Case Report:
Pathological Features of Aberrant Pancreatic Development in Congenital Hyperinsulinism Due to ABCC8 Mutations

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Abstract. We describe a patient with congenital hyperinsulinism with previously unreported pathological findings including normal to decreased number of insulin-positive cells with very few enlarged nuclei, aberrant distribution of glucagon-positive cells, and a non-insulin producing adenomatous focus of unusual morphology. Molecular analysis showed that the patient was a compound heterozygote for two mutations of the ABCC8 gene: a previously unreported nonsense mutation (R841X) and a missense mutation (D1471N) that has been previously described. This case suggests that abnormal function of ABCC8 may result in aberrant pancreatic development.

Keywords: congenital hyperinsulinism, ABCC8 gene mutation, pancreatic development, glucagon

Introduction

Congenital hyperinsulinism (CHI, MIM 256450), characterized by profound hypoglycemia related to inappropriate insulin secretion, may be associated with either diffuse insulin hypersecretion or focal adenomatous hyperplasia [1]. Both forms of CHI have similar clinical presentations, but they differ in management and molecular pathogenesis.

Diffuse hyperinsulinism, characterized by presence of enlarged islet cell nuclei throughout the pancreas, is due to recessive mutations in ABCC8 [2,3] or KCNJ11 [4]. All β-cells are functionally abnormal, and infants with diffuse hyperinsulinism require near total pancreatectomy to achieve control of blood glucose levels.

Focal hyperinsulinism occurs sporadically, and is characterized by presence of adenomatous hyperplasia within an otherwise normal pancreas with islet cell nuclei of normal size. It can be treated by resection of a focus of adenomatous hyperplasia. A third entity with localized islet cell nuclear enlargement (LINE) has been proposed recently [5], which represents a clinical, histological, and potentially genetically distinct entity.

Case Report

The patient was a male infant, born at 36 wk of gestation that was complicated by penicillin-treated maternal syphilis and diet-corrected gestational diabetes. His birth weight was 1780 g (<10th percentile), length 47 cm (50th percentile), and fronto-occipital circumference 32.5 cm (25th-50th percentile). Shortly after birth, he developed hypothermia and hypoglycemia (blood glucose, 32 mg/dl) with hyperinsulinemia (plasma insulin, 31 µU/ml), and an abnormal response to the glucagon stimulation test. The infant’s hypoglycemia was poorly responsive to diazoxide and he underwent a pancreatectomy. A focal lesion was noted on frozen section and the operation was stopped after 75% of the pancreatic tissue had been removed. Four days post-surgery, hypoglycemia recurred and octreotide treatment was restarted. Only after 95% removal...
of the pancreas was the hypoglycemia controlled. Post-operatively, he developed diabetes requiring insulin therapy and pancreatic exocrine insufficiency requiring enzyme replacement therapy. The family history was positive for multiple miscarriages in the mother, and type 2 diabetes in several relatives on both the maternal and paternal sides of the family.

A male sibling had died of a presumed sudden infant death syndrome.

**Pathological findings.** Pathological examination of the pancreas showed variably sized islets, but no giant islets. Very few enlarged nuclei without nuclear hyperchromasia were evident in the
resection specimens and these were from insulin-producing cells, as shown by insulin immunohistochemical staining (Incstar). Normal to decreased numbers of insulin-positive cells were present in all sections of the pancreas (Fig. 1). Aberrant distribution and increased number of glucagon-producing cells was noted on glucagon immunohistochemical staining (Incstar). The glucagon immunostain, which was expected to show a typical peripheral distribution in the Langerhans islet (Fig. 2B) demonstrated instead an aberrant pattern of almost entire occupation of the islets (Fig. 2A), and formation of tubulo-insular complexes that are expected from insulin-producing cells (Fig. 3). In the body of the pancreas a nodule of pseudoglandular/tubular hyperplasia, composed of solid areas and epithelial tubular structures, was identified (Fig. 4A). Insulin, glucagon, chromogranin (DAK-A3, Dako) and neuron specific enolase (BBS/NC/V1-H14, Dako) immunostains were all negative (not shown). Pancreatic immunostain was weakly positive (Fig. 5A). Proliferative marker Ki-67 (MIB1, Immunotech) did not show increased activity in comparison with other ducts (Fig. 5B). Based on ultrastructural analysis, the nodule was composed of tubules of epithelial cells intermixed with exocrine acinar cells (Figs. 4B,C).

Molecular findings. Genomic DNA was extracted from blood by standard methods. PCR primers were designed for amplification of 38 segments encompassing all coding sequences and flanking introns of the ABCC8 gene. Complete sequence information was obtained for all 38 amplicons and revealed a C>T change at nucleotide position 2521 leading to a premature stop codon at position 841.
(R841X) and a G>A change at nucleotide position 4411 resulting in the substitution of aspartate with asparagine at codon 1471 (D1471N). Parents were both available for testing. The patient’s father was found to carry the c.2521C>T mutation in heterozygous state and the patient’s mother was found to carry the c.4411G>A mutation in heterozygous state.

Discussion

In our patient, molecular analysis of the ABCC8 gene confirmed the clinical and pathological diagnosis of the diffuse form of congenital hyperinsulinism and revealed the presence of two distinct mutations: a novel nonsense mutation (R841X) and a missense mutation (D1471N) that was previously reported by Sharma et al [6]).

The most reliable morphological criteria for the evaluation of familial hyperinsulinism are the 3-fold enlargements of β-cells nuclei, which are considered to be a good marker to differentiate the diffuse from the focal form. To our knowledge, adenoma or adenoma-like lesions have not been reported in the diffuse form [7].

At the pathological level, our patient exhibited features of dysgenetic pancreas with diffuse form of nesidioblastosis, abnormal glucagon-producing cell distribution, aberrant tubulo-insular complexes composed of glucagon-producing cells, and a focus of pseudogludular-tubular epithelial hyperplasia, negative for insulin and glucagon production. All these features are unusual, especially the presence of an adenoma-like lesion, which, upon electron microscopic examination and immunohistochemical characterization was interpreted as an area of de-differentiated or not yet differentiated exocrine pancreas, and not responsible for clinical symptoms of hyperinsulinism. The possibility that ductal cell hyperplasia is attributable to treatment prior to surgery, such as intravenous glucose, diazoxide, and other therapy, has been discussed recently [8] and may be applicable in our case. Interestingly, multiple sections of the resected pancreas showed normal or decreased number of insulin-positive cells, confirming that the disease can be potentially due to fewer high insulin-expressing β-cells. This finding suggests that severe mutations, such as perhaps the R841X, are potentially associated with severe dysregulation of insulin production, resulting in the clinical phenotype by affecting a small fraction of β-cells.

In the last few years, opinions regarding the pathogenesis of CHI have been shifting from a presumed abnormal pancreatic development [9] to derangements of the metabolic pathways that regulate insulin secretion. However, our case suggests that ABCC8 may be involved in the proper development of pancreatic endocrine and exocrine tissue, and that pancreatic dysgenesis may be present in at least a subgroup of cases.

References