

CLINICAL FEATURES OF 52 NEONATES WITH HYPERINSULINISM

PASCALE DE LONLAY-DEBENEY, M.D., FLORENCE POGGI-TRAVERT, M.D., JEAN-CHRISTOPHE FOURNET, M.D.,
CHRISTINE SEMPOUX, M.D., CARLO DIONISI VICI, M.D., FRANCIS BRUNELLE, M.D., GUY TOUATI, M.D.,
JACQUES RAHIER, M.D., PH.D., CLAUDINE JUNIEN, M.D., PH.D., CLAIRE NIHOUL-FÉKÉTÉ, M.D.,
JEAN-JACQUES ROBERT, M.D., PH.D., AND JEAN-MARIE SAUDUBRAY, M.D.

ABSTRACT

Background Neonatal hyperinsulinemic hypoglycemia is often resistant to medical therapy and is often treated with near-total pancreatectomy. However, the pancreatic lesions may be focal and treatable by partial pancreatic resection.

Methods We studied 52 neonates with hyperinsulinism who were treated surgically. The type and location of the pancreatic lesions were determined by preoperative pancreatic catheterization and intraoperative histologic studies. Partial pancreatectomy was performed in infants with focal lesions, and near-total pancreatectomy was performed in those with diffuse lesions. The postoperative outcome was determined by measurements of plasma glucose and glycosylated hemoglobin and by oral glucose-tolerance tests.

Results Thirty neonates had diffuse beta-cell hyperfunction, and 22 had focal adenomatous islet-cell hyperplasia. Among the latter, the lesions were in the head of the pancreas in nine, the isthmus in three, the body in eight, and the tail in two. The clinical manifestations were similar in both groups. The infants with focal lesions had no symptoms of hypoglycemia and had normal preprandial and postprandial plasma glucose and glycosylated hemoglobin values and normal results on oral glucose-tolerance tests after partial pancreatectomy (performed in 19 of 22 neonates). By contrast, after near-total pancreatectomy, 13 of the patients with diffuse lesions had persistent hypoglycemia, type 1 diabetes mellitus developed in 8, and hyperglycemia developed in another 7; overall, only 2 patients with diffuse lesions had normal plasma glucose concentrations in the first year after surgery.

Conclusions Among neonates with hyperinsulinism, about half may have focal islet-cell hyperplasia that can be treated with partial pancreatectomy. These neonates can be identified through pancreatic catheterization and intraoperative histologic studies. (N Engl J Med 1999;340:1169-75.)

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CONGENITAL hyperinsulinism is characterized by an inappropriate oversecretion of insulin. It is the most common cause of recurrent hypoglycemia in neonates^{1,2} and can cause irreversible brain damage.¹⁻³ It is often resistant to medical therapy,^{1,4} and pancreatectomy is often necessary to prevent recurrent hypoglycemia.^{1,5-8} Neonates with hyperinsulinism may have ei-

ther focal or diffuse abnormalities of the beta cells of the pancreas.⁹⁻¹⁴

The focal abnormalities are manifested as adenomatous islet-cell hyperplasia (hereafter called focal hyperinsulinism). This disorder is associated with the loss of the maternal allele from chromosome 11p15, leading to unbalanced expression of imprinted genes involved in the control of cell growth; somatic reduction to hemizygoty or homozygoty of a paternally inherited mutation of the gene for the sulfonylurea receptor type 1 (*SURI*) leads to hyperinsulinism.^{15,16}

The diffuse abnormalities are manifested as beta-cell hyperfunction (hereafter called diffuse hyperinsulinism). This condition is a heterogeneous disorder involving the gene encoding the sulfonylurea receptor^{17,18} or the inward-rectifying potassium channel ($K_{IR} 6.2$)^{19,20} in recessively inherited hyperinsulinism,²¹ the glucokinase gene²² or other loci²³ in dominantly inherited hyperinsulinism, and the glutamate dehydrogenase gene²⁴ in cases in which hyperammonemia is associated with hyperinsulinism.

The therapeutic outcome in these neonates is heavily dependent on distinguishing between the two types of hyperinsulinism. Neonates with diffuse hyperinsulinism who are unresponsive to drug or dietary treatment require near-total pancreatectomy; the risk of diabetes mellitus in these children later in life is high.^{5,25,26} Conversely, neonates with focal hyperinsulinism can be treated with partial pancreatectomy^{6,27} if the region of focal adenomatous islet-cell hyperplasia can be identified. We describe a series of 52 neonates with hyperinsulinism — 22 with focal hyperinsulinism and 30 with diffuse hyperinsulinism.

METHODS

Between 1985 and 1998, we studied 52 neonates referred to our hospital for pancreatic surgery because of persistent hyperinsulinism. All had hypoglycemia both while fasting and postprandially (plasma glucose concentration, <54 mg per deciliter [3.0 mmol per liter]) within 72 hours after birth, with hyperinsuline-

From the Departments of Pediatrics (P.L.-D., F.P.-T., G.T., J.-J.R., J.-M.S.), Pathology (J.-C.F.), Radiology (F.B.), and Surgery (C.N.-E) and INSERM Unité 383, Génétique, Chromosome, et Cancer (C.J.), Hôpital des Enfants Malades, Paris; the Department of Pathology, Cliniques Universitaires St. Luc, Université de Louvain, Brussels, Belgium (C.S., J.R.); and the Division of Metabolism, Ospedale Bambino Gesù, Rome (C.D.V.). Address reprint requests to Dr. Saudubray at the Fédération de Pédiatrie, Service de Métabolisme, Hôpital des Enfants Malades, 149 rue de Sèvres, 75743 Paris CEDEX 15, France.

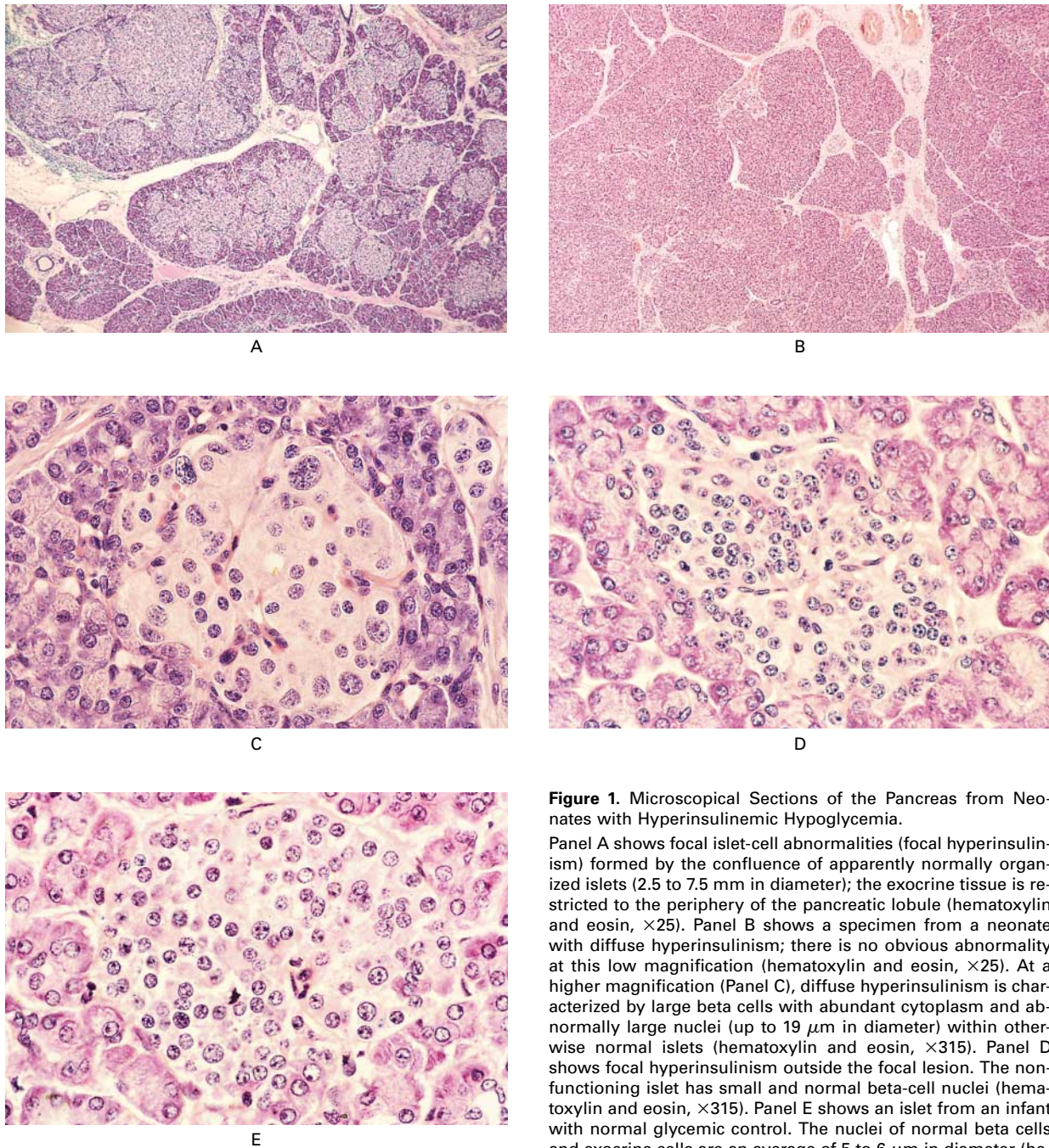


Figure 1. Microscopical Sections of the Pancreas from Neonates with Hyperinsulinemic Hypoglycemia.

Panel A shows focal islet-cell abnormalities (focal hyperinsulinism) formed by the confluence of apparently normally organized islets (2.5 to 7.5 mm in diameter); the exocrine tissue is restricted to the periphery of the pancreatic lobule (hematoxylin and eosin, $\times 25$). Panel B shows a specimen from a neonate with diffuse hyperinsulinism; there is no obvious abnormality at this low magnification (hematoxylin and eosin, $\times 25$). At a higher magnification (Panel C), diffuse hyperinsulinism is characterized by large beta cells with abundant cytoplasm and abnormally large nuclei (up to 19 μm in diameter) within otherwise normal islets (hematoxylin and eosin, $\times 315$). Panel D shows focal hyperinsulinism outside the focal lesion. The non-functioning islet has small and normal beta-cell nuclei (hematoxylin and eosin, $\times 315$). Panel E shows an islet from an infant with normal glycemic control. The nuclei of normal beta cells and exocrine cells are an average of 5 to 6 μm in diameter (hematoxylin and eosin, $\times 315$).

mia (plasma insulin concentration, $>10 \mu\text{U}$ per milliliter [60 pmol per liter]) and an increase in the plasma glucose concentration of 50 to 80 mg per deciliter (2.8 to 4.4 mmol per liter) in response to the subcutaneous or intramuscular administration of glucagon. All the neonates required the intravenous administration of glucose at high rates (>10 mg per kilogram of body weight per minute) to maintain plasma glucose concentrations above 60 mg per deciliter (3.3 mmol per liter), and hypoglycemia persisted in all through the first month of life. All the neonates

were treated with diazoxide (15 mg per kilogram per day orally, given in three doses), with little benefit in all but three of them, and therefore central venous feeding for nearly all was required.⁴ At the time of surgery, 22 of the infants had focal hyperinsulinism and 30 had diffuse hyperinsulinism, as determined pathologically (Fig. 1).^{9,13,28}

Preoperative studies included transhepatic catheterization of the portal vein and selective catheterization of the pancreatic vein while the neonates were under general anesthesia to locate

the time of catheterization underwent surgery. The others also underwent surgery if they had resistance to or could not tolerate treatment with diazoxide. Tissue samples were collected intraoperatively from the head, the isthmus, the body, and the tail of the pancreas and were immediately examined by conventional microscopy.²⁸ The lesions of diffuse hyperinsulinism were characterized by beta cells with large nuclei and abundant cytoplasm in all pancreatic specimens. These infants underwent near-total pancreatectomy. Partial pancreatectomy was performed when the biopsy specimens showed no abnormal nuclei but did show shrunken cytoplasm in the beta cells, producing a pattern of crowded beta cells.^{9,28} In such cases, additional tissue samples were taken in order to localize the lesion, on the basis of the data obtained from the pancreatic catheterization. After the pancreas was resected, a final series of samples was examined to ensure that the surrounding pancreatic tissue was normal.

All resected pieces of pancreas were assessed by conventional microscopy and histomorphometric studies,^{9,13,28} and DNA was extracted in order to characterize the lesions further. We performed DNA analysis of all available resected samples obtained before 1996 and of all resected samples from neonates with focal hyperinsulinism who underwent surgery thereafter. The specimens were also analyzed for loss of maternal alleles from chromosome 11p15.^{15,16} In addition, we searched for mutations in the first and second domains of the nucleotide-binding fold (NBF1 and NBF2) of the *SUR1* gene^{17,18} in samples of peripheral-blood lymphocytes from all the neonates and their parents.

Plasma glucose was measured before and after feedings before the infants were discharged from the hospital. Plasma glucose and glycosylated hemoglobin were measured; in addition, oral glucose-tolerance tests were performed periodically thereafter in 11 of the infants with focal hyperinsulinism and in 15 of those with diffuse hyperinsulinism. Plasma glucose concentrations of less than 54 mg per deciliter while the infant was eating a normal diet and taking no medication were considered to indicate persistent hypoglycemia. The results of an oral glucose-tolerance test were considered to be normal when the plasma glucose concentration was less than 200 mg per deciliter (11.1 mmol per liter) 30 and 60 minutes after glucose ingestion and less than 140 mg per deciliter (7.8 mmol per liter) after 120 minutes.³¹

All studies were performed with the written consent of the parents. The results in the two groups were compared with use of nonparametric Mann-Whitney tests and analysis of variance.

RESULTS

Clinical and Biochemical Characteristics

The clinical and biochemical characteristics of the neonates in the two groups were similar (Table 1), with the exception that the mean gestational age was significantly lower among the neonates with diffuse hyperinsulinism. The rates of intravenous infusion of glucose required to maintain plasma glucose concentrations higher than 60 mg per deciliter were similar in the two groups. Only one neonate with focal hyperinsulinism and two with diffuse hyperinsulinism responded to treatment with diazoxide. The ages of the infants in both groups were similar at the time of surgery. All but five infants underwent surgery before the age of eight months.

Pancreatic Catheterization

Transhepatic catheterization of the portal and pancreatic veins was performed in 45 neonates. Among the 22 neonates with focal hyperinsulinism, the site of localized hypersecretion of insulin was identified in 17, the site could not be identified in 2, and the

TABLE 1. CLINICAL CHARACTERISTICS OF THE NEONATES WITH FOCAL OR DIFFUSE HYPERINSULINISM.*

CHARACTERISTIC	FOCAL HYPERINSULINISM (N=22)	DIFFUSE HYPERINSULINISM (N=30)
Sex — M/F	7/15	11/19
Cesarean delivery — no. (%)	7 (32)	9 (30)
Birth weight — kg	3.7±0.7	3.7±0.7
Gestational age — wk	39.3±1.3	37.2±2.8†
Birth weight for gestational age >90th percentile — no. (%)	10 (45)	14 (47)
First symptom of hypoglycemia — no. (%)‡		
Seizure	11 (50)	16 (53)
Hypothermia	0	1 (3)
Hypotonia	1 (5)	1 (3)
Loss of consciousness	5 (23)	3 (10)
Detected fortuitously	5 (23)	9 (30)
Initial plasma glucose — mg/dl§	18±4	18±4
Plasma insulin — μU/ml¶	20±11	22±19
Glucose-infusion rate — mg/kg/min	16.1±3.7	16.4±3.7
Median age at surgery — days**	91	95

*Plus-minus values are means ±SD.

†P<0.01.

‡Because of rounding, percentages do not total 100.

§Initial plasma glucose is the first measurement of plasma glucose during an episode of hypoglycemia. To convert values for glucose to millimoles per liter, multiply by 0.05551.

¶Plasma insulin is the mean of all measurements made at a plasma glucose concentration of <54 mg per deciliter (3 mmol per liter), with only one value used per patient. To convert values for insulin to picomoles per liter, multiply by 6.

||Values are the rate of glucose administration (intravenous or oral) needed to maintain plasma glucose concentrations of at least 54 mg per deciliter.

**For those who underwent surgery twice, the age at the time of the first intervention is given.

procedure was not performed in 3 (Table 2). Among the 30 neonates with diffuse hyperinsulinism, diffuse insulin hypersecretion was identified in 17, localized insulin hypersecretion was suspected in 7, the results were inconclusive in 2, and the procedure was not performed in 4. The seven neonates who did not undergo catheterization underwent surgery before the procedure was available for very young neonates at our hospital or underwent surgery at another hospital before they were referred to us. No infants had any complications resulting from the catheterization.

Focal Hyperinsulinism

Among the neonates with focal hyperinsulinism, nine had lesions of focal adenomatous islet-cell hyperplasia in the head of the pancreas, three in the isthmus, eight in the body, and two in the tail (Table 2). The loss of the maternal allele from chromosome 11p15 was sought in 14 lesions and was found in all. Mutation analysis of the NBF1 and NBF2 domains

TABLE 2. LOCATION OF LESIONS AS DETERMINED BY PANCREATIC VENOUS CATHETERIZATION AND HISTOLOGIC EXAMINATION, EXTENT OF PANCREATECTOMY, AND GENETIC CHARACTERISTICS OF THE 22 NEONATES WITH FOCAL HYPERINSULINISM.*

TREATMENT AND PATIENT NO.	AGE AT SURGERY	LOCATION BY CATHETERIZATION	LOCATION BY HISTOLOGIC EXAMINATION	EXTENT OF PANCREATIC RESECTION	LOH IN LESION†	MUTATION OF <i>SUR1</i> GENE‡
Partial pancreatectomy						
1	99 days	Head	Head	Head	ND	None
2	234 days	Body	Body	Body	Yes	None
3	117 days	Tail	Tail	Tail	Yes	R1421C§
4	91 days	Head	Head	Head	Yes	None
5	237 days	Body	Body	Body and tail	Yes	None
6	91 days	Body	Body	Body and tail	ND	None
7	73 days	Unknown	Body	Body and tail	ND	ND
8	142 days	Unknown	Body	Body and tail	Yes	None
9	27 mo	Head	Head	Head	ND	None
10	36 days	Body	Body	Body and tail	ND	del4138CGAC¶
11	139 days	Head	Head	Head	Yes	None
12	36 days	Isthmus	Isthmus	Isthmus and body	Yes	None
13	66 days	Body	Body	Body and tail	ND	ND
14	84 days	Isthmus	Isthmus	Isthmus and body	Yes	R842G
15	58 days	Head	Head	Head	ND	ND
16	66 days	Head	Head	Head	Yes	None
17	69 days	Head	Head	Head	Yes	R1494W**
18	44 days	Isthmus	Isthmus	Isthmus	Yes	None
19	99 days	Tail	Tail	Tail	Yes	ND
Near-total pancreatectomy						
20	88 days	ND	Body	Near-total	ND	ND
21	19 mo	ND	Head	Near-total	Yes	ND
22	20 mo	ND	Head	Near-total	Yes	R1494W**

*ND denotes not determined.

†LOH denotes loss of heterozygosity (loss of the maternal allele from chromosome 11p15 in the focal lesion).

‡Mutation of *SUR1* gene refers to heterozygous mutations in the NBF1 and NBF2 domains in peripheral-blood lymphocytes from the patients and their fathers; other exons of the *SUR1* gene were not studied.

§R1421C was a missense mutation due to a C→T transition at position 4261.

¶This mutation was a deletion of four nucleotides, CGAC, at positions 4138 to 4141 and the insertion of three nucleotides, GTG.

||This missense mutation was due to a C→G transversion at position 2524.

**This missense mutation was due to a C→T substitution at position 44810.

of the *SUR1* gene in peripheral-blood lymphocytes was performed on samples from 16 neonates, of whom 5 had mutations, all of paternal origin.

Nineteen of the 22 infants with focal lesions underwent partial pancreatectomy, and all 19 had localized lesions. None of them had hypoglycemia, and all had normal postprandial plasma glucose concentrations during the immediate postoperative period. All were subsequently able to eat normally, and none had hypoglycemia, high glycosylated hemoglobin values, or (among the 11 tested) abnormal glucose tolerance, and none required further surgery or any medical treatment during a mean follow-up period of 3.6 years (range, 0.7 to 8.2).

Three infants with focal hyperinsulinism underwent near-total pancreatectomy. One underwent surgery before pancreatic catheterization was available.

A small lesion was retrospectively identified in the body of the pancreas, and the rest of the pancreas was normal. This child had to be treated with insulin at the age of nine years because of increasing hyperglycemia. The other two infants initially underwent resection of the body and tail of the pancreas at other hospitals; we extended the pancreatectomy in each because of persistent, severe hypoglycemia. In both children hyperplastic lesions were found in the head of the pancreas and resected. Both now have no hypoglycemia.

Diffuse Hyperinsulinism

The results of histologic testing performed intraoperatively revealed diffuse beta-cell hyperfunction, confirming the findings on pancreatic catheterization in 17 neonates with diffuse hyperinsulinism and provid-

ing the basis for the diagnosis in the remaining 13. All 30 underwent near-total pancreatectomy. Six underwent further pancreatic resection 1 to 10 months after the first operation because of recurrent severe hypoglycemia. These 30 children were followed for a mean of 4.6 years (range, 0.1 to 13.7). Thirteen had persistent hypoglycemia, including four of the six who had a second operation. Eight of the 13 were treated with glucocorticoids or octreotide, but these medications could be discontinued within three years after surgery, after which hypoglycemia during fasting was prevented by the nighttime administration of raw cornstarch. Type 1 diabetes developed in eight children; the onset occurred immediately after surgery in six, at eight years of age in one, and at nine years of age in one. Seven others had high postprandial plasma glucose concentrations or abnormal results on the glucose-tolerance test but, as of this writing, have not required insulin; postprandial hyperglycemia was associated with preprandial hypoglycemia in five of these children. Thus, only two children have had no recurrence of hypoglycemia and no hyperglycemia, but they underwent surgery less than one year before this report was written. Nineteen required treatment for exocrine pancreatic insufficiency.

DISCUSSION

In neonates, hyperinsulinemic hypoglycemia rarely responds to diazoxide, the standard drug used to treat hyperinsulinism.¹⁻⁴ Among the 52 neonates in this study, only 3 had a response to diazoxide. In the 13 years during which we conducted our study, 11 neonates with hyperinsulinemic hypoglycemia were successfully treated with this drug, and therefore did not undergo surgery (and thus were not included in this study). Although octreotide has been used with some success,^{32,33} pancreatic surgery is often required. Most surgeons recommend near-total pancreatectomy,^{3,5,8} but the risk of subsequent diabetes mellitus is high.^{5,25,26}

The prognosis for some neonates with hyperinsulinemia has dramatically improved since it was recognized that those with focal hyperinsulinism could be treated effectively with partial pancreatectomy. In pathological terms, focal hyperinsulinism is a hyperplastic adenomatosis that, unlike beta-cell adenoma, is invisible to the naked eye (i.e., it does not affect the lobular architecture of the pancreas) and is composed of hyperplastic islets with numerous beta cells in the center and other types of cells at the periphery. It occurs in neonates rather than in older children and adults.^{9,34} Diffuse hyperinsulinism, inappropriately referred to as nesidioblastosis, is characterized by subtle morphologic changes in endocrine cells, involving the entire pancreas and consisting of hypertrophied insulin cells with large hyperchromatic nuclei suggestive of functional hyperactivity in an otherwise histologically normal pancreas.^{9,13}

The surgical treatment of the two disorders differs greatly. Neonates with diffuse hyperinsulinism require near-total pancreatectomy, whereas those with focal hyperinsulinism should be treated with partial pancreatectomy.^{6,27,28,35} Although it became less severe with time, persistent hypoglycemia was present in many of the infants with diffuse hyperinsulinism in our study after surgery, and many others had either hyperglycemia or overt diabetes. These results, like those of other studies,^{1,3,5,25,26} indicate that better medical treatments are needed for neonates with diffuse hyperinsulinism. By contrast, the 19 neonates who had focal hyperinsulinism and underwent partial pancreatectomy had no hypoglycemia after surgery.

Thus, it is important to look for focal hyperinsulinism, because neonates with this disorder can benefit from partial pancreatectomy. In this series, in which there was probably no recruitment or referral bias, 42 percent of the neonates could be treated with partial pancreatectomy. Most of the neonates referred to our clinic had conditions that were resistant to medical treatment, but such resistance is characteristic of most cases of neonatal hyperinsulinism.⁴ The similarity of the symptoms and biochemical findings in the two groups indicates that insulin secretion is similarly disordered in both.

In the absence of any distinctive clinical or biochemical features, all available means should be used to differentiate between focal and diffuse lesions before surgery. Factitious hypoglycemia,³⁶ hyperinsulinism with hyperammonemia,²⁴ and the carbohydrate-deficient glycoprotein syndrome (unpublished data) should be ruled out before complex investigations are initiated. Children with familial cases are generally likely to have diffuse hyperinsulinism, whereas cases involving one of a set of identical twins are probably focal.¹⁵ However, familial cases of hyperinsulinism are rare in our experience.

Our findings regarding the molecular changes underlying focal and diffuse hyperinsulinism have raised the possibility of differentiating the two by molecular testing. However, the search for mutations of the *SURI* and *K_{ir}6.2* genes, which would permit differentiation between homozygous and heterozygous cases, is currently of limited use in clinical practice. Standard radiologic studies of the pancreas do not identify small focal lesions. Thus, transhepatic pancreatic catheterization and venous sampling are currently the only preoperative procedures available for determining the site of focal insulin hypersecretion.^{29,30} These procedures correctly located the lesion in 89 percent of the neonates with focal hyperinsulinism who underwent catheterization in our study. This degree of accuracy is crucial in view of the fact that nine focal lesions were located in the head of the pancreas, whereas surgeons usually resect pancreatic tissue by first removing the tail and

body of the pancreas. The two infants who underwent partial pancreatectomy that was unsuccessful because the lesions were in the right upper part of the head of the pancreas are good examples of what can now be avoided. The data obtained from pancreatic catheterization were misinterpreted or not useful for 35 percent of the neonates with diffuse hyperinsulinism, and therefore the final decision about treatment must always be based on the histologic findings obtained intraoperatively.²⁸

In conclusion, hyperinsulinemic hypoglycemia in neonates is often caused by focal adenomatous islet-cell hyperplasia. This disorder can be recognized by transhepatic pancreatic catheterization and intraoperative histologic studies and can be treated effectively with partial pancreatectomy, which is effective and carries little risk of causing diabetes mellitus.

Supported by a grant (3.4594.99) from the Fonds de la Recherche Scientifique Médicale.

We are indebted to Drs. J.P. Bonnefont, M.C. Brusset, D. Jan, K. Laborde, S. Lyonnet, D. Martin, A. Munnich, Y. Revillon, and C. Sevin from Hôpital Necker-Enfants Malades; and to the numerous physicians from France, Belgium, Greece, Italy, Norway, and Switzerland who referred the neonates in the study to us.

REFERENCES

- Stanley CA. Hyperinsulinism in infants and children. *Pediatr Clin North Am* 1997;44:363-74.
- Bruining GJ. Recent advances in hyperinsulinism and the pathogenesis of diabetes mellitus. *Curr Opin Pediatr* 1990;2:758-65.
- Thomas CG Jr, Underwood LE, Carney CN, Dolcourt JL, Whitt JJ. Neonatal and infantile hypoglycemia due to insulin excess: new aspects of diagnosis and surgical management. *Ann Surg* 1977;185:505-17.
- Touati G, Poggi-Travert F, Ogier de Baulny H, et al. Long-term treatment of persistent hyperinsulinaemic hypoglycaemia of infancy with diazoxide: a retrospective review of 77 cases and analysis of efficacy-predicting criteria. *Eur J Pediatr* 1998;157:628-33.
- Shilyanski J, Fisher S, Cutz E, Perlman K, Filler RM. Is 95% pancreatectomy the procedure of choice for treatment of persistent hyperinsulinemic hypoglycemia of the neonate? *J Pediatr Surg* 1997;32:342-6.
- Hyperinsulinismes de l'enfant: à propos d'une série de 56 cas (1984-1994). In: Poggi-Travert F, Rahier J, Brunelle F, Fékété C, Saudubray JM. *Journées Parisiennes de pédiatrie*. Paris: Flammarion Médecine-Sciences, 1994:29-42.
- Thornton PS, Alter CA, Katz LE, Baker L, Stanley CA. Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism. *J Pediatr* 1993;123:637-43.
- Spitz L, Bhargava RK, Grant DB, Leonard JV. Surgical treatment of hyperinsulinaemic hypoglycaemia in infancy and childhood. *Arch Dis Child* 1992;67:201-5.
- Sempoux C, Guiot Y, Lefevre A, et al. Neonatal hyperinsulinemic hypoglycemia: heterogeneity of the syndrome and keys for differential diagnosis. *J Clin Endocrinol Metab* 1998;83:1455-61.
- Nesidioblastosis. In: Solcia E, Capella C, Klöppel G. *Tumors of the pancreas*. Atlas of tumor pathology. 3rd series. Fascicle 20. Washington, D.C.: Armed Forces Institute of Pathology, 1997:238-43.
- Goossens A, Gepts W, Saudubray JM, et al. Diffuse and focal nesidioblastosis: a clinicopathological study of 24 patients with persistent neonatal hyperinsulinemic hypoglycemia. *Am J Surg Pathol* 1989;3:766-75.
- Goudswaard WB, Houthoff HJ, Koudstaal J, Zwierstra RP. Nesidioblastosis and endocrine hyperplasia of the pancreas: a secondary phenomenon. *Hum Pathol* 1986;17:46-54.
- Rahier J, Fält K, Müntefering H, Becker K, Gepts W, Falkmer S. The basic structural lesion of persistent neonatal hypoglycaemia with hyperinsulinism: deficiency of pancreatic D cells or hyperactivity of B cells? *Diabetologia* 1984;26:282-9.
- Jaffé R, Hashida Y, Yunis EJ. Pancreatic pathology in hyperinsulinemic hypoglycemia of infancy. *Lab Invest* 1980;42:356-65.
- de Lonlay P, Fournet JC, Rahier J, et al. Somatic deletion of the imprinted 11p15 region in sporadic persistent hyperinsulinemic hypoglycemia of infancy is specific of focal adenomatous hyperplasia and endorses partial pancreatectomy. *J Clin Invest* 1997;100:802-7.
- Verkarre V, Fournet JC, de Lonlay P, et al. Paternal mutation of the sulfonylurea receptor (SUR1) gene and maternal loss of 11p15 imprinted genes lead to persistent hyperinsulinism in focal adenomatous hyperplasia. *J Clin Invest* 1998;102:1286-91.
- Thomas PM, Cote GJ, Wohllk N, et al. Mutations in the sulfonylurea receptor gene in familial persistent hyperinsulinemic hypoglycemia of infancy. *Science* 1995;268:426-9.
- Nestorowicz A, Wilson BA, Schoor KP, et al. Mutations in the sulfonylurea receptor gene are associated with familial hyperinsulinism in Ashkenazi Jews. *Hum Mol Genet* 1996;5:1813-22.
- Thomas P, Ye Y, Lightner E. Mutation of the pancreatic islet inward rectifier Kir6.2 also leads to familial persistent hyperinsulinemic hypoglycemia of infancy. *Hum Mol Genet* 1996;5:1809-12.
- Nestorowicz A, Inagaki N, Gono T, et al. A nonsense mutation in the inward rectifier potassium channel gene, Kir6.2, is associated with familial hyperinsulinism. *Diabetes* 1997;46:1743-8.
- Thornton PS, Sumner AE, Ruchelli ED, Spielman RS, Baker L, Stanley CA. Familial and sporadic hyperinsulinism: histopathologic findings and segregation analysis support a single autosomal recessive disorder. *J Pediatr* 1991;119:721-4.
- Glaser B, Kesavan P, Heyman M, et al. Familial hyperinsulinism caused by an activating glucokinase mutation. *N Engl J Med* 1998;338:226-30.
- Kukuvitis A, Deal C, Arbour L, Polychronakos C. An autosomal dominant form of familial persistent hyperinsulinemic hypoglycemia of infancy, not linked to the sulfonylurea receptor locus. *J Clin Endocrinol Metab* 1997;82:1192-4.
- Stanley CA, Lieu YK, Hsu BLY, et al. Hyperinsulinemia and hyperammonemia in infants with regulatory mutations of the glutamate dehydrogenase gene. *N Engl J Med* 1998;338:1352-7.
- Leibowitz G, Glaser B, Higazi AA, Salameh M, Cerasi E, Landau H. Hyperinsulinemic hypoglycemia of infancy (nesidioblastosis) in clinical remission: high incidence of diabetes mellitus and persistent β -cell dysfunction at long-term follow-up. *J Clin Endocrinol Metab* 1995;80:386-92.
- Labrune P, Lechevallier S, Rault M, Odievre M. Diabetes mellitus 14 years after subtotal pancreatectomy for neonatal hyperinsulinism. *J Pediatr Surg* 1990;25:1246-7.
- Lyonnet S, Bonnefont JP, Saudubray JM, Nihoule-Fekete C, Brunelle F. Localisation of focal lesion permitting partial pancreatectomy in infants. *Lancet* 1989;2:671.
- Rahier J, Sempoux C, Fournet JC, et al. Partial or near-total pancreatectomy for persistent neonatal hyperinsulinaemic hypoglycaemia: the pathologist's role. *Histopathology* 1998;32:15-9.
- Brunelle F, Negre V, Barth MO, et al. Pancreatic venous samplings in infants and children with primary hyperinsulinism. *Pediatr Radiol* 1989;19:100-3.
- Dubois J, Brunelle F, Touati G, et al. Hyperinsulinism in children: diagnostic value of pancreatic venous sampling correlated with clinical, pathological and surgical outcome in 25 cases. *Pediatr Radiol* 1995;25:512-6.
- The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1998;21:Suppl 1:S5-S19.
- Glaser B, Hirsch HJ, Landau H. Persistent hyperinsulinemic hypoglycemia of infancy: long-term octreotide treatment without pancreatectomy. *J Pediatr* 1993;123:644-50.
- Horev Z, Ipp M, Levey P, Daneman D. Familial hyperinsulinism: successful conservative management. *J Pediatr* 1991;119:717-20.
- Bordi C, Ravazzola M, Pollak A, Lubec G, Orci L. Neonatal islet cell adenoma: a distinct type of islet cell tumor? *Diabetes Care* 1982;5:122-5.
- Craver RD, Hill CB. Cure of hypoglycemic hyperinsulinism by enucleation of a focal islet cell adenomatous hyperplasia. *J Pediatr Surg* 1997;32:1526-7.
- Scarlett JA, Mako ME, Rubenstein AH, et al. Factitious hypoglycemia: diagnosis by measurement of serum C-peptide immunoreactivity and insulin-binding antibodies. *N Engl J Med* 1977;297:1029-32.