Coexistence in the Same Family of Both Focal and Diffuse Forms of Hyperinsulinism

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Neonatal hyperinsulinism is the most important cause of hypoglycemia in infancy (1,2). The inappropriate oversecretion of insulin is responsible for profound hypoglycemia, requiring aggressive treatment to prevent brain damage (1–3). Neonatal hyperinsulinism is often resistant to medical therapy (1–4), and pancreatectomy is required for many sufferers (1,5–6). The histopathological lesions associated with neonatal hyperinsulinism may be described as diffuse or focal (7–8). Focal adenomatous islet cell hyperplasia is sporadic and has been demonstrated to arise in individuals who have a germline mutation in the paternal allele of the sulfonylurea receptor 1 ABCC8 gene (9,10) or the inward-rectifying potassium channel Kir6.2 (KCNJ11) (10) in addition to a somatic loss of the maternally derived chromosome region 11p15 in adenomatous pancreatic β-cells (9–11). Diffuse hyperinsulinism may be familial and arises from the autosomal recessive inheritance of mutations in both ABCC8 (12) and KCNJ11 (13–14) genes. The therapeutic outcome for the patients is heavily dependent on distinguishing between the two histopathological lesions. Diffuse hyperinsulinisms, which are unresponsive to medical treatment, require extensive pancreatectomy, with a high risk of diabetes (5,15–16). Conversely, focal hyperinsulinism can be cured by limited pancreatectomy (6,17). Genetic counseling is dramatically different, as focal hyperinsulinism is considered a sporadic molecular event with a very low recurrence risk (10,18), while diffuse hyperinsulinism is inherited in a recessive pattern for neonatal onset forms (12–14,19) and in dominant or sporadic transmission for late-onset hyperinsulinism (19). We present here the first case of coexistence of both focal and diffuse neonatal hyperinsulinism in the same consanguineous family with a dramatically different treatment and outcome.

RESEARCH DESIGN AND METHODS

— The first child, a boy, of a consanguineous couple (first cousins) of Portuguese ancestry (Fig. 1) presented at birth with an increased weight and body length. He presented with hypoglycemic seizures during the first day of life. Repeated hypoglycemias (ranging from 1.7 to 2.3 mmol/l, reference range >2.7) were found during the 1st month, associated with high insulin levels (ranging from 5.5 to 18 mU/l, reference range <0.4 in hypoglycemia) consistent with the diagnosis of persistent neonatal hyperinsulinism. Medical treatment with diazoxide and somatostatin along with high-glucose dietary treatment failed to control hypoglycemia. A transhepatic pancreatic catheterization with venous sampling of glucose, insulin, and C-peptide, as previously described (17), revealed hypersecretion of insulin in the lower part of the pancreatic body. Via pancreatic surgery with a preoperative histological analysis, a focal lesion of 15 mm of diameter on the lower part of the pancreatic body was identified.

The second child, a girl, also suffered from neonatal hypoglycemic seizures. Treatment by diazoxide, nifedipin, and injection of somatostatin was not successful, and the child was infused with high doses of glucose (15 mg · kg^{-1} · mn^{-1}) and continuous infusion of glucagon (2 mg/day). An ^{18}F-fluoro-L-DOPA positron emission tomography study was performed, showing a diffuse uptake of the radiotracer in the pancreatic area, compatible with a diffuse form of hyperinsulinism.

RESULTS

— A limited pancreatectomy fully cured the first child, who, now 6 years old, is healthy with no relapse of hypoglycemia. Loss of 11p15 heterozygosy of maternal origin was found in the lesion with positive proinsulin staining in β-cells (Fig. 1*A*) and absence of expression of the p57 protein (Fig. 1*B*). A paternally inherited heterozygous mutation of the ABCC8 gene (G228D) was also identified. The maternal genotype was not tested. As focal hyperinsulinism is sporadic, reassuring genetic counseling was given in another center.

On the second child, a near-total pancreatectomy was performed after a peroperative histological confirmation of the diffuse form (Fig. 1*C*), and the child developed signs of diabetes requiring insulin injections a few weeks after surgery. Moreover, the child acquired neurological impairment with psychomotor retardation due to repeated hypoglycemic seizures, with brain atrophy on the magnetic resonance imaging scan. Molecular analysis of the ABCC8 gene displayed a homozygous mutation identical to the one found in the first child at the heterozygous form. Both parents were found heterozygous for this mutation (Fig. 1).

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

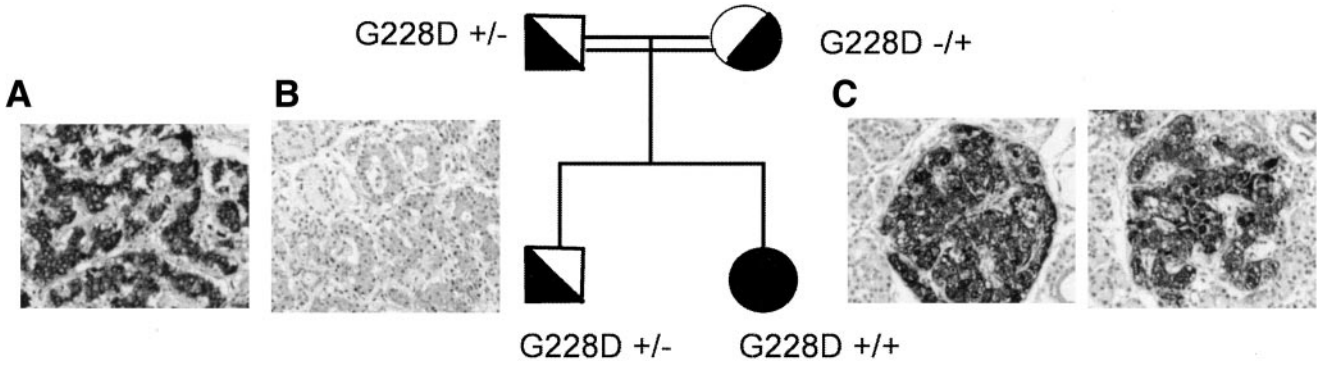

Figure 1—*Pedigree of a consanguineous couple with two children presenting with hyperinsulinism. Both parents are heterozygous for the G228D mutation (half-black symbol) on the ABCC8 gene. The first child is heterozygous like his parents but developed a focal form of hyperinsulinism. The focal lesion has been confirmed by histology, showing positive proinsulin staining* (A). *P57, a maternal-origin protein, is not expressed on the focal lesion* (B). *The second child is homozygous for the G228D mutation (full black symbol) and has diffuse hyperinsulinism, confirmed by histological examination, showing positive proinsulin staining in all surgical samples taken from different parts of the pancreas* (C).

CONCLUSIONS — We present here the first report on both focal (sporadic) and diffuse (familial) forms of hyperinsulinism occurring in the same family and showing well-characterized genetic patterns. In the first child, a paternally inherited ABCC8 mutation associated with a loss of the maternal wild-type chromosome in the pancreatic lesion was responsible for the focal lesion. Paternal and maternal mutations in the ABCC8 gene due to consanguinity were responsible for the recurrence of hyperinsulinism in the second child, with a diffuse pattern. Recent estimations from France, Japan, and the U.S. suggested that 40–65% of all hyperinsulinism patients have a focal form (20,21). Usually, genetic counseling in cases of focal hyperinsulinism is reassuring, as the paternally inherited ABCC8 mutation and the loss of the maternal 11p15 allele in the pancreatic cells are two independent genetic events. Indeed, loss of 11p15 heterozygosy may be regarded as the "second hit" according to Knudson's model, based on the paradigm of retinoblastoma (22), whereas the germline, inherited mutation may be regarded as the "first hit". However, unlike mutations of genes involved in-cell growth or DNA repair, the germline ABCC8 mutation is not expected to trigger the "second hit," unless by chance. Thus, the rate of somatic mutation (loss of 11p15 maternal allele) and, consequently, the risk of having another child with a focal form remains low. By contrast, in this consanguineous family, the risk of occurrence of a diffuse form of hyperinsulinism was 25%, as the risk for the offspring to be the carrier of a heterozygous mutation was 50%. The global risk for recurrence of hyperinsulinism in this family, focal or diffuse, was finally equal to the risk of relapse of a diffuse form.

In conclusion, this familial presentation confirms the possibility of the occurrence of focal hyperinsulinism in consanguineous families. Genetic counseling should be prudent in consanguineous families and should include molecular screening for both parents, regardless of the histological form of hyperinsulinism.

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