

Original Article

Persistent hyperinsulinemic hypoglycemia of infancy: a clinical and pathological study of 19 cases in a single institution

Jiwei Li^{1*}, Yangyang Ma^{2*}, Mengxing Lv¹, Jun Zhou¹, Baihui Liu³, Kuiran Dong³, Xianmin Xiao³, Lian Chen²

¹Department of Pathology, Kunming Children's Hospital, Kunming, Yunnan Province, China; Departments of ²Pathology, ³Surgery, Fudan University Children's Hospital, Shanghai, China. *Equal contributors.

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Abstract: Objective: To study the clinical and pathological features of persistent hyperinsulinemic hypoglycemia of infancy. Method: The clinical and pathological data of 19 cases of persistent hyperinsulinemic hypoglycemia of infancy were retrieved and reviewed from the medical records in Children's Hospital of Fudan University. Results: There were 13 boys and 6 girls. The age interval was from 16 days to 7 months, and the average age was 2.71 ± 2.23 months. The blood glucose concentrations ranged from 0.57 to 3.0 mmol/L (average value 1.60 ± 0.75 mmol/L) and the serum insulin concentrations ranged from 3.1 to 79.4 uIU/ml (average value 27.89 ± 21.81 uIU/ml) at the time of one week before operation. The size of lesion was between 2 cm to 6.5 cm in maximum diameter (average value 4.04 ± 1.18 cm). 19 cases were divided into three types according to the pathological classification criteria: focal type (1 case), diffuse type (17 cases) and atypical type (1 case). The enucleation of the nodule was given for the patient of focal type and subtotal pancreatectomy was administrated for diffuse and atypical type patients. The blood glucose concentrations ranged from 3.0 to 12.4 mmol/L (average value 6.21 ± 2.69 mmol/L) at the time of one month after operation. The difference between the preoperative blood glucose concentrations and the postoperative blood glucose concentrations was statistically significant (1.6037 ± 0.7458 mmol/L vs. 6.2105 ± 2.6882 mmol/L, $P < 0.05$). Insulin was positive for the multiple pancreatic islets, and the ki-67 index was between 5% and 8%. P57^{kip2} was negative. 19 patients were followed up for a period of 2 to 38 months. 13 cases recovered well without any complications, and 6 cases had postoperative hyperglycemia and need a medication to control the blood glucose concentrations. Conclusion: Persistent hyperinsulinemic hypoglycemia of infancy mainly occurred in infants. Boys had the predominance and the most common pathological type was the diffuse type. The different surgical methods (focal type with lesion enucleation, diffuse and atypical type with subtotal pancreatectomy), were effective for different patients, and most of patients had a good prognosis. Early diagnosis and appropriate treatment to maintain euglycemia remained the mainstay of management to prevent postoperative complications. Therefore, the correct pathological classification could help clinicians to find effective treatment and improve the outcome.

Keywords: Persistent hyperinsulinemic hypoglycemia of infancy, clinical and pathological study

Introduction

The syndrome of persistent hyperinsulinemic hypoglycemia of infancy (PHHI) was first proposed by Laidlaw in 1938 [1], and it was referred to the condition of severe hypoglycemia in infants caused by dysregulated insulin secretion [2, 3]. Patients of PHHI usually presented with poor feeding, lethargy and irritability, or more severe symptoms such as apnoea, seizures or even coma [4-7].

Clinical diagnosis of PHHI mainly depends on the clinical indications which have been described with the Whipple's triad: symptoms of hypoglycemia; glycaemic levels less than 50 mg/dl; the quick relief of symptoms after ingestion of carbohydrates or intravenous administration of glucose solutions [8]. However, clinical indications are not sufficient for surgery.

As an important auxiliary examination, radiography provides valuable information. PET scan

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Table 1. Clinicopathological data of 19 cases of PHHI

NO	Sex	Age	PrFBG (mmol/L)	PIC (uIU/ml)	PT	SM	LS (cm)	PoFBG (mmol/L)	FT	Complication
1	F	2 ms	0.9	23.9	F	lesion enucleation	2	3.0	21 ms	N
2	M	3 ms	1.3	3.1	D	Subtotal pancreatectomy	5.5	5.9	33 ms	N
3	M	28 ds	2.6	25.7	D	Subtotal pancreatectomy	3	7.1	12 ms	H
4	F	7 ms	1.6	28.9	D	Subtotal pancreatectomy	5	12.4	11 ms	H
5	M	2 ms	2.8	33.3	D	Subtotal pancreatectomy	4.5	4.4	2 ms	N
6	M	2 ms	1.6	11.97	D	Subtotal pancreatectomy	3.5	5.2	14 ms	N
7	F	17 ds	2.2	51.0	D	Subtotal pancreatectomy	3	7.8	11 ms	H
8	M	6 ms	1.8	25.0	D	Subtotal pancreatectomy	4	4.8	3 ms	N
9	M	16 ds	1.1	4.9	D	Subtotal pancreatectomy	3.2	4.3	38 ms	N
10	M	2 ms	0.7	26.7	D	Subtotal pancreatectomy	5	5.3	15 ms	N
11	M	3 ms	1.8	12.2	D	Subtotal pancreatectomy	4.8	6.4	29 ms	N
12	M	31 ds	0.57	19.4	D	Subtotal pancreatectomy	3.2	3.7	30 ms	N
13	M	26 ds	2.1	79.4	D	Subtotal pancreatectomy	4	8.0	6 ms	H
14	F	2 ms	0.7	11.3	D	Subtotal pancreatectomy	5	11.2	27 ms	H
15	M	21 ds	1.0	75.2	D	Subtotal pancreatectomy	2	5.3	25 ms	N
16	F	6 ms	1.2	49.3	D	Subtotal pancreatectomy	4	10.3	16 ms	H
17	M	7 ms	1.1	7.5	D	Subtotal pancreatectomy	6.5	4.0	14 ms	N
18	F	4 ms	3.0	13.4	D	Subtotal pancreatectomy	5	5.9	31 ms	N
19	M	25 ds	2.4	27.7	A	Subtotal pancreatectomy (operations for twice)	2; 1.5	3.0	15 ms	N

M, male; F, female; ds, days; ms, months; PrFBG, preoperative fasting blood glucose concentrations (at the time of one week before operation); PIC, preoperative serum insulin concentrations (at the time of one week before operation); PT, pathological type; D, diffuse; F, focal; A, atypical; SM, surgical method; LS, lesion size in maximum diameter, cm, centimeters; PoFBG, postoperative fasting blood glucose concentrations (at the time of one month after operation); FT, Follow-up time; N, none; H, hyperglycemia.

is very popular and important for surgery to detect hyperfunctional pancreatic islets and localizes the lesion in focal types of PHHI [9-13]. Although it has a lot of advantages, PET is expensive and invasive, and has radiation damage. Besides, we cannot use PET to get a definite distinction between diffuse and transitional type [14].

Therefore pathological study has an important value for the diagnosis of PHHI. The classic classification of PHHI is divided into two types: focal type and diffuse type. But some of the latest researches suggest that there may be an atypical type between these two types [15].

Owing to the paucity of PHHI, this study was conducted to elucidate the clinical and pathological features of PHHI in 19 children.

Materials and methods

Medical records

19 cases of PHHI were retrieved from the medical records in Children's Hospital of Fudan University between 2011 and 2015 with the permission of the ethics committee. The data we collected included the fasting blood glucose concentration at the time of one week before operation (PrFBG) and the serum insulin con-

centrations at the time of one week before operation (PIC), postoperative fasting blood glucose concentrations at the time of one month after operation (PoFBG), pathological types, surgical methods, lesion size and follow-up.

Histopathological studies

With pathologic examination, all of the resected pancreatic specimens were fixed in 10% buffered formalin and embedded in paraffin. Block step sections (5 μm) were cut and stained conventionally with hematoxylin and eosin (HE).

Immunohistochemistry

Immunohistochemical staining with antibodies for Insulin (2D11-H5; Roche, Shanghai, China; prediluted), Ki-67 (monoclonal; Roche, Shanghai, China; prediluted), and P57^{kip2} (MAB-0317; Roche, Shanghai, China; prediluted) were performed using the EnVision method. Insulin was positive in membrane. Ki-67 and P57^{kip2} were positive in nucleus.

Statistical methods

Comparative t-test was used to deal with the PrFBG and PoFBG. Statistical analysis was performed using the Statistical Program for Social Science 17.0.

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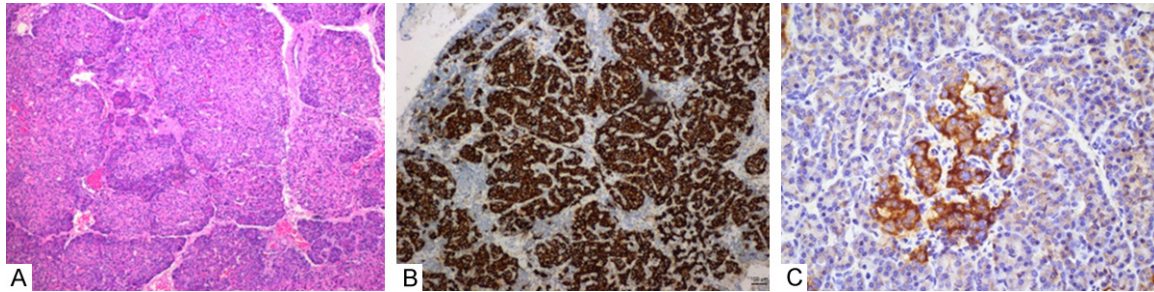


Figure 1. Pathologic features of focal type. A: HE stained sections of involved pancreas demonstrated β cells with an enlarged cytoplasm and a large Golgi region ($\times 100$). B: Insulin staining of the islets showed apparently normally structured islets with a large core of β cells and a peripheral rim of endocrine non- β cells ($\times 100$). C: p57^{KIP2} was negative for islets in nucleus ($\times 400$).

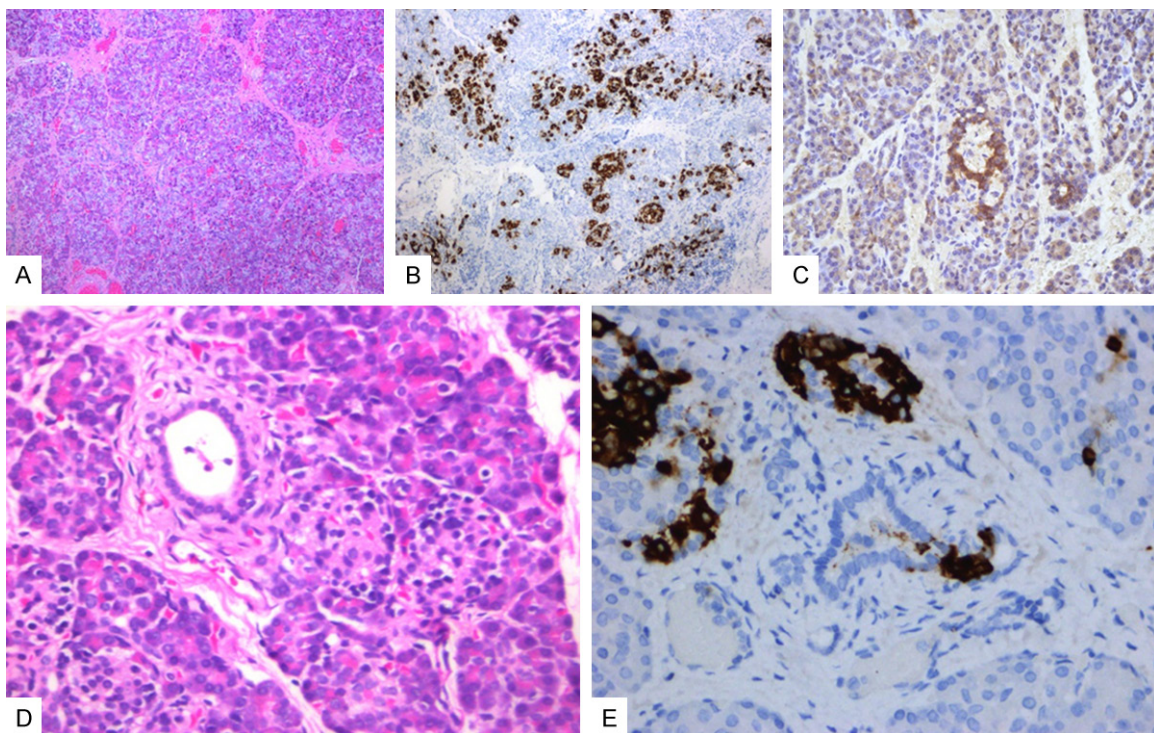


Figure 2. Pathologic features of diffuse type. A: HE stained sections of involved pancreas demonstrated β cells with abundant clear cytoplasm and nuclear pleomorphism including hyperchromasia, nuclear enlargement, and prominent nucleoli ($\times 100$). B: Insulin staining of the islets showed variable islet hyperplasia ($\times 100$). C: p57^{KIP2} was negative for islets in nucleus ($\times 400$). D: Cell budding adhered around the ductal epithelium as a ductulo-insular complex ($\times 200$). E: Insulin staining displayed the proliferative cells originated from the ductal epithelium ($\times 200$).

Results

The clinicopathological data of 19 cases were collected and summarized in **Table 1**: there were 13 boys and 6 girls, and the sex ratio (male: female) was 2:1; the age interval was from 16 days to 7 months with the average age 2.71 ± 2.23 months and the median age 2 months; 36.8% of patients presented in neonates; the PrFBG of infants ranged from 0.57 to 3.0 mmol/L with the average value 1.60 ± 0.75

mmol/L; the PIC ranged from 3.1 to 79.4 uIU/ml with the average value 27.89 ± 21.81 uIU/ml; there were one focal case (5.25%), seventeen diffuse cases (89.5%) and one atypical case (5.25%); the size of lesion was between 2 cm to 6.5 cm in maximum diameter with the average value 4.04 ± 1.18 cm; the PoFBG ranged from 3.0 to 12.4 mmol/L with the average value 6.21 ± 2.69 mmol/L. The difference between the PrFBG and PoFBG was statistically significant (1.6037 ± 0.7458 mmol/L vs. $6.2105 \pm$

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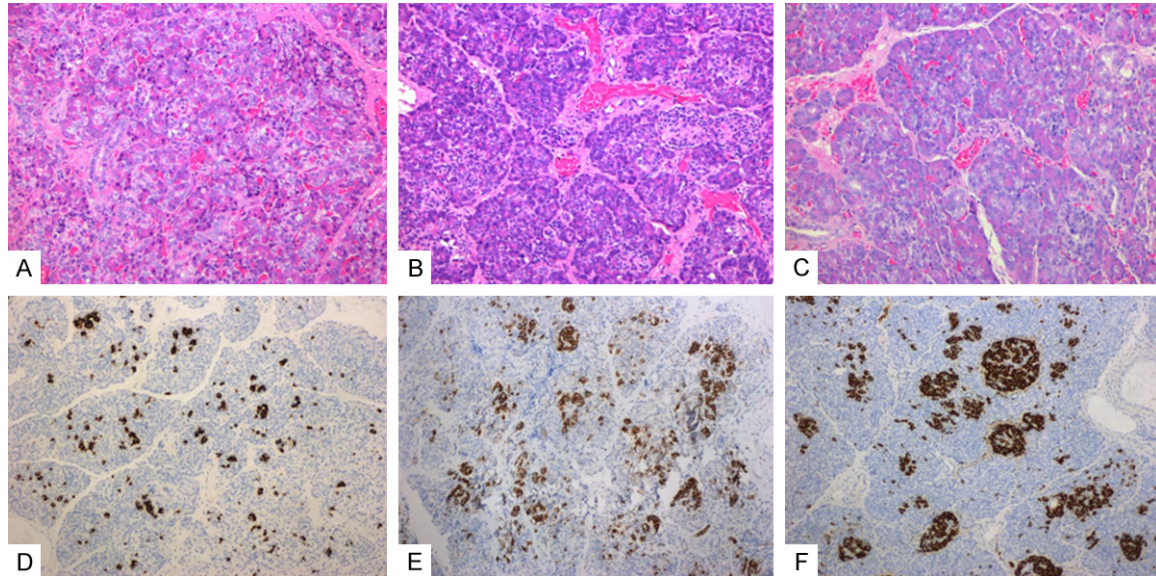


Figure 3. Pathologic features of three different subtypes of diffuse type. A-C: HE stained sections of involved pancreas demonstrated variable islet hyperplasia: subtype I, single or several was dispersedly distributed in pancreas (A, $\times 100$); subtype II, a number of multiple β cells constituted islets or nests (B, $\times 100$); subtype III, hundreds of multiple β cells constituted bigger islets or nests (C, $\times 100$). D-F: Insulin staining of the islets showed β cells with abundant clear cytoplasm and nuclear pleomorphism: subtype I, the multiple β cells were dispersed (D, $\times 100$); subtype II, multiple β cells constituted islets (E, $\times 100$); subtype III, multiple β cells constituted bigger cell islets or nests (F, $\times 100$).

2.6882 mmol/L, $P < 0.05$). All children were followed up. Thirteen cases recovered well without any complications, and six cases had post-operative hyperglycemia. Insulin was positive for the multiple pancreatic islets. Ki-67 index was between 5% and 8% and helped us to know that the lesion was hyperplasia. P57^{KIP2} was negative in all the cases.

Images of typical cases of three different pathological types were shown as follows.

Focal type

The lesion was smaller than 15 mm and the β cells had an enlarged cytoplasm and a peripheral rim of endocrine non- β cells (Figure 1A and 1B). P57^{KIP2} was negative for islets in nucleus (Figure 1C).

Diffuse type

There was a hyperfunction of every islet of Langerhans within the pancreas in the diffuse type cases (Figure 2A and 2B). The multiple β cells had enlarged hyperchromatic nuclei and clear cytoplasm. P57^{KIP2} was negative for islets in nucleus in all the diffuse cases (Figure 2C). Cell budding adhered around the ductal epithe-

lium as a ductulo-insular complex, and islets were well demarcated as islet or lobulated structure (Figure 2D and 2E).

In addition, we observed 17 diffuse type cases detailedly in morphology and divided them into three subtypes:

Subtype I: the majority of the multiple β cells, single or several, was dispersedly distributed in pancreatic lobule, and only a few cells constituted islets (Figure 3A and 3D).

Subtype II: the number of multiple β cells was more than subtype I, and dozens of cells apparently constituted islets (Figure 3B and 3E).

Subtype III: dozens or hundreds of multiple β cells obviously constituted bigger islets or nests, and also had a mixture of the structure of subtype I or II (Figure 3C and 3F).

Atypical type

We observed the coexistence of hyperfunctional islets with some abnormal giant beta cell nuclei, and resting small and round islets in a segmental distribution (Figure 4A). The lesion had a mixture of parts of diffuse and focal

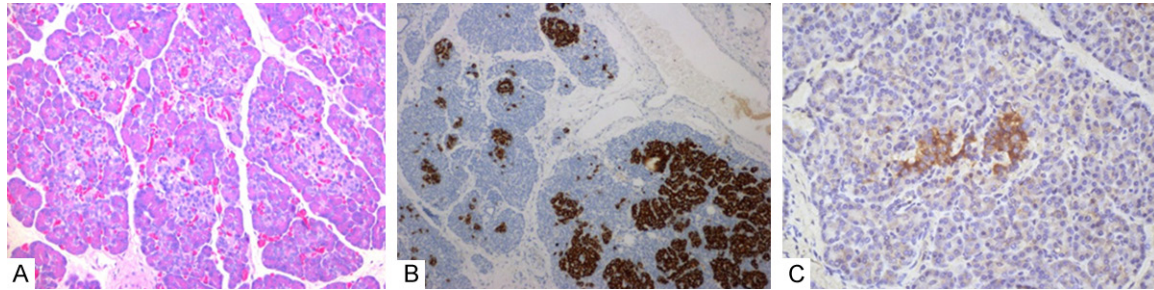


Figure 4. Pathologic features of atypical type. A: HE stained sections of involved pancreas demonstrated variable islet hyperplasia ($\times 200$). B: Insulin staining of the islets showed several to a few dozen cells composed an islet, loose structure like the diffuse type; The same tissue and the different view, a large core of β cells with a peripheral rim of endocrine non- β cells, dense structure like the focal form ($\times 200$). C: P57^{KIP2} was negative for islets in nucleus ($\times 400$).

lesion (**Figure 4B**). P57^{KIP2} was negative for islets in nucleus (**Figure 4C**).

Discussion

The first description with histomorphology of PHHI was defined by G. Laidlaw as a diffuse and disseminated proliferation of islet cells budding off from ducts in the 1980 [1, 16, 17]. Although the syndrome was proposed for more than 70 years, PHHI was still uncommon [18]. We collected clinical and histological data of 19 cases between 2011 and 2015, which was a much larger data in China and even was uncommon in Asia. The morbidity of PHHI in the general population was between 1/4000 and 1/2500, and increased every year in communities [19]. Our data showed that the male accounted for 68.4% of all the cases, which was consistent with previous reports. We observed that the patients older than one year were rarely seen, and the youngest was only 16 days old. The age at onset had been found early in life, a few hours or days after birth [20]. The blood glucose concentrations, serum insulin concentrations and clinical symptoms of our patients met the diagnostic criteria: insulin levels increased, and hypoglycemia levels were detectable less than 2.5 mmol/L [2, 20]. Therefore, it was very important to make an accurate classification of PHHI in morphology.

According to a large number of literatures, the classic classification of PHHI included focal and diffuse type. About 95% of our cases were these types. The focal type was rare in infants, and was less than 30% [21]. The only one focal type of our patients was accorded with the pathologic features of literature, which had an enlarged cytoplasm and a peripheral rim of

endocrine non- β cells. After preoperative examination, the patient underwent lesion enucleation, and the main pancreatic duct was preserved. The PoFBG became 3.0 mmol/L. With 21 months follow-up, the patient recovered well without any complications. According to the reports, the focal type could be cured with a limited lesion enucleation which reduced the risk of diabetes mellitus and exocrine pancreatic deficiency [22].

In our study, the diffuse type was the most common type in PHHI. 89.5% of our cases were this type, and it accounted for more than 70% in the literature [18]. The pathologic feature of diffuse type was that it had hyperfunction of every islet of Langerhans within the pancreas. Although the diffuse type was common, we still didn't have a comprehensive understanding for its rarity. All patients of diffuse type were resistant to diazoxide, and were given subtotal pancreatectomy [23]. The long-term curative effect was good in 64.7% of our diffuse cases. 35.3% had high PoFBG, which was less than the literature. It had been reported that about 50% of diffuse type had postoperative complications [23, 24]. According to the result, we had to think about whether we did excessive resection in part of patients. Meanwhile, some scholars considered surgical procedures (partial and targeted pancreatectomy by laparoscope) and management with PoFBG, reduced diabetes mellitus and exocrine pancreas insufficiency. Therefore, they proposed an opinion of subtype, and there should be reasonable surgical method for this type [25]. However, these reports didn't provide histomorphological description, which weren't helpful for further studies. In our study, we made a deep research with the histomorphology of the diffuse type cases,

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and proposed three subtypes classification: I, II and III. Subtype I, 6 cases (35.3% of diffuse) were more like hyperplasia and β cells were dispersedly distributed in pancreatic lobule; subtype II, 8 cases (47.1% of diffuse) apparently constituted islets or nests with dozens of β cells; subtype III, 3 cases (17.6% of diffuse) had bigger islets or nests. All of the subtypes were given subtotal pancreatectomy. 11 cases had good prognosis, but 6 cases (2 cases from subtype I, 3 cases from subtype II, and 1 case from subtype III) had postoperative hyperglycemia. Unfortunately there was no relationship between the subtype and the prognosis in our study. Further research was needed.

In addition, new research considered that there was a transition type between focal and diffuse type [26]. Fortunately, we observed a patient of atypical type (5% of all our cases) and PET showed several nodes (<15 mm). This patient underwent pancreatic head resection (10% pancreas). Pathological study of atypical type found that the coexistence of hyperfunctional islets had some abnormal giant beta cell nuclei, and resting small and round islets, in a segmental distribution. Especially, the lesions were mixed with structure of diffuse and focal types. Therefore, the patient underwent the second laparoscopic pancreatectomy and finally had been took 95% of the pancreas. The PoBGC was 3.0 mmol/L and the patient had good prognosis. With an overall evaluation, we believed that the accurate pathological types could help to choose reasonable surgical method and avoid excessive resection leading to sequela.

Recently, the genetic research developed very rapidly. It was reported that the encoded enzymes were influenced by genetic mutation, which were responsible for insulin secretion from the pancreatic β cells: the focal adenomatous lesion was associated with a paternally inherited mutation in *ABCC8/KCNJ11* genes and loss of the maternal 11p15 allele in the β -cells [27, 28]. The diffuse type was secondary to a mutation of one of the genes of the KATP-dependent channel [29, 30], which was composed of 2 subunits: the sulfonylurea receptor, *ABCC8*, and a member of the inwardly rectifying potassium channels, *KCNJ11*. The transitional type was due to mutations in the *GLUD1*, *GK* and *SLC16A1* genes [26, 31]. *P57^{KIP2}* was paternally imprinted, and thus was candidate gene for enhanced cell proliferation [32, 33]. Wh-

ereas in 40-50% of the patients, the genetic cause was still unknown [34]. So we examined *p57^{KIP2}* in immunohistochemistry for all types and they were negative in nucleus.

In spite of the rarity of PHHI, our studies indicated many important clinical and pathological features: mainly occurred in infants, boys had the predominance and the most common type was the diffuse type; the surgical method (focal type with lesion enucleation, diffuse and atypical type with subtotal pancreatectomy) was effective and had good long-term outcome; early diagnosis and appropriate treatment to maintain euglycemia remained the mainstay of management to prevent postoperative complication. However, with the increased incidence, we should realize that the traditional surgery was no longer optimal for the diffuse subtypes and atypical type. Although they presented the same symptoms, the classification had delicate distinction in morphology. We should quantify the surgical method and range with accurate classification, use laparoscope to enucleate appropriate lesion, and collect postoperative data to evaluate prognosis. This procedure might provide a more effective treatment and decrease postoperative risk. Finally, we hope our study might help clinicians institute appropriate management to improve outcome.

In summary, we report a series of 19 cases of PHHI and make a preliminary clinicopathological study of these cases. More data are needed to promote the progressive realization of PHHI and reduce the complication of the surgery.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Lian Chen, Department of Pathology, Children's Hospital of Fudan University, Shanghai, China. Tel: (86) 21-6493-1728; Fax: (86) 21-6493-1914; E-mail: doctchenlian@163.com

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