The Focal Form of Persistent Hyperinsulinemic Hypoglycemia of Infancy

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Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is a disorder characterized by unregulated insulin release, leading to profound hypoglycemia with a major risk of brain damage if not recognized early. The occurrence of PHHI is low in the Western world (~1/50,000 live births), but it can be as high as 1/2,500 live births in communities with high consanguinity. PHHI may be differentiated from the other causes of neonatal hypoglycemia by demonstrating the persistence of an inappropriate serum insulin level, irrespective of blood glucose concentration, associated with a hypoketosis and a spectacular response to glucagon (1).

In most cases and particularly those with severe hyperinsulinemic hypoglycemia of neonatal onset, medical therapy is not effective and, thus, surgery is mandatory to prevent permanent brain damage. Histological analyses of the resected pancreatic specimens have revealed that the disease does not correspond to a single pathological entity (2,3). Indeed, two different forms, which require radically different treatments, are recognized: a diffuse and a focal form. In the diffuse form of the disease, although the pancreas looks normal both macro- and microscopically, a large or even near-total pancreatectomy is often not sufficient to cure the patient. On the contrary, in the focal form characterized by the presence of a small pancreatic "tumor," the patient may be cured by a partial resection often restricted to the lesion. Clinically, the two forms are similar. The differential diagnosis can be made only by selective venous catheterization and insulin dosages associated with examination of intraoperative frozen sections (4–5). The focal form, which represents one-third of all cases in our series, is the subject of this study.

MORPHOLOGY

The small pancreatic β-cell tumor that characterizes the focal form is not an insulinoma. Indeed, the lobular architecture of the pancreas with focal PHHI is preserved and the lesion is often invisible to the naked eye. The lesion consists of conglomerated islets occasionally separated by a few exocrine acini. As in normal islets, immunohistochemical studies demonstrate α-, δ-, and PP cells localized around β-cell cores. On the contrary, insulinomas are often macroscopically visible and are mostly composed of β-cells arranged in nests or cords with an abundant fibrovascular stroma. The focal pancreatic lesion of neonates has been called focal adenomatous hyperplasia.

By the point-counting technique, we have demonstrated the differences in the cellular composition of these two lesions: the volume density of β-cells is indeed significantly lower in focal adenomatous hyperplasia than in insulinoma, whereas that of δ-cells is significantly higher in focal adenomatous hyperplasia than in insulinoma.

PATHOGENESIS

The intraoperative pancreatic frozen sections performed to diagnose and localize the focal form of PHHI were used by de Lonlay et al. (6) to demonstrate by genetic analysis the specific loss of the maternal allele of the chromosome region 11p15 in cells of focal adenomatous hyperplasia, whereas it did not occur in the normal adjacent pancreas (6). This chromosomic region is submitted to parental imprinting, which means that some genes in this area are expressed only by the maternal allele, whereas other genes are expressed on the paternal allele and silent on the maternal one. In the p15 region of chromosome 11, it is known that the tumor suppressor gene H19 is maternally expressed whereas IGF-2 is paternally expressed. In focal adenomatous hyperplasia, therefore, the somatic deletion of the maternal imprinted 11p15 region leads to the loss of H19. By contrast, IGF-2, a growth factor playing a central role in pancreatic tumorigenesis, is still expressed. It is likely that the abolition of H19 expression and the persistent expression of IGF-2 may play a role in the pathogenesis of the lesion.

To support this hypothesis, we have studied the β-cell proliferation rate in the pancreata of infants with focal adenomatous hyperplasia, diffuse PHHI, and insulinoma, and then compared it with the values found in the pancreata of 18 normoglycemic age-matched control subjects. We performed a double immunohistochemical technique detecting simultaneously Ki67, a nuclear endogenous antigen present only during cell proliferation, and insulin as a pancreatic β-cell marker (7). The study clearly indicates that the labeling index (number of Ki67-labeled β-cell nuclei/1,000 β-cell nuclei) is significantly higher in subjects with focal adenomatous hyperplasia (77.6 ± 10.9; $n = 7$) than in either age-matched control subjects (19.9 ± 6.9; $P < 0.005$) or subjects with insulinoma (27.9 ± 13.7; $P < 0.025$; $n = 4$) or diffuse PHHI (29.4 ± 7.4; $P < 0.001$; $n = 7$) (Fig. 1).

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PHHI, persistent hyperinsulinemic hypoglycemia of infancy; SUR1, sulfonylurea receptor.

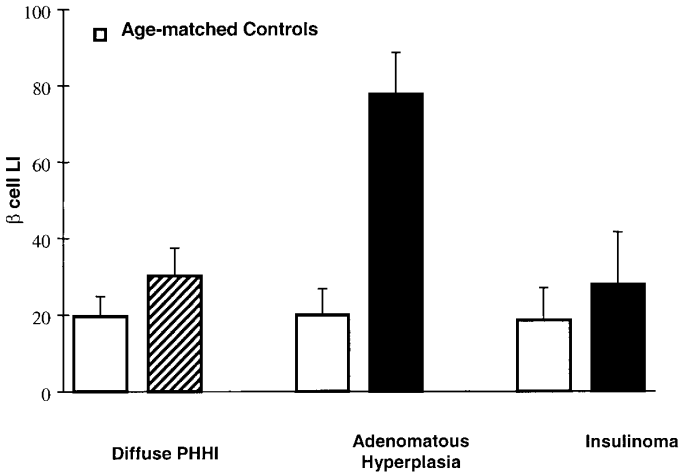

FIG 1. The β-cell labeling index (LI) for subjects with diffuse PHHI, adenomatous hyperplasia, and insulinoma, as modified from a previous study (7).

Thus, this study of β-cell proliferation demonstrates the existence of an abnormal proliferation in adenomatous hyperplasia that could be related to the presence of IGF-2 expression in the absence of H19.

We then studied the expression of IGF-2 protein and IGF-2 mRNA in focal adenomatous hyperplasia. The presence of the peptide was demonstrated by immunohistochemistry in the lesion with a variable staining intensity in cells that were mostly insulin-secreting cells. IGF-2 mRNA, detected by in situ hybridization, was restricted to β-cells.

A paternal sulfonylurea receptor (SUR1) mutation was demonstrated by the same group (8) in some patients of the same series of focal PHHI. The expression of SUR1 protein and SUR1 mRNA in focal adenomatous hyperplasia remains to be investigated.

CONCLUSION

The focal form of PHHI is related to the presence of a small pancreatic tumor called focal adenomatous hyperplasia, which has totally different morphological features from those of an insulinoma. It is cured by a selective resection limited to the lesion. Its occurrence appears to be the result of a cellular hyperproliferation secondary to the expression of IGF-2 in the absence of H19.

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