the literature, there are a few cases that presented with similar clinical picture.