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Hyperinsulinism in children: diagnostic value of pancreatic venous sampling correlated with clinical, pathological and surgical outcome in 25 cases

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Abstract. Neonatal hypoglycemia represents an emergency of heterogeneous etiology. The occurrence of persistent hypoglycemia caused by hyperinsulinism has not been well established. Some authors claim that it may be more common than previously suggested. The diagnostic goal is to distinguish hyperinsulinemia from other causes of hypoglycemia because management strategies differ. The diagnosis of persistent hypoglycemia attributable to hyperinsulinism is made when insulin secretion is excessive or inappropriate (> 10 μIU/ml). Medical management includes frequent feeding, high hydrocarbon intake, glucagon, diazoxide, somatostatin or steroid treatment. In case of resistance to medical intervention, surgery consisting of subtotal pancreatectomy is performed to avoid neurological sequelae. However, pediatric organic hypoglycemia secondary to hyperinsulinism can be caused by either diffuse or focal pancreatic lesions. Differentiation between these two types of lesion is necessary since partial pancreatectomy can prevent diabetes. In this prospective study, pancreatic venous sampling (PVS) was evaluated for the preoperative localization of lesions in 25 children with hyperinsulinism and correlated with surgical, pathological and clinical outcome. PVS is the most accurate preoperative technique for localizing focal lesions in children. Besides being safe and effective, it has the great advantage of detecting focal secretion, thus reducing the need for extensive surgery.

Persistent idiopathic hypoglycemia secondary to hyperinsulinism in infancy is a rare condition. However, some authors maintain that it may be more common than previously suggested [1]. If untreated, hypoglycemia can produce mental retardation, seizures and even death. Early adequate control of blood glucose can therefore prevent these sequelae. Once the diagnosis of hyperinsulinism has been made, immediate medical or surgical treatment should be undertaken. The diagnosis of hyperinsulinism is established by demonstrating an inappropriate elevation of serum insulin during multiple hypoglycemic episodes. Patients with symptoms appearing during the first 48 h of life are categorized as having the neonatal form, while those showing signs after 1 month are classified as having the delayed form.

Two pathological types of hyperinsulinism have been described. The focal type consists of hyperplasia of a zone within a normal pancreas, whereas the diffuse type presents as diffuse hyperplasia of Langerhans cells in the pancreas.

Pancreatic venous sampling (PVS) was first used by Swedish radiologists to localize pancreatic secreting tumors in adults. Localization of secreting hyperplasia was possible with PVS, whereas anatomical examination and surgical exploration were not very effective [2, 3]. The aim of our study was to evaluate PVS for the preoperative localization of focal pancreatic hyperplasia while mapping the prevalence of the focal lesions in both neonatal and delayed forms of hyperinsulinism. Correlations between PVS, pathological and operative findings were also analyzed.

Materials and methods

Between 17 March 1986 and 27 November 1990, 25 patients (13 females, 12 males) underwent a preoperative radiological localization procedure. They ranged in age from 21 days to 13 years at the time of PVS. Eleven patients (five females, six males) presented the neonatal form of hyperinsulinism with seizures and se-

Table 1. Neonatal hyperinsulinism operated: correlation between pancreatic venous sampling and pathological findings

Pathology	Pancreatic venous sampling			
	Focal	Diffuse	Indeterminate	Total
Focal	3	0	2	5
Diffuse	1	3	2	6
Total	4	3	4	11

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Table 2. Neonatal hyperinsulinism operated: correlation between clinical, pathological and surgical findings

Patient	Sex	Age at onset	Diazoxide	PVS	Surgery	Pathology	Follow-up 1
	Male	1 h	N	I	PC	F	PI
2	Male	1 h	N	I	PC	D	Hypoglycemia
3	Male	13 h	N	D	PC	D	–
4	Female	24 h	N	F	PC	D	–
5	Female	1 h	N	I	D	D	Diabetes
6	Female	24 h	N	I	PC	F	Cured
7	Female	25 h	N	F	F	F	Cured
8	Male	24 h	N	D	PC	D	Hyperglycemia
9	Female		N	F	F	F	Cured
10	Male	24 h	N	D	PC	D	Insulinopenia
11	Male	40 h	N	F	F	F	Cured

D, Delayed; F, focal; I, indeterminate; N, diazoxide resistant; PC, subtotal pancreatectomy; PI, pancreatic insufficiency; PVS, pancreatic venous sampling

Table 3. Delayed hyperinsulinism operated: correlation between pancreatic venous sampling and pathological findings

Pathology	Pancreatic venous sampling			
	Focal	Diffuse	Indeterminate	Total
Focal	11	0	0	11
Diffuse	1	0	2	3
Total	12	0	2	14

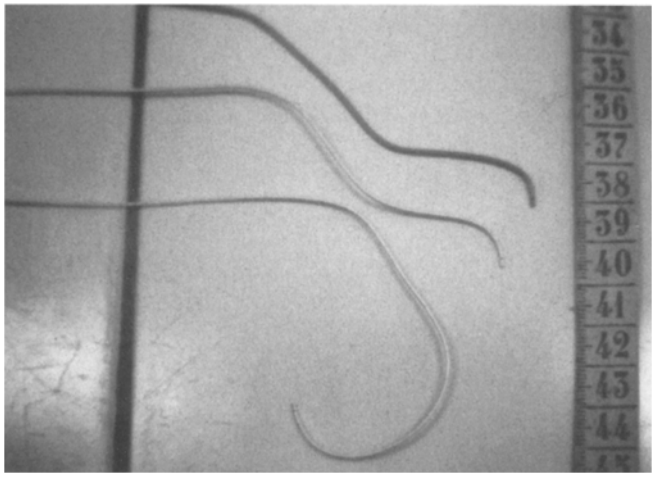

Fig. 1. Catheters specially designed for pancreatic venous sampling

vere hypoglycemia (Tables 1, 2). The delayed form was manifested by 14 patients (8 females, 6 males) ranging in age from 1 month to 3 years (Tables 3, 4).

Hyperinsulinism was primarily diagnosed in all patients on the basis of inappropriately high levels of serum insulin occurring at the same time as hypoglycemia. Lower concentrations of blood free fatty acids and ketone bodies, as well as an abnormal response to an insulin secretagogue such as glucagon supported this diagnosis.

Medical management included frequent feeding, intravenous administration of glucose through either peripheral or central venous lines and diazoxide, somatostatin and glucagon treatments.

Pancreatic venous samplings

PVS was performed in patients between the age of 21 days and 6.5 months for the neonatal form and between 3 and 13 months for the delayed form. All drugs were stopped 7 days before PVS. With the patient under general anesthesia without halothane, PVS was undertaken via percutaneous transhepatic catheterization. Ultrasound was used to identify the portal vein prior to puncture of the liver on the midaxillary line with an 18-G catheter needle [4]. Specially designed 3-F or 4.1-F catheters (Fig. 1) were inserted into the portal system without sheathing. The first catheter was used for the splenic vein, the second for the mesenteric veins and the third for selecting pancreaticoduodenal veins of the head. Phlebography with ioxaglate (Hexabrix) injection to document the blood sampling sites allowed us to chart the venous anatomy. The greatest number of pancreatic veins was sampled in the head, isthmus, body and tail areas (Fig. 2 a, b). Insulin and glucose were measured in different samples with the results being reported on a PVS map. Capillary blood sugar levels were monitored regularly during the procedure to ensure that glycemia was under 3.5 mmol/l. The procedure was completed by percutaneous cholecystography for proper localization of the terminal common bile duct. No arteriography was performed. Hormonal radioimmunoassay included insulin measurement.

Focal and diffuse types of lesion were distinguished by the presence of localized insulin hypersecretion, for which the insulin peak had to be 2.5 times higher than the lowest portal value (Fig. 3 a, b). It was correlated with both histological and clinical criteria established in postoperative patients. Histological criteria were verified by one of us (J. R.) on the basis of nuclear size, nuclear crowding, volume density and proinsulin levels as described elsewhere [5, 6]. The clinical outcome desired was normalization of blood glucose after surgery.

Results

Neonatal form

Among the 11 neonatal cases, the final diagnosis was of 5 focal and 6 diffuse lesions. PVS accuracy was 54.5 % with six correct diagnoses, one misdiagnosis and four indeterminate diagnoses (Tables 1, 5). It is essential to note that no focal lesion was misdiagnosed as being diffuse.

The patients with diffuse ($n = 3$) and indeterminate ($n = 4$) hyperinsulinism underwent subtotal pancreatectomy (95–95 %). Follow-up revealed that two patients, one with a focal and the other with a diffuse lesion, had diabetes and exocrine pancreatic insufficiency. One diffuse lesion patient presented relative insulopenia and two had persistent hypoglycemia. Two patients were lost for follow-up.

Table 4. Delayed hyperinsulinism operated: correlation between clinical, pathological and surgical findings

Patient	Sex	Age at onset	Diazoxide	PVS	Surgery	Pathology	Follow-up
1	Female	3 months	N	F	F	F	C
2	Male	2 months	N	F	F	F	C
3	Male	3 months	N	I	PC	D	
4	Male	9 months	Y	F	F	F	C
5	Female	3 months	N	F	F	F	C
6	Male	3.5 months	N	F	F	F	C
7	Female	4 months	Y	F	F	F	C
8	Female	1.5 months	N	F	F	F	
9	Male	3 months	N	I	PC	D	
10	Female	10 months	Y	F	F	F	C
11	Female	4 months	Y	F	F	F	C
12	Female	7 months	Y	F	PC	D	
13	Female	6 months	Y	F	F	F	C
14	Male	5 years	Y	F	F	F	C

C, Cured; D, Delayed; F, focal; I, indeterminate; N, diazoxide resistant; PC, subtotal pancreatectomy; PVS, pancreatic venous sampling; Y, diazoxide sensitive

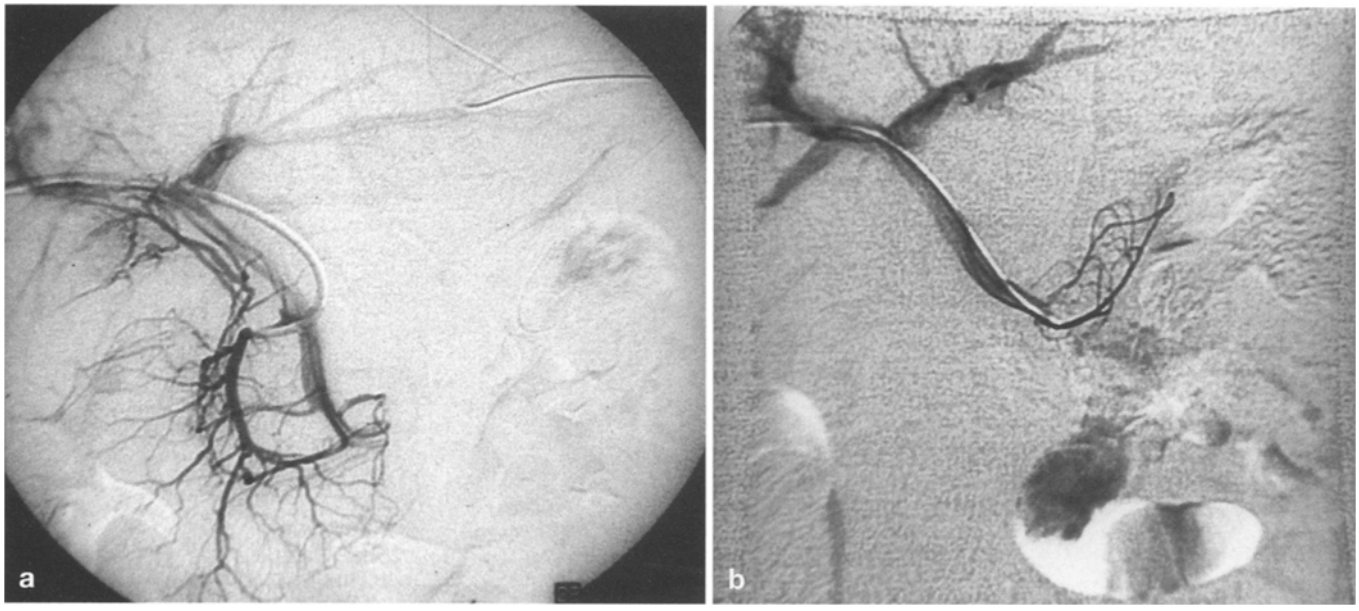

Fig. 2. **a** Pancreaticoduodenal veins of the head. **b** Dorsal pancreatic vein opacification

Delayed form

Of the 14 cases of the delayed form, the final diagnosis was 11 focal and 3 diffuse lesions. PVS accuracy was 78%. PVS diagnostic value was significantly different in the two groups, with 100% correct diagnosis of focal lesions (Table 3). Morphologically, the findings of phlebography were always normal, even in patients with focal hypersecretion.

Clinical outcome

Patients with focal hyperinsulinism demonstrated by PVS and pathology had no recurrence (Table 4).

Complications

There were no complications during the procedure. The blood sugar level ranged between 2.5 and 5 mmol/l. Severe hypoglycemia did not develop in any patient during PVS. After the procedure, only three complications occurred: two patients had abdominal pain, while the third presented thrombopenia in association with splenomegaly, but without splenic vein thrombosis as verified by ultrasonography. These conditions resolved spontaneously without specific treatment. No renal failure occurred in our series despite the use of large doses of contrast medium, which reached 3 to 4 mg/kg in some cases.

Discussion

Hypoglycemia in children with hyperinsulinism can be fatal if left untreated. It may lead to mental retardation, especially in the neonatal form. Early medical and

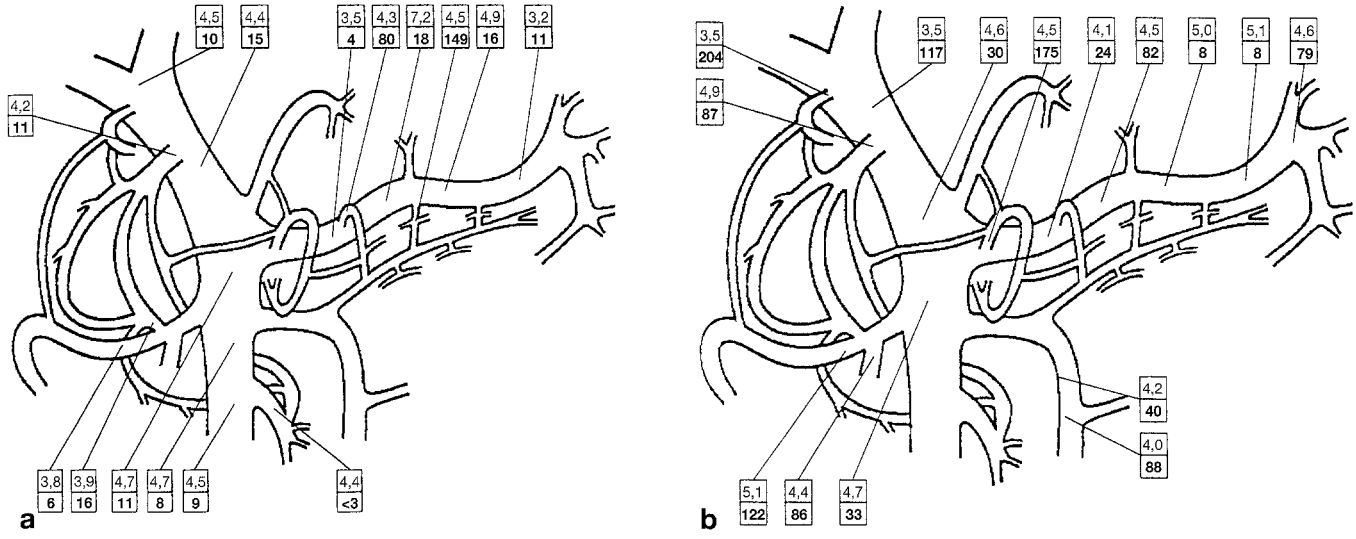

Fig. 3. **a** Mapping of insulin levels in neonatal hyperinsulinism with focal secretion. *Numbers* at the top represent glucose levels and those at the bottom insulin levels. **b** Mapping of insulin levels in delayed hyperinsulinism with diffuse secretion. *Numbers* at the top represent glucose levels and those at the bottom insulin levels

Table 5. Pancreatic venous sampling in operated and nonoperated patients

Hyperinsulinism	Operated	Not operated	Total
Neonatal	11	2	13
Delayed	14	13	27
Total	25	15	40

surgical treatments are necessary to prevent brain damage. In the newborn, glucose consumption in the brain represents 60–70 % of basal metabolism [7]. The most important biochemical change is the inappropriate elevation of plasma insulin concentrations in relation to blood glucose [8, 9]. The exact definition of hyperglycemia is still controversial [8, 10] but our group decided on a blood glucose level lower than 2.8 mmol/l in infants and 2.2 mmol/l in newborns.

The etiopathogenesis of diffuse or focal abnormalities of insulin-producing B cells is still unknown [6, 8, 9]. Many imaging procedures have been used for preoperative localization of pancreatic insulinomas in adults. Arteriography has been employed in children [11] but in large series of adults its sensitivity varies from 29 % to 90 % [4, 12]. In a recent publication, Doppman et al. described the use of arterial stimulation and venous sampling (ASVS) in four patients by intra-arterial injection of an insulin secretagogue to locate insulinomas [13]. Calcium was selected as the insulin-releasing stimulant. The localization of secretion was verified by surgery in three of these four patients. Further examination with calcium ASVS will be necessary to confirm the value of this method [13]. The reported sensitivity of CT detection of pancreatic insulinomas ranges from about 30 % to 66 % [14–16]. Preoperative ultrasonographic localization was described in five children aged 12–16 years, in whom three focal lesions were found [17]. In adults, preoperative ultrasonographic localization of insulinomas detected 61 % of the lesions while intraoperative ultrasonography correctly identified 84 % [14]. We have had limited experience with intraoperative ultrasonography in children. Three patients were investigated without identification of the lesion. It is difficult to conduct a good examination in small infants weighting 5–10 kg.

Until now, subtotal pancreatectomy (85–95 %) was the only treatment technique available for infants in whom hyperinsulinism was confirmed and who did not respond to diazoxide therapy [18, 19].

Our results show that the accuracy of PVS was 54.5 % in the neonatal form of hyperinsulinism. However, in all cases where PVS was inaccurate, it was performed with blood glucose levels higher than 3.5 mmol/l. In our early experience, we noticed that general anesthesia almost invariably increased blood glucose for several hours. The exact mechanism is unknown, but inhibition of insulin secretion and diminution of glucose consumption are probable. We recommend PVS only when blood glucose is below 3.5 mmol/l. In the neonatal form, we demonstrated that focal hyperinsulinism was more frequent (45 %) than described in the literature. PVS findings were correlated with pathological outcome in three cases, permitting partial resection without complications and a complete cure. These focal lesions are probably not as rare as generally considered since 137 cases were reported up to 1981 [20, 21].

In the delayed form, the accuracy of diagnosis was 78.6 %. Eleven focal lesions were correlated with the pathological findings, and these patients were cured without complications. One diffuse type was misdiagnosed as a focal type because of hyperglycemia during PVS. The indeterminate diagnosis of a pathologically diffuse type was secondary to hyperglycemia during PVS.

For the two groups overall accuracy was 64 %. Most problems were encountered at the beginning of PVS. Our experience showed that PVS must be used only

when the blood glucose level is lower than 3.5 mmol/l and that a maximum number of veins draining different parts of the pancreas should be sampled. We hope that future studies will help to ameliorate the accuracy of diagnosis of focal type hyperinsulinism by establishing more precise and specific criteria.

In conclusion, PVS is feasible in children, but requires a high level of expertise both for the procedure and for pathological evaluation. It is the only preoperative diagnostic technique available. PVS has good diagnostic value and major therapeutic consequences, allowing dedicated partial resection to prevent diabetes and exocrine pancreatic insufficiency. Further studies in these patients and longer follow-up are needed to elucidate the mechanism of hyperinsulinism.

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