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Heterogeneity of persistent hyperinsulinaemic hypoglycaemia. A series of 175 cases

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Abstract Hyperinsulinism is a heterogeneous disorder characterised by severe hypoglycaemia due to an inappropriate oversecretion of insulin. In a personal series of 175 patients investigated for hyperinsulinaemic hypoglycaemia over the last 20 years, we review clinical presentations, molecular studies and therapeutic management of hyperinsulinism. There were 98 neonatal-onset patients, including 86 permanent hyperinsulinism and 12 transient forms, 68 with infancy-onset and nine with childhood-onset. Hyperammonaemia was found in 12 out of 69 patients tested, 4 neonates and 8 infants. Neonates were clinically more severely affected than infants. Diagnosis of infancy-onset hyperinsulinism was often delayed because of less profound hypoglycaemia and better tolerance to hypoglycaemia. Neonates required higher rates of iv glucose than infants to maintain normal plasma glucose levels (16 mg/kg per min versus 12 mg/kg per min). Only 16% of neonates were diazoxide-sensitive compared to 66% of the infants. Neonates with hyperammonaemia or transient hyperinsulinism were diazoxide-sensitive. Most neonates were pancreatectomised whereas 65% of the infants were treated medically. Among surgically-treated patients, 47% had a focal adenomatous hyperplasia (31 neonates and 13 infants) and 53% a diffuse form of hyperinsulinism (39 neonates and 11 infants). Diazoxide-responsiveness in the focal and diffuse forms did not differ in both neonates and infants; it depended only upon the age of onset of hypoglycaemia. One or two mutations, *SUR1* or *KIR6.2*, were found in 41 of 73 neonates who were investigated and in 13/38 infants using polymerase chain reaction-single strand conformational polymorphism analysis of both genes. Almost all patients with *SUR1* (38/41) or *KIR6.2* (5/7) mutations were resistant to diazoxide. Ten patients with hyperinsulinism-hyperammonaemia syndrome had a mutation in the glutamate dehydrogenase gene (three neonates and seven infants) after reverse transcriptase-polymerase chain reaction and sequence analysis of cDNA. No mutation was found by polymerase chain reaction-single strand conformational polymorphism in

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the glucokinase gene. Eight of nine patients with childhood onset hyperinsulinism were treated surgically and histological examination confirmed an adenoma in each case. *Conclusion:* the clinical severity of hyperinsulinism varies mainly with age at onset of hypoglycaemia. The heterogeneity of hyperinsulinism has major consequences in terms of therapeutic outcome and genetic counselling.

Keywords Focal adenomatous hyperplasia · Hyperammonaemia · Hyperinsulinism · Persistant hyperinsulinaemic hypoglycaemia of infancy · *SUR1*/*KIR6.2* genes

Introduction

Hyperinsulinism is the most common cause of recurrent hypoglycaemia in early infancy [11,17]. The inappropriate oversecretion of insulin is responsible for profound hypoglycaemia which requires aggressive treatment to prevent irreversible brain damage [1, 15, 16, 17, 19, 23,24]. Two histopathological lesions, focal or diffuse, are responsible for hyperinsulinism, and they are related to genetic heterogeneity [13,14]. The focal lesion is characterised by a focal adenomatous hyperplasia associated with the loss of the maternal allele from chromosome 11p15 and a somatic reduction to homozygosity of a paternally inherited mutation in either of the genes encoding the two subunits of the K^+_{ATP} channel, the sulphonylurea receptor type 1 (*SUR1,* MIM 600509) or the inward-rectifying potassium channel (*KIR6.2,* MIM 600937) [3,25]. The diffuse lesions are manifested as β-cell hyperfunction in the whole pancreas and involve the *SUR1* [9, 10, 11, 20,22] or the *KIR6.2* [12,21] genes in recessively or more rarely dominantly inherited hyperinsulinism [9], the glucokinase gene (*GK,* MIM 138079) [8] or other loci [10] in dominantly inherited hyperinsulinism, and the glutamate dehydrogenase gene (*GLUD1,* MIM 13830) in cases in which hyperammonaemia is associated with hyperinsulinism [18, 26,27].

Focal and diffuse forms of hyperinsulinaemic hypoglycaemia (MIM 601820) can occur in both neonatal-onset (hypoglycaemia within the first 3 days of life) and infancy-onset patients, while childhood-onset hypoglycaemia (after the 1st year of life) is usually due to adenomas. The therapeutic outcome in patients depends on distinguishing between these entities because the therapeutic approach and genetic counselling differ radically. Focal lesions are effectively treated by limited pancreatic resection [2] while diffuse lesions which are unresponsive to drug or dietary treatment require extensive pancreatectomy with a high risk of diabetes mellitus [15, 16, 19,23].

We review here the clinical presentation and molecular studies of hyperinsulinism based upon our personal experience of 175 patients over the past 20 years.

Patients and methods

Between 1975 and 1999, a total of 175 patients have been investigated for hyperinsulinism at the Necker-Enfants Malades Hospital. Of these, 133 patients were referred from French paediatric units and 42 from six European countries. These patients were born to 171 unrelated families. There were 98 neonates (Table1), 68 infants (Table 2) and nine children (Table 3).

The diagnostic criteria were fasting and post-prandial hypoglycaemia (Table 4) with hyperinsulinaemia (plasma insulin concentrations >10 mU/l), high rates of intravenous glucose (>10 mg/kg per min) required to maintain the blood glucose above 3 mmol/l, and a positive response to the subcutaneous or intramuscular administration of glucagon (plasma glucose concentration increase by 2 to 3 mmol/l following 0.5 mg glucagon).

The patients were initially treated in local paediatric units and were referred to our hospital for investigation of hyperinsulinism. Although our approach to the disease has changed with time, including the more recent developments, our general protocol was as follows: blood glucose was maintained at 3–6 mmol/l with appropriate methods including continuous drip feeding, intravenous administration of glucose at high rates (>10 mg/kg per min), mostly through a central line catheter, and continuous intravenous administration of glucagon (1–2 mg/day). Hyperammonaemia was checked (retrospectively performed for the last 2 years) and for familial cases of hypoglycaemia or parental consanguinity. Diazoxide treatment (Tables1, 2, 3 and 4) was tested in all the patients at 15 mg/kg per day divided into three doses. The criterion of efficacy was the normalisation of blood glucose (>3 mmol/l) for at least 5 consecutive days, before and after each meal in normally fed patients, after iv glucose and any other medications had been stopped [24]. Octreotide (a long-lasting analogue of somatostatin) has been systematically tried since 1998, at 5–60 μg/kg per day, divided into three subcutaneous injections [7]. A leucine-restricted diet was tested in specific patients consisting of 200 mg/kg leucine per meal. Transient forms (<1 month) of neonatal-onset hyperinsulinism were ruled out (Tables1 and 5). Transhepatic selective pancreatic venous catheterisation (Tables1, 2 and 3) was performed, under general anaesthesia, to locate the insulin hypersecretion [5]. Samples of venous blood were collected from all regions of the pancreas for measurements of plasma glucose, insulin and C-peptide. Typically in focal hyperinsulinism, plasma insulin and C-peptide concentrations were high in one or several samples from contiguous areas, with low concentrations in the remaining samples. In diffuse hyperinsulinism, plasma insulin and C-peptide levels were high in all samples. Pancreatic catheterisation was not performed before the age of 1 month to exclude patients with transient forms, or in patients with hyperammonaemia who were likely to have diffuse hyperinsulinism [27]. Patients who were thought to have focal hyperinsulinism and those who resisted or could not tolerate medical treatment [2] underwent surgery (Tables1, 2, 3 and 5). Intraoperative histological examination was mandatory for the final surgical decision. Focal hyperinsulinism was treated by limited pancreatectomy. Diffuse hyperinsulinism required near-total pancreatectomy; all resected pieces of pancreas were investigated extensively by conventional microscopic and histomorphometric studies (Tables1, 2 and 3) [13,14].

Pancreatic DNA was analysed for loss of maternal alleles from the 11p15 region [3,25]. We searched for mutations in the *SUR1*, *KIR6.2*, glucokinase (*GK*) or glutamate dehydrogenase (*GLUD1*) genes in leucocytes of the patients and their parents [8, 18, 20,21]. Molecular analysis used polymerase chain reaction-single strand conformational polymorphism to study all *SUR1*, *KIR6.2* [6] and *GK* exons whereas *GLUD1* gene was investigated by reverse transcriptase-polymerase chain reaction and sequence analysis of cDNA. *SUR1* mutations were searched for in 115 patients and *KIR6.2* mutations in 92 patients (Tables1, 2, 3 and 6). Glucokinase was studied in a limited number of diazoxide-sensitive patients (Table6) and glutamate dehydrogenase in patients with hyperammonaemia only (Table6).

Table 1 Characteristics of patients ($n=98$) with neonatal-onset hypoglycaemia in the first 3 days of life. Familial pertains to affected sib and pancreatic catheterisation revealed diffuse or localised hyperinsulinism. (*Consang* consanguinity, *NBF* no mutation found in NBF1 and NBF2 regions only, *ND* not determined, *NI* not interpretable, *NO* not operated, *Resist* resistant, *Sens* sensitive, + heterozygous mutation, + + homozygous or compound heterozygous mutation)

Patient number	Sex	Origin	Family	Year of birth	Weight (g)	Diazoxide	Glucose (mg/kg per min)	Catheterisation	Age at surgery (years)	Pancreatectomy	Histology	*SUR1*	*KIR6.2*	Hyperamonaemia	References[a]
Diffuse															
1	M	France	Familial	1982	3774	Resist	18	Diffuse	0.2	Subtotal	Diffuse	+ +	Normal	Normal	
3	F	France	Sporadic	1984	5150	Resist	16	Diffuse	13	Subtotal	Diffuse	Normal	Normal	Normal	
4	F	Africa	Sporadic	1984	4040	Resist	10	ND	0.22	Subtotal	Diffuse	ND	ND	ND	[2,24]
5	M	France	Sporadic	1985	3640	Resist	16	Diffuse	0.46	Subtotal	Diffuse	Normal	Normal	Normal	[2,24]
6	M	Italy	Sporadic	1986	4900	Resist	21	NI	0.16	Subtotal	Diffuse	+	Normal	ND	[24]
7	F	Italy	Familial	1986	3700	Resist	18	Diffuse	10/5	Subtotal	Diffuse	ND	ND	ND	
8	M	France	Sporadic	1986	4160	Resist	17	NI	0.21	Subtotal	Diffuse	Normal	Normal	Normal	[2,24]
9	M	France	Sporadic	1987	3270	Resist	21	Diffuse	0.17	Subtotal	Diffuse	+ +	Normal	ND	[2,24]
10	F	Algeria	Sporadic	1988	3900	Resist	24	Diffuse	0.45	Subtotal	Diffuse	+ +	Normal	ND	[2, 14,24]
11	F	Africa	Sporadic	1989	2700	Resist	14	Focal	0.35	Subtotal	Diffuse	Normal	Normal	ND	[2, 14,24]
12	F	Italy	Sporadic	1990	3350	Resist	16	Diffuse	1.08	Subtotal	Diffuse	+	Normal	ND	[2, 14,24]
13	F	France	Sporadic	1990	2680	Resist	16	Diffuse	0.08	Subtotal	Diffuse	Normal	+	ND	[2,24]
14	F	France	Sporadic	1990	4110	Resist	17	NI	1.05	Subtotal	Diffuse	Normal	Normal	Normal	[2, 14,24]
15	M	Turkey	Consang	1992	4280	Resist	20	Diffuse	0.13	Subtotal	Diffuse	Normal	+	ND	[2, 14,24]
16	F	France	Sporadic	1993	3840	Resist	17	Diffuse	0.26	Subtotal	Diffuse	ND	ND	ND	[2,14]
17	F	France	Sporadic	1993	3220	Resist	18	Diffuse	0.48	Subtotal	Diffuse	+	Normal	ND	[2,14]
18	F	Italy	Sporadic	1993	3500	Resist	18	Focal	0.47	Subtotal	Diffuse	+	Normal	ND	[2,14]
19	F	France	Sporadic	1994	3900	Resist	24	Diffuse	0.27	Subtotal	Diffuse	ND	ND	ND	[2]
20	M	France	Sporadic	1994	3330	Resist	18	ND	0.11	Subtotal	Diffuse	Normal	Normal	ND	[2,14]
21	F	France	Sporadic	1995	2460	Resist	12	Diffuse	0.3	Subtotal	Diffuse	+	Normal	ND	[2,14]
22	M	France	Sporadic	1995	5620	Resist	13	Diffuse	0.25	Subtotal	Diffuse	Normal	Normal	Normal	[14]
23	F	Algeria	Consang	1995	3880	Resist	20	NI	0.34	Subtotal	Diffuse	Normal	Normal	ND	[2,14]
24	F	Israel	Familial	1996	3880	Resist	19	Diffuse	0.28	Subtotal	Diffuse	+ +	Normal	Normal	[2]
25	F	France	Familial	1996	4620	Resist	19	Diffuse	0.13	Subtotal	Diffuse	+ +	Normal	Normal	[2]
26	M	Antilles	Sporadic	1996	3820	Resist	13	Diffuse	0.23	Subtotal	Diffuse	Normal	Normal	Normal	[2]
27	F	Belgium	Sporadic	1996	3140	Resist	8	ND	0.32	Subtotal	Diffuse	+	Normal	ND	[2]
28	F	Algeria	Sporadic	1996	2440	Resist	17	Diffuse	0.31	Subtotal	Diffuse	+	Normal	ND	[2]
29	F	Italy	Sporadic	1996	3560	Resist	16	Diffuse	0.7	Subtotal	Diffuse	+	Normal	Normal	[2]
2	M	France	Sporadic	1997	5150	Resist	16	Diffuse	1.24	Subtotal	Diffuse	+!	ND	Normal	[2]
30	M	France	Sporadic	1997	3700	Resist	17.4	NI	0.25	Subtotal	Diffuse	NBF	ND	Normal	[2]
31	F	Israel	Familial	1997	4240	Resist	13	ND	0.13	Subtotal	Diffuse	+ +	Normal	Normal	[2]
32	M	France	Sporadic	1997	3800	Resist	20	Focal	0.78	Subtotal	Diffuse	+	Normal	Normal	[14,24]
33	F	Norway	Familial	1997	4860	Resist	16	Diffuse	0.22	Subtotal	Diffuse	+	Normal	ND	[2]
34	F	France	Sporadic	1998	4450	Resist	18	Diffuse	0.15	Subtotal	Diffuse	NBF	ND	Normal	[2]
35	F	Turkey	Familial	1998	4350	Resist	22	Diffuse	0.32	Subtotal	Diffuse	NBF	ND	Normal	
36	F	Antilles	Sporadic	1998	3900	Resist	20	ND	0.41	Subtotal	Diffuse	ND	ND	Normal	
37	M	France	Sporadic	1998	4200	Resist	20	Diffuse	0.15	Subtotal	Diffuse	+[b]	ND	Normal	
38	M	Belgium	Familial	1991	2960	Resist	13	Focal	0.3	Partial	Diffuse	Normal	Normal	ND	[2, 14,24]
39	F	Switz	Sporadic	1994	3700	Resist	12	ND	3.56	Partial	Diffuse	+ +	ND	Normal	[2]
Focal															
40	F	France	Sporadic	1979	3600	ND	16	Focal	0.28	Partial	Isthmus	ND	ND	ND	[24]
41	M	Italy	Sporadic	1989	4200	Resist	18	ND	0.16	Partial	Tail	NBF	Normal	ND	
42	F	Italy	Sporadic	1990	3370	Resist	12.5	Diffuse	0.2	Partial	Tail	+	ND	Normal	[2, 6, 14,24]
43	F	France	Sporadic	1990	4370	Resist	16	Focal	0.1	Partial	Tail	+	ND	Normal	[2, 6, 14,24]

Table 1 (Continued)

Patient number	Sex	Origin	Family	Year of birth	Weight (g)	Diazoxide	Glucose (mg/kg per min)	Catheteri-sation	Age at surgery (years)	Pancrea-tectomy	Histology	*SUR1*	*KIR6.2*	Hyperam-monaemia	References[a]
44	M	France	Sporadic	1990	2250	Resist	17	Focal	0.16	Partial	Head	ND	ND	ND	[2, 14, 24]
45	F	France	Sporadic	1991	4760	Resist	16	Focal	1.6	Partial	Corpus	+	ND	Normal	[2, 3, 6, 25]
46	F	Italy	Sporadic	1992	3380	Resist	15	Focal	0.18	Partial	Tail	ND	ND	ND	[2, 14,24]
47	M	Italy	Sporadic	1993	3450	Resist	16	Focal	0.27	Partial	Head	+	ND	ND	[2, 6, 14]
48	F	France	Sporadic	1994	4110	Resist	15	Focal	0.32	Partial	Tail	+	ND	Normal	[2, 3, 6, 25]
49	F	France	Sporadic	1994	4420	Resist	18	Focal	0.25	Partial	Head	Normal	Normal	Normal	[2, 3, 6, 14, 25]
50	F	France	Sporadic	1994	3140	Resist	22	ND	0.39	Partial	Corpus	Normal	ND	Normal	[2, 3, 6, 14, 25]
51	M	Belgium	Sporadic	1994	4250	Resist	26	Focal	0.12	Partial	Isthmus	+	ND	Normal	[2, 3, 6, 14, 25]
52	M	Greece	Sporadic	1995	3990	Resist	12	Focal	0.27	Partial	Head	+	ND	Normal	[2,6]
53	F	Italy	Sporadic	1995	2700	Resist	15	Focal	0.65	Partial	Corpus	+	ND	Normal	[2,6]
54	F	Greece	Sporadic	1995	3500	Resist	15	Focal	0.38	Partial	Head	Normal	ND	Yes	[2, 3, 6, 14, 25]
55	M	France	Sporadic	1995	2400	Resist	18	NI	0.2	Partial	Corpus	Normal	Normal	Normal	[3,25]
56	F	France	Sporadic	1995	3220	Resist	16	Focal	0.1	Partial	Corpus	Normal	ND	Normal	[2, 3, 6, 25]
57	M	France	Sporadic	1995	3130	Resist	19	Focal	0.23	Partial	Isthmus	+	ND	Normal	[2, 3, 6, 14, 25]
58	M	Italy	Sporadic	1996	3450	Resist	21	Focal	0.18	Partial	Tail	Normal	ND	Normal	[2, 3, 6, 25]
59	M	Norway	Sporadic	1996	4340	Resist	15	Focal	0.19	Partial	Head	+	ND	Normal	[2, 6, 25]
60	F	Italy	Sporadic	1997	2970	Resist	13	NI	0.25	Partial	Tail	Normal	ND	Normal	[2, 6]
61	F	Norway	Sporadic	1997	4540	Resist	10	Focal	0.64	Partial	Corpus	Normal	ND	Normal	[2, 6]
62	F	Belgium	Sporadic	1998	4400	Resist	20	Focal	0.12	Partial	Head	+	Normal	Normal	[6]
63	M	Belgium	Sporadic	1998	3770	Resist	16	ND	0.16	Partial	Head	+	Normal	ND	
64	M	Italy	Sporadic	1999	3770	Resist	12	NI	0.32	Partial	Isthmus	NBF	Normal	ND	[6]
65	M	France	Sporadic	1979	3160	Sens	15	Focal	1.31	Subtotal	Head	Normal	ND	Normal	[24]
66	F	France	Sporadic	1985	3460	Resist	17	ND	0.07	Subtotal	Corpus	Normal	ND	Normal	[2, 24]
67	F	France	Sporadic	1986	4350	Resist	16	ND	0.24	Subtotal	Head	+	ND	Normal	[2, 6, 24]
68	F	Italy	Sporadic	1989	2900	Resist	14	NI	0.45	Subtotal	Head	ND	ND	ND	[14,24]
69	F	France	Sporadic	1993	4450	Sens	12	ND	2.29	Subtotal	Head	Normal	Normal	Yes	[2, 6]
70	F	Italy	Sporadic	1994	3900	Resist	9	Focal	1.6	Subtotal	Tail	NBF	ND	ND	[14]
Hyperammonaemia															
71	F	Italy	Sporadic	1986	4000	Sens	6.5	Diffuse				ND	ND	Yes	
72	F	Italy	Sporadic	1993	3100	Sens	13	NI				ND	ND	Yes	
73	M	France	Familial	1994	3900	Sens	11	NI				ND	ND	Yes	
74	M	Belgium	Sporadic	1997	2700	Sens	12	ND				ND	ND	Yes	
No surgery															
75	M	France	Sporadic	1983	2380	Sens	11	Diffuse				NBF	ND	ND	[24]
76	F	France	Sporadic	1987	3100	Resist	10	Diffuse				ND	ND	Normal	[24]
77	M	France	Sporadic	1991	3700	Sens	14	ND				NBF	ND	Normal	
78	M	France	Sporadic	1992	3450	Sens	17	Diffuse				Normal	Normal	Normal	
79	M	France	Sporadic	1993	3500	nd	12	ND				Normal	Normal	ND	
80	M	France	Familial	1994	2340	nd	18	ND				+	Normal	Normal	
81	M	France	Sporadic	1994	4510	Resist	7	ND				+	Normal =	Normal	
82	F	Tunisia	Sporadic	1994	2500	Sens	15	ND				ND	ND	ND	
83	M	Italy	Sporadic	1995	3950	Resist	10	NI				Normal	Normal	ND	
84	M	Israel	Familial	1995	3650	Resist	17	Diffuse				+ +	Normal	ND	
85	M	France	Sporadic	1996	3900	Resist	6	NI				+	Normal	Normal	
86	F	Réunion	Sporadic	1996	3000	Sens	9	NI				NBF	ND	Normal	

Transient											
87	M	France	Sporadic	1990	3010	ND	17	ND	ND	ND	ND
88	F	France	Sporadic	1992	2180	ND	16	ND	+	Normal	ND
89	F	France	Sporadic	1994	4630	Sens	13	ND	ND	ND	ND
90	M	France	Sporadic	1994	4800	ND	20	ND	ND	ND	ND
91	M	Italy	Sporadic	1995	3390	ND	20	ND	ND	ND	ND
92	M	France	Sporadic	1997	4720	ND	11	ND	ND	ND	ND
93	M	France	Sporadic	1997	3470	ND	15	ND	ND	ND	ND
94	M	France	Sporadic	1998	3920	ND	8	ND	ND	ND	Normal
95	F	Italy	Sporadic	1998	3580	Sens	9	ND	NBF	ND	Normal
96	F	Turkey	Sporadic	1998	2300	Sens	13	ND	ND	ND	Normal
97	M	France	Sporadic	1998	3000	ND	14	ND	ND	ND	Normal
98	F	France	Sporadic	1998	3400	ND	16	ND	ND	ND	Normal

[a]The numbers of referenced patients is slightly lower than those reported in [6] and [24] because patients from other centres were included in these studies
[b]One *SUR1* mutation found, but NBF1 and NBF2 regions only were studied

Results

Clinical features and molecular bases

Neonatal-onset hyperinsulinaemic hypoglycaemia

A total of 12 patients with neonatal hyperinsulinism recovered completely within the 1st month of life. These transient forms of hyperinsulinism were not due to gestational diabetes. Eight of these patients did not require any treatment, while the other four were sensitive to diazoxide.

Neonatal-onset hyperinsulinism persisted after the 1st month of age in the other 86 patients. Many of them were macrosomal at birth and 30% required caesarian section. Almost 50% of the neonates had seizures as the revealing symptom of hypoglycaemia (Table1). Other symptoms were hypotonia, cyanosis, hypothermia or abnormal movements such as tremor. Hypoglycaemia was detected by routine assay of blood glucose in 11 cases. The plasma glucose concentration at time of the first symptoms was often extremely low (Table1). High rates of continuous oral and intravenous glucose were required in all the patients to keep plasma glucose concentration at 3–6 mmol/l (Table1). Some 14 neonates were diazoxide-sensitive and were treated medically. Hyperammonaemia was retrospectively found in four of them. The other neonates, the majority of them, did not respond to diazoxide treatment (Table1). They were also resistant to octreotide when this treatment was tried ($n=12$). Consequently, 70 underwent pancreatic surgery (Table4). Among the neonates who were treated surgically, 31 had a focal adenomatous hyperplasia and 39 had diffuse hyperinsulinism (Table4). Focal and diffuse forms did not differ in revealing symptoms, rates of continuous glucose administration or diazoxide-response. The focal lesions were located in the head ($n=12$), isthmus ($n=4$), body ($n=6$) and tail of the pancreas ($n=8$). One last patient had an unusual bifocal lesion located in the pancreatic head and body. The clinical outcome of the first 52 patients with neonatal hyperinsulinism has been previously reported. The difference between the post-surgical outcome of focal and diffuse hyperinsulinism in 18 additional patients is identical [2].

As shown in Table5, there were neither familial cases nor consanguinity for patients with focal hyperinsulinism. Each focal lesion was linked to a maternal loss of an 11p15 allele. Mutations in *SUR1* and *KIR6.2* genes were found in both focal and diffuse hyperinsulinism (Tables5 and 6). Inherited mutations were of both parental origin in the diffuse cases but always of paternal origin for patients with a focal lesion. Only one neonate with a detected inherited *KIR6.2* mutation was diazoxide-sensitive [6]. All neonates with *SUR1* and *KIR6.2* mutations were diazoxide-resistant. Three neonates with hyperam-

Table 2 Characteristics of patients ($n = 68$) with infancy-onset hypoglycaemia within the 1st year of life. (*CDG* congenital disorder of glycosylation, *Consang* consanguinity, *NBF* no mutation found in NBF1 and NBF2 regions only, *ND* not determined, *NI* not interpretable, *NO* not operated, *Resist* resistant, *Sens* sensitive, + heterozygous mutation, ++ homozygous or compound heterozygous mutation)

Patient number	Sex	Origin	Family	Year of birth	Weight (g)	Age of onset (months)	Diazoxide	Glucose (mg/kg per min)	Catheterisation	Age at surgery (years)	Pancreatectomy	Histology	*SUR1*	*KIR6.2*	Hyperammonaemia	References[a]
Diffuse																
99	M	France	Sporadic	1988	3320	3	Resist	8.5	Diffuse	0.47	Subtotal	Diffuse	Normal	Normal	ND	[24]
100	F	France	Sporadic	1993	3600	3	Resist	15	Diffuse	1.32	Subtotal	Diffuse	Normal	Normal	ND	
101	F	France	Sporadic	1994	4470	6	Resist	13	Diffuse	0.73	Subtotal	Diffuse	Normal	+	ND	[14]
102	M	Tunisia	Consang	1995	5000	1	Resist	13	Focal	0.64	Subtotal	Diffuse	++	Normal	ND	
103	F	France	Sporadic	1984	2950	3	Sens	12	Focal	6.49	Partial	Diffuse	Normal	Normal	ND	[24]
104	F	Italy	Familial	1987	2850	4	Sens	13	Diffuse	0.79	Partial	Diffuse	Normal	Normal	ND	[14,24]
105	M	France	Sporadic	1987	4350	9	Sens	11	ni	4.27	Partial	Diffuse	ND	ND	Normal	[24]
106	F	France	Sporadic	1988	3820	6	Sens	11	Focal	2.52	Partial	Diffuse	Normal	Normal	Normal	[24]
107	F	Italy	Sporadic	1991	2440	3	Resist	12	Focal	1.15	Partial	Diffuse	ND	ND	ND	[24]
108	F	France	Sporadic	1998	3800	5	ND	14	Focal	0.52	Partial	Diffuse	NBF	ND	Normal	
Focal																
109	F	France	Sporadic	1977	2900	7	Sens	12	Focal	13.5	Partial	Head	ND	ND	ND	[24]
110	F	France	Sporadic	1985	3750	3	Resist	16	Focal	0.38	Partial	Tail	+	Normal	ND	[6, 24]
111	F	France	Sporadic	1987	3280	4	Sens	13	Focal	2.02	Partial	Head	+	Normal	ND	[6,24]
112	F	France	Sporadic	1987	2850	3	Resist	11	Focal	0.41	Partial	Head	ND	ND	ND	[24]
113	F	France	Sporadic	1988	3150	1.5	Sens	12.5	Focal	0.51	Partial	Head	+	Normal	ND	[6,24]
114	F	Italy	Sporadic	1989	3600	6	Sens	10	Focal	1.47	Partial	Head	ND	ND	ND	[24]
115	F	France	Sporadic	1990	3935	3	Resist	14	NI	0.38	Partial	Corpus	ND	ND	ND	[14,24]
116	F	France	Sporadic	1991	3670	3.5	Sens	12	Focal	1.3	Partial	Corpus	Normal	Normal	Normal	[6,24]
117	F	France	Sporadic	1995	4700	2.5	Resist	15	Focal	0.44	Partial	Tail	+	Normal	Normal	[6,25]
118	F	France	Sporadic	1997	3810	3	Resist	11	NI	0.33	Partial	Tail	Normal	Normal	Normal	[6]
119	M	France	Sporadic	1998	4000	3.5	Resist	17	Focal	0.76	Partial	Tail	NBF	ND	Normal	
120	F	France	Sporadic	1983	3900	4	Resist	11	NI	0.72	Subtotal	Head	ND	ND	ND	[24]
121	M	France	Sporadic	1987	4500	2	Resist	12.5	Focal	0.28	Subtotal	Corpus	Normal	+	Normal	[6,24]
Hyperammonaemia																
122	M	France	Sporadic	1986	3900	8	Sens	11	ND	NO			ND	ND	Yes	
123	F	Italy	Sporadic	1992	3200	5	Sens	12	Diffuse	NO			ND	ND	Yes	[24]
124	M	France	Sporadic	1994	3800	3	Sens	14	ND	NO			ND	ND	Yes	
125	F	Italy	Sporadic	1995	2800	5	Sens	12	Diffuse	NO			ND	ND	Yes	
126	M	France	Sporadic	1996	2500	1.5	Sens	12	ND	NO			ND	ND	Yes	
127	F	France	Familial	1996	2800	11	Resist	9	Diffuse	1.05	Partial	Diffuse	ND	ND	Yes	
128	M	Tunisia	Familial	1997	3100	3	Sens	11	ND	NO			ND	ND	Yes	
129	F	Belgium	Sporadic	1997	2500	2.5	Sens	15	ND	NO			ND	ND	Yes	
No surgery																
130	M	France	Sporadic	1978	3410	5.5	Sens	12	NI	NO			Normal	Normal	Normal	[24]
131	F	France	Sporadic	1982	4080	8	Sens	12	Focal	NO			Normal	Normal	ND	[24]
132	M	Vietnam	Familial	1982	2800	9	Sens	ND	ND	NO			NBF	ND	Normal	[24]
133	M	France	Familial	1985	2500	12	Sens	ND	Diffuse	NO			ND	ND	Normal	[24]
134	F	France	Sporadic	1988	3230	10	Sens	ND	Focal	NO			ND	ND	ND	[24]
135	M	France	Familial	1989	3600	6	Resist	ND	ND	NO			+	Normal	ND	
136	F	Portugal	Sporadic	1989	2890	7	Sens	12	ND	NO			ND	ND	ND	[24]
137	M	Italy	Sporadic	1989	3270	9	Resist	10	Diffuse	NO			+	Normal	ND	[24]
138	M	Tunisia	Familial	1989	3888	4	Sens	ND	Diffuse	NO			Normal	Normal	ND	[24]
139	F	France	Familial	1990	3170	12	ND	ND	ND	NO			Normal	Normal	ND	[24]

140	M	Italy	Sporadic	1992	3500	10	Sens	10	Diffuse	NO			ND	ND	ND	
141	M	Lebanon	Sporadic	1992	3800	12	Resist	ND	Diffuse	NO			Normal	Normal	ND	
142	M	France	Sporadic	1992	3300	3	Sens	ND	NI	NO			Normal	+	ND	[24]
143	F	France	Familial	1992	2460	3	Resist	ND	ND	NO			+	Normal	ND	
144	F	France	Familial	1992	2410	4	Resist	ND	ND	NO			+	Normal	ND	
145	F	Italy	Sporadic	1993	3300	5.5	Sens	10	ND	NO			+	Normal	ND	
146	M	Italy	Consang	1993	3800	5	Sens	9.3	Diffuse	NO			ND	ND	ND	
147	M	Belgium	Sporadic	1994	4300	4	Sens	ND	ND	NO			ND	ND	ND	
148	F	France	Sporadic	1994	2850	6.5	Sens	11	ND	NO			Normal	Normal	ND	
149	F	Germany	Sporadic	1994	2900	4	Sens	18	Diffuse	NO			NBF	ND	Normal	
150	M	France	Sporadic	1994	3410	6	Sens	12	ND	NO			NBF	ND	Normal	
151	F	France	Sporadic	1995	3880	8	Sens	9	NI	NO			Normal	Normal	Normal	
152	M	France	Sporadic	1995	2860	4.5	Resist	ND	NI	NO			ND	ND	ND	
153	M	France	Sporadic	1995	2130	7	Sens	14	NI	NO			NBF	ND	ND	
154	F	France	Sporadic	1995	4200	7	Sens	11	ND	NO			ND	ND	ND	
155	M	Tunisia	Sporadic	1996	2460	10	Sens	12	ND	NO			ND	ND	Normal	
156	M	France	Sporadic	1996	3290	2.5	Sens	9	ND	NO			Normal	Normal	Normal	
157	M	France	Sporadic	1996	3281	2	Sens	19	Focal	NO			Normal	Normal	ND	
158	F	Algeria	Familial	1996	3720	2.5	ND	6	ND	NO			Normal	Normal	ND	
159	F	France	Sporadic	1996	3370	1.5	Sens	12	ND	NO			ND	ND	ND	
160	M	France	Sporadic	1997	3400	24	Sens	ND	ND	NO			NBF	ND	Normal	
161	M	Italy	Sporadic	1997	3500	5	Sens	13	Diffuse	NO			ND	ND	ND	
162	M	France	Sporadic	1998	3000	6	Sens	ND	Focal	NO			ND	ND	ND	[24]
163	F	France	Sporadic	1998	3520	4	Sens	7	ND	NO			NBF	ND	Normal	
Munchausen																
164	F	France	Sporadic	1991	3300	1	ND	ND	ND	NO			ND	ND	ND	
165	F	Italy	Sporadic	1995	3250	6	Resist	12.7	ND	2.5	Partial	Normal	ND	ND	ND	
CDG																
166	F	France	Sporadic	1997	3300	2.5	ND	12	ND	NO			ND	ND	ND	[4]

[a]The numbers of referenced patients is slightly lower than those reported in [6] and [24] because patients from other centres were included in these studies

Table 3 Characteristics of patients ($n = 9$) with childhood-onset hypoglycaemia after the 1st year of life. (*ND* not determined, *Resist* resistant, *Sens* sensitive)

Patient number	Sex	Origin	Family	Year of birth	Weight (g)	Age of onset (years)	Diazoxide	Glucose (mg/kg per min)	Catheterisation	Age at surgery (years)	Pancreatectomy	Histology	Hyperammonaemia	Reference
167	F	Greece	Sporadic	1975	3700	14	ND	ND	ND	16	Partial	Adenoma	ND	[24]
168	F	France	Sporadic	1977	3900	11	Sens	ND	Focal	12.2	Partial	Adenoma	ND	[24]
169	M	France	Sporadic	1985	3080	5	Sens	ND	ND	6	Partial	Adenoma	ND	[24]
170	M	Spain	Sporadic	1985	2800	8	Sens	ND	Focal	8.3	Partial	Adenoma	Normal	
171	M	Greece	Sporadic	1986	3600	4	ND	ND	Diffuse	5	Partial	Adenoma	ND	
172	M	France	Sporadic	1988	3350	5	Sens	ND	ND	6.3	Partial	Adenoma	ND	[24]
173	M	Guyana	Sporadic	1990	4320	2	ND	ND	ND	NO			ND	
174	M	France	Familial	1991	4120	6	ND	4	ND	6	Partial	Adenoma	Normal	
175	F	Algeria	Sporadic	1997	3600	15	Resist	ND	Diffuse	15	Partial	Adenoma	ND	

monaemia had a mutation in the glutamate dehydrogenase gene.

Infancy-onset hyperinsulinaemic hypoglycaemia

Among the 68 patients with infancy-onset hyperinsulinism, 2 were considered to have a Munchausen-by-proxy syndrome and 1 had a congenital disorder of glycosylation [4]. The patients with isolated hyperinsulinism were often macrosomal at birth. More than 50% had seizures as the first symptom of hypoglycaemia; the other symptoms were hypotonia and loss of consciousness. Hypoglycaemia was detected fortuitously in only two cases, but parents remembered that episodes of paleness or hypotonia had occurred before the diagnosis was made. Most infants had good clinical tolerance of hypoglycaemia during hospitalisation, suggesting that diagnosis could have been delayed in many cases. Rates of glucose administration to maintain normal plasma glucose were lower in infancy-onset than in neonatal-onset hypoglycaemic patients (Table2) and only 78% of them required continuous drip feeding. The majority of patients were diazoxide-sensitive, so that 41 were treated medically and only 24 required surgery. Among the operated patients, 13 had a focal adenomatous hyperplasia (6 in the head, 3 in the body, 4 in the tail of the pancreas) and 11 had a diffuse hyperinsulinism (Table 4). There was no difference in the rates of continuous glucose administration between the unoperated patients, the patients with focal lesion and those with diffuse hyperinsulinism.

Eight infants had associated hyperammonaemia (Table4). Four of these patients were sensitive to a leucine-restricted diet. Three patients were resistant to dietetic treatment but were treated with diazoxide. The last patient (patient 6) underwent surgery before the diagnosis of hyperammonaemia was known, because of diazoxide-unresponsiveness. However the dietetic treatment had not been tried before surgery, but it was effective on post-operative residual hypoglycaemia. The histological study of this patient revealed a diffuse form.

SUR1 or *KIR6.2* mutations were found in 13 infancy-onset patients, with 5 focal, 6 non operated and only 2 diffuse hyperinsulinism (Table5). Seven patients with hyperammonaemia had a mutation in the glutamate dehydrogenase gene. No mutation was found in the glucokinase gene in 15 diazoxide-sensitive infants.

Children

Nine children were investigated for hyperinsulinaemic hypoglycaemia occurring between 3 and 6 years of age. The patients were macrosomal at birth (Table3). Of these patients, 50% had seizures as the revealing

Table 4 Summary of clinical characteristics of 175 patients with hyperinsulinaemic hypoglycaemia

Parameter	Neonatal-onset ($n=98$)	Infancy-onset ($n=68$)	Childhood-onset ($n=9$)
Boys/girls	44/54	29/39	6/3
Birth weight (kg)	3.65 ± 0.7	3.4 ± 0.6	3.6 ± 0.6
Seizures as first symptom (% of patients)	41	64	55
Initial plasma glucose (mmol/l; mean ± 1 SD and range)[a]	0.98 ± 0.5 (0–1.6)	1.88 ± 0.8 (0.5–2.3)	2.0 ± 0.7 (0.9–2.5
Plasma insulin (mU/l; mean ± 1 SD and range)[b]	21 ± 25 (3–115)	17 ± 12 (3–36)	16 ± 10 (5–39)
Glucose infusion rate (mg/kg per.min; mean ± 1 SD and range)	16.0 ± 4 (6–24)	12.0 ± 3.0 (0–17)	–
Patients requiring glucose (%)	100	78	11
Diazoxide sensitivity (n/n tested)	14/86	42/63	4/5

[a]Initial plasma glucose: first plasma glucose measured at the time of hypoglycaemia
[b]Plasma insulin: value at the time of one episode of hypoglycaemia (value at the time of first hypoglycaemic episode often not available)

Table 5 Summary of types of hyperinsulinism in 175 patients with hyperinsulinaemic hypoglycaemia

Type of hyperinsulinism	Neonatal-onset ($n=98$)	Infancy-onset ($n=68$)	Childhood-onset ($n=9$)
Transient	12	–	–
Secondary[a]	0	3	0
No surgery	16	43	1
Surgically operated			
Focal adenomatous hyperplasia	31	13	0
Diffuse hyperinsulinism	39	10	0
Adenoma (insulinoma)	0	0	8
Hyperammonaemia (n/n tested)	4/42	8/26	0/2

[a]Secondary: two case of Munchausen and one congenital disorder of glycosylation

Table 6 Summary of genetic studies in patients with hyperinsulinaemic hypoglycaemia. More details concerning these mutations are given in [26]. (*DZX R* diazoxide resistant, *DZX S* diazoxide sensitive, *ND* not determined)

	Neonatal-onset ($n=98$)	Infancy-onset ($n=68$)	Childhood-onset ($n=9$)
Familial cases	11[a]	11[b]	1
Consanguinity	2[a]	2[b]	0
SUR1 mutation (n/n tested)	37/73 5 Non-operated (all DZX R) 13 Focal (all DZX R) 19 Diffuse (all DZX R)	10/38 5 Non operated (4 DZX R) 4 Focal (2 DZX R) 1 Diffuse (DZX R)	0/4
KIR6.2 mutation (n/n tested)	4/58 2 Focal (1 DZX R) 2 Diffuse (all DZX R)	3/30 1 Non-operated (DZX S) 1 Focal (DZX R) 1 Diffuse (DZX R)	0/4
GLUD1 mutation (n/n tested)	3/3	7/8	ND
GK mutation (n/n tested)	0/9	0/15	ND

[a]Familial cases in eight neonates with diffuse forms, two non-operated and one with hyperammonaemia. Consanguinity in two neonates with diffuse form
[b]Familial cases in one infant with diffuse form, eight non-operated and two with hyperammonaemia. Consanguinity in one infant with diffuse form and one non-operated

symptom of hypoglycaemia, but only one required low rates of continuous oral glucose. Four were initially treated with diazoxide before surgery and only one was diazoxide-resistant. Eight underwent a limited pancreatectomy and post-operative histology confirmed an adenoma or insulinoma in each case (Table4). The last patient was sensitive to diazoxide and did not undergo surgery.

One patient had familial hypoglycaemia due to a mutation in the *MEN1* gene and another had Recklinghausen syndrome. A loss of allele in the 11p15 to 11p13 region was found in one of two other pancreatic samples studied.

Discussion

Hyperinsulinism is a heterogeneous condition with important differences related to the age of onset of the symptoms, the histological form of insulin hypersecretion and the mutations. First, there is a clear difference between hyperinsulinaemic hypoglycaemia occurring within the first days of life (neonatal-onset), the 1st year of life (infancy-onset), and that starting later (childhood-onset). Neonatal-onset patients have more severe clinical features than infancy-onset patients. Treatment of hyperinsulinaemic neonates is difficult, requiring high rates of iv glucose. Glucose must be given via a central venous catheter and often needs to be associated with continuous intravenous infusion of glucagon. Medical treatments must be tried once the plasma glucose concentration is under control. However, most neonates do not respond to the currently known drugs and must undergo pancreatectomy [2]. The management of hyperinsulinaemic hypoglycaemia is easier in infancy-onset than in neonatal-onset patients, as the former are generally sensitive to medical treatment. Hyperinsulinaemic hypoglycaemia is a condition with several aetiologies and specific causes should be looked for in particular clinical situations.

A minority of patients with neonatal onset is responsive to diazoxide; most of them have a transient form of hyperinsulinism or they have the syndrome of hyperinsulinism associated with hyperammonaemia [18, 26,27]. Hyperammonaemia must be routinely searched for in both neonatal- and infancy-onset patients, whether or not they respond to diazoxide. It was found in 5% of the neonates and 30% of the infants who were tested. These patients must not undergo pancreatic catheterisation and a leucine-restricted diet must be tested. Rare causes of secondary hyperinsulinism, such as a congenital disorder of glycosylation [4] or a Munchausen-by-proxy syndrome, should also be routinely eliminated before invasive investigations and surgical treatment are undertaken.

Isolated hyperinsulinaemic hypoglycaemia is histologically heterogeneous, with potentially dramatic implications for the extent of pancreatectomy (when indicated) and long-term patient outcome. Late-onset hypoglycaemia, after 1 year of life, strongly suggests an adenoma which is cured by its removal.

Both focal adenomatous hyperplasia and diffuse hyperinsulinism are found in neonatal- and infancy-onset patients. No clinical symptom can help distinguish between the two histological forms [2]. It is crucial to identify the focal lesions, as 46% of our surgically-treated patients had a focal lesion (29 neonates and 13 infants) and hypoglycaemia was cured by a limited pancreatic resection. It is also crucial to precisely locate the focal lesion, because surgeons usually resect pancreatic tissue by first removing the tail and the body of the pancreas, while it was in the head of the pancreas in more than 33% of cases. Preoperative classical radiology of the pancreas, including echotomography, CT scan and MRI, do not identify the focal lesions. They are also too small to be detected during surgery. The aim of pancreatic venous catheterisation, with measurement of insulin in the various pancreatic veins, is to locate the lesion [5]. Pancreatic catheterisation should not be performed before the 1st month of life because of transient forms or in patients with hyperammonaemia who are likely to have diffuse hyperinsulinism. Intra-operative histological examination makes the final distinction between diffuse and focal lesions and limited pancreatic resections are guided by the results of pancreatic catheterisation [14].

The various histological forms of hyperinsulinism correspond to specific genetic abnormalities. The focal form is due to a loss of the maternal allele of the 11p15 region restricted to the lesion with reduction to homozygosity of a paternally inherited mutation in the *SUR1* or *KIR6.2* genes [3,25]. The somatic character of the lesion suggests a sporadic occurrence that is confirmed by the lack of familial forms.

Diffuse forms probably correspond to heterogeneous entities that remain to be clarified. The majority of cases of neonatal-onset hyperinsulinaemic patients were associated with the *SUR1* and *KIR6.2* genes. Some were homozygous for the mutations, as reported in other populations. However, only one mutation of either gene, either of paternal or maternal origin, was detected in the majority of these patients. Only two infancy-onset patients, with diffuse hyperinsulinism, had a *SUR1* or *KIR6.2* mutation. Most patients with *SUR1* or *KIR6.2* mutations were resistant to diazoxide, whatever the focal or diffuse type of the lesion.

Despite the genetic heterogeneity of hyperinsulinism, the clinical characteristics of hypoglycaemia vary principally with the age at onset. Only diazoxide-sensitive neonates tend to have transient or associated hyperinsulinism, while a late onset of hypoglycaemia is linked to an adenoma (insulinoma). The treatment of hyperinsulinaemic hypoglycaemia is the main difficulty in neonates, whereas an important concern in infancy-onset hyperinsulinism is delayed diagnosis because of good tolerance of hypoglycaemia. Infants medically treated are probably underestimated in this study because most patients who were referred from other countries were resistant to diazoxide and underwent pancreatic catheterisation that only our radiologist could perform. K^+_{ATP} channel mutations are responsible for at least 50% of the diffuse cases of neonatal hyperinsulinism and for 84% of focal cases [6]. By contrast, few mutations were found in infancy-onset diffuse hyperinsulinism. The heterogeneity of hyperinsulinism has major consequences in terms of outcome because the therapeutic approach and genetic counselling differ radically.

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