Eur J Pediatr (1997) 156: 754–757

ENDOCRINOLOGY

T. Meissner · W. Brune · E. Mayatepek

Persistent hyperinsulinaemic hypoglycaemia of infancy: therapy, clinical outcome and mutational analysis

Received: 20 November 1996 / Accepted: 14 April 1997

Abstract Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) is an autosomal recessive disorder characterized by irregular insulin secretion leading to hypoglycaemia. Recently, mutations in the sulphonylurea receptor (SUR) have been described in association with PHHI. We studied clinical symptoms, therapy, long-term outcome and mutational analysis in 14 patients with PHHI. In 8 patients subtotal pancreatectomy was performed whereas 6 responded to conservative treatment with diazoxide. Psychomotor retardation was found in 6 patients, most of them after a delayed diagnosis. A G-to-A point mutation in one allele of the SUR gene was detected by loss of a MspI restriction site in only one patient.

Conclusion Early diagnosis and therapy in PHHI is essential to prevent brain damage. In one patient mutational analysis suggested compound heterozygosity for a known and an as yet unidentified mutation in the SUR gene.

Key words Persistent hyperinsulinaemic hypoglycaemia of infancy · Nesidioblastosis · Sulphonylurea receptor · Mutational analysis · Pancreatectomy

Abbreviations *PHHI* persistent hyperinsulinaemic hypoglycaemia of infancy *SUR* sulphonylurea receptor

Introduction

Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI), also known as nesidioblastosis or familial hyperinsulinism, is the most common cause of recurrent severe hypoglycaemia in infancy [2]. It is characterized by an irregular insulin secretion leading to inappropriately raised plasma insulin concentration compared to blood glucose levels. Most patients show typical symptoms of hypoglycaemia during the first days of life but there may be also a milder or delayed onset. Once diagnosis is confirmed the priority of treatment is to maintain normal blood glucose levels to prevent brain damage. Initial high dose glucose infusions (>15 mg/kg/min) may be insufficient to maintain euglycaemia, and glucagon or somatostatin infusions are necessary. The mainstay of medical treatment is oral diazoxide. If diazoxide fails in preventing hypoglycaemia, near total pancreatectomy is recommended [5, 6].

Recently, loss of function mutations in the sulphonylurea receptor (SUR) gene were found to be associated with PHHI [7]. The SUR seems to be closely associated or even part of the ATP-dependent potassium channel (K_{ATP} channel) of pancreatic β-cells, which regulates insulin secretion [1]. The first two mutations were found in the nucleotide binding fold-2 (NBF-2) of the SUR in ten families mainly of eastern Saudi Arabian origin [8]. Homozygous loss of a restriction enzyme recognition site cosegregated with the phenotype and proved an autosomal recessive inheritance of PHHI.

We report our clinical experience with 14 PHHI patients seen over the last 20 years. In ten patients mutational analysis was performed to evaluate the frequency of the two yet known mutations in the NBF-2 of the SUR gene.

Patients and methods

A total of 14 patients (7M, 7F) with PHHI were included in this study. Diagnosis of PHHI was confirmed in each patient by low blood ketone bodies and low free fatty acids during hypoglycaemia and a repeated pathologically increased insulin/glucose ratio of >0.5. In patients who did not respond to treatment with diazoxide and glucagon, subtotal pancreatectomy was performed. In all of these cases the typical histological signs of diffuse nesidioblastosis were found.

T. Meissner · E. Mayatepek (✉)
Division of Metabolic Diseases,
University Children's Hospital Im Neuenheimer Feld 150,
D-69120 Heidelberg, Germany,
Tel.: +49-6221-562311, Fax: +49-6221-564388

W. Brune
Max-von-Pettenkofer Institute of Virology,
Wurmtalstrasse 221, D-81375 München, Germany

Table 1 Clinical, laboratory, histological and mutational analysis data of patients with PHHI (*ND* not determined)

Patient no.	Actual age [years]	Origin	Gestational age [weeks]	Birth weight [g]	Age of first symptoms/ diagnosis	Insulin/ glucose ratio	Long-term treatment	Age at surgery	Histological signs of nesidioblastosis	Mutation in the SUR gene[a]	Psychomotor retardation[b]	Further remarks
1	3	Turkish	40	3350	6 days/6 days	1.1	diazoxide	–	–	–	–	consanguinity
2	3	Polish	27	1010	4 months/2 years	0.8	diazoxide, somatostatin	–	–	–	++	
3	7	German	40	3400	6 months/13 months	0.5	diazoxide	–	–	ND	++	
4	10	German	41	3650	2 days/2 days	2.8	diazoxide	–	–	–	–	
5	18	German	40	3080	8 months/13 months	1.8	diazoxide	–	–		–	
6	20	German	31	1700	5 months/6 months	0.5	diazoxide	–	–	ND	+	
7	2	Turkish	40	4510	4 weeks/4 weeks	2.0	7/8 pancreatectomy, diazoxide, somatostatin	2 months	+	ND	–	
8	3	Turkish	40	3230	8 weeks/8 weeks	0.5	7/8 pancreatectomy, diazoxide, somatostatin	3 months	+	ND	+	
9	4	Rumanian	40	3520	5 months/14 months	1.0	7/8 pancreatectomy glucagon, diazoxide	16 months	+	–	++	epilepsy
10	10	Turkish	39	4700	1 day/1 day	4.3	7/8 pancreatectomy, diazoxide, glucagon	3 weeks	+	+ (MspI)		
11	11	German	40	3250	1 day/1 day	0.5	7/8 pancreatectomy, glucagon	5 months	+	–	–	
12	15	German	31	1700	2 days/4 years	0.7	7/8 pancreatectomy	4 years	+	–	+++	petit mal
13	18	German	41	5320	1 day/1 day	0.8	4/5 pancreatectomy, 1 × reoperation, diazoxide	8 months, 6 years	+	–	–	diabetes mellitus (onset with 16 years)
14	20	German	41	4500	5 days/5 days	2.0	4/5 pancreatectomy, 2 × reoperation, diazoxide	4 months, 6 years, 9 years	+	–	–	brother of no. 13, diabetes mellitus (onset with 16 years)

[a] – = no mutation detected; + = mutation detected
[b] – = absent; + = mild, ++ = moderate, +++ = severe

Ten families were investigated for the two as yet identified mutations in the NBF-2 of the SUR gene by restriction digest of PCR-amplified gene fragments with endonucleases MspI and NciI as already described [7]. Sequence analysis of PCR products was performed using an automated DNA sequencing apparatus (Applied Biosystems).

Results

Clinical, biochemical and mutational findings of all 14 patients are summarized in Table 1.

Seven patients showed typical recurrent hypoglycaemia during the first days of life. Seven patients became symptomatic during their 1st year of life and were diagnosed with delay of up to 4 years after the initial manifestation. Eight patients required subtotal pancreatectomy, two of them (patients 13, 14) needed further revision because of persistent severe episodes of hypoglycaemia probably due to an initially less extended resection. After pancreatectomy most patients showed, at least for a period of some months, less severe and less frequent episodes of hypoglycaemia still requiring further medication. At the age of 16 years two patients developed an insulin dependent diabetes mellitus. None of the patients undergoing near total pancreatectomy developed any signs of malabsorption.

Six patients responded well to treatment with diazoxide (up to 10 mg/kg/day) not requiring subtotal pancreatectomy. In most patients treated with diazoxide moderate hypertrichosis was noted but no further side-affects were observed.

Psychomotor retardation was present in six patients, in four of them after a delayed diagnosis.

In nine patients restriction digest of PCR-amplified DNA was normal. One female patient (patient 10) showed heterozygous loss of a MspI restriction site. Heterozygosity for a G-to-A splice site mutation was subsequently confirmed by sequence analysis. The patient's asymptomatic mother was also heterozygous for this mutation. These findings suggest the presence of an additional, yet unidentified, mutation on the second SUR allele of this patient.

Discussion

In this study we evaluated clinical findings and therapeutic strategies in 14 patients with PHHI. Most important for clinical outcome of these patients was an early diagnosis. More than one third of our patients were diagnosed with delay. In these patients psychomotor retardation was already present when the diagnosis of PHHI was made. Neurological deficits are probably caused by untreated repeated and prolonged episodes of hypoglycaemia. Except one, all patients diagnosed early during the first weeks of life showed normal psychomotor development regardless of whether they responded to medical treatment or required surgery. Even though PHHI is a rare disease, it should always be ruled out in infants presenting with neurological symptoms consistent with hypoglycaemia. In some cases repeated determinations of the insulin/glucose ratio are necessary to prove hyperinsulinism.

In our experience, normoglycaemia can be easily achieved after near total pancreatectomy. This may spare long-term hospitalisation in early childhood as well as repeated injections and frequent blood glucose measurements. On the other hand there is a yet unknown risk of diabetes mellitus which seems to present many years after surgery and usually not before puberty.

Nearly half of our patients responded well to diazoxide not requiring pancreatectomy. These patients might represent a milder type of hyperinsulinism. Up to now, there is only limited experience with the long-acting somatostatin analogue octreotide [3, 10] or nifedipine [4] as alternative medications. At least octreotide seems to be indicated only in patients with less severe hyperinsulinism, good social setting and excellent compliance [8]. Nevertheless, if medical treatment fails in maintaining euglycaemia within a reasonable time, we recommend near total pancreatectomy.

Mutational analysis revealed for the first time compound heterozygosity for a known and an as yet unidentified mutation in the SUR gene. Since only one patient with a mutation in the NBF-2 of the SUR gene could be identified in this group of patients, studies of a larger number of patients are necessary to determine the frequency of these mutations in PHHI. Moreover, our results and recent findings [9] provide evidence that further mutations exist in other regions of the SUR gene associated with PHHI. Therefore, more data are necessary before an appropriate correlation between phenotype and genotype can be made. However, in some cases mutational analysis already provides a new diagnostic tool for prenatal and early neonatal diagnosis of this disorder.

References

1. Ashcroft SJ, Ashcroft FM (1992) Properties and functions of ATP-sensitive K-channels. Cell Signal 2:197–214
2. Aynsley-Green A, Polak JM, Bloom SR, Gough MH, Keeling J, Ashcroft SJH, Turner RC, Baum JD (1981) Nesidioblastosis of the pancreas: definition of the syndrome and the management of the severe neonatal hyperinsulinaemic hypoglycaemia. Arch Dis Child 56:496–508
3. Glaser B, Hirsch HJ, Landau H (1993) Persistent hyperinsulinemic hypoglycaemia of infancy: long-term octreotide treatment without pancreatectomy. J Pediatr 123:644–650
4. Lindley KJ, Dunne MJ, Kane C, Shepherd RM, Squires PE, James RFL, Johnson PRV, Eckhardt S, Wakeling E, Dattani M, Milla PJ, Aynsley-Green A (1996) Ionic control of β cell function in nesidioblastosis. A possible therapeutic role for calcium channel blockade. Arch Dis Child 74:373–378
5. Spitz L, Bhargava RK, Grant DB, Leonard JV (1992) Surgical treatment of hyperinsulinaemic hypoglycaemia in infancy and childhood. Arch Dis Child 67:201–205
6. Thomas CG, Guenca RE, Azizkhan RG, Underwood LE, Carney CN (1988) Changing concepts of islet cell dysplasia in neonatal and infantile hyperinsulinism. World J Surg 12:598–609

7. Thomas PM, Cote GJ, Wohllk N, Haddad B, Mathew PM, Rabl W, Aguilar-Bryan L, Gagel RF, Bryan J (1995) Mutations in the sulfonylurea receptor gene in familial persistent hyperinsulinemic hypoglycemia of infancy. Science 268:426–429
8. Thomas PM, Cote GJ, Wohllk N, Mathew PM, Gagel RF (1996) The molecular basis for familial persistent hyperinsulinemic hypoglycaemia of infancy. Proc Assoc Am Physiol 108:14–18
9. Thomas PM, Wohllk N, Huang E, Kuhnle U, Rabl W, Gagel RF, Cote GJ (1996) Inactivation of the first nucleotide-binding fold of the sulfonylurea receptor, and familial persistent hyperinsulinemic hypoglycemia of infancy. Am J Hum Genet 59:510–518
10. Thornton PS, Alter CA, Levitt Katz LE, Baker L, Staneley CA (1993) Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism. J Pediatr 123:637–643