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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Pancreatic involvement in Japanese patients with von Hippel-Lindau disease: results of a nationwide survey

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Abstract
Background The frequency and prognosis of pancreatic endocrine tumors (PNET)/pancreatic cystic tumors (PCT) in Japanese patients with von Hippel-Lindau disease (VHL) are still open to question.
Methods We conducted the first nationwide epidemiological study of VHL disease in Japan to elucidate this question. Data on 377 VHL patients (PNET, 53; PCT, 152) were reported, and then their clinical characteristics were analyzed.
Results PNET was found in 14.1 % and PCT in 40.3 %; 4.5 % had both. The onset of PNET and PCT mostly occurred at 30–39 years of age (median ages, 34 and 33 years, respectively). Metastasis was observed in 7.5 % of PNET patients at diagnosis, and 64.2 % underwent surgery including enucleation, partial and total pancreatectomy, and bypass surgery. Two patients received non-surgical therapies. No PNET-related deaths were observed. In PCT patients, no metastasis was observed at diagnosis, and 9.2 % underwent surgery or drainage. According to the classification system without or with adrenal pheochromocytoma, the VHL patients studied herein were subdivided into 313 (83 %) with VHL type 1 and 64 (17 %) with VHL type 2; 29 (9.3 %) and 24 (37.5 %) patients had PNET with VHL type 1 and 2, suggesting that patients with VHL type 2 were significantly more related to PNET than those with VHL type 1 ($P < 0.01$).
Conclusions This study showed no significant difference in the epidemiology of pancreatic involvement between Japanese and non-Japanese VHL patients. Concerning the prognosis, follow-up study is needed.

Keywords Pancreas · von Hippel-Lindau disease · Neuroendocrine tumor · Pancreatic cystic tumor

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Introduction

The causative gene for von Hippel-Lindau disease (VHL) lies on the short arm of chromosome 3, and VHL is inherited in an autosomal dominant manner [1]. VHL is an intractable disease characterized by various tumors, primarily hemangioblastoma of the central nervous system (CNS), retinal hemangioblastomas, renal cell carcinoma, adrenal pheochromocytoma, pancreatic tumor, endolymphatic sac tumors and epididymal cysts [2]. In Europe and the USA, 1 in 36,000 people [2] and 1 family in 1,000,000 [3] are affected by VHL. Onset occurs in a wide range of age groups from infants/children of <10 years to up to 70 years of age [2]. The most common causes of death in patients with VHL are CNS hemangioblastomas and renal cancer, yielding a reported mean age at death of 40.9 years [4]. Currently, the prevalence of VHL in the Japanese population, the frequencies of individual tumor type and

the onset factors are unknown. In this study, we conducted the first epidemiological study of pancreatic diseases associated with VHL in Japan. We report the data on pancreatic endocrine tumors (PNETs) and pancreatic cystic tumors (PCTs) associated with VHL.

Methods

We conducted an epidemiological study of VHL-associated diseases as is recommended for research by the Rare/Intractable Disease Project of the Ministry of Health, Labor, and Welfare of Japan. In the first survey, we asked 4,545 Japanese medical doctors with specialties in neurosurgery (1,141), ophthalmology (1,149), urology (1,200) and pancreatic diseases (1,055) whether they had treated patient(s) with VHL during the 2 years from April 2009 to March 2011. Subsequently, in a second survey, an inquiry-based investigation was conducted in 228 medical institutions that replied that they had been treating patients diagnosed with VHL. In each VHL patient, investigations of all VHL-related diseases were performed, including age of onset of the VHL-related disease, sex, family history of VHL, with or without genetic surveillance, information on survival, existence of distant metastases, the kinds of the treatment and the ages received. For some of the patients, enough information about family history of VHL and genetic surveillance could not be obtained so they were excluded from the analysis. Replies were obtained from 86 of the 228 institutions; therefore, the response rate was 37.7 %. Information was collected on 377 patients with VHL, which included 53 cases of PNET and 152 cases of PCT. In this study, we report the data obtained from these patients with concurrent PNET and PCT. The diagnosis of PNET and PCT was basically made using imaging modalities, and for patients who received surgical treatment, the diagnosis was confirmed by histological findings.

Results

PNET associated with VHL

Among the 377 patients with VHL, 53 had PNET, and the frequency of concurrent PNET was 14.1 % (Table 1). Twenty patients were male and 33 were female; therefore, the frequency of concurrent PNET was slightly higher in females. The age at onset ranged from 14 to 55 years, and the median age was 34 years. The onset frequency was highest in the 35–39-year age group (Fig. 1). According to data reported in Europe and the USA, 8–17 % of patients with VHL have concurrent PNET [2], which is consistent with the data obtained in Japan. In Japan, metastasis of PNET was observed in 4 of 53 patients (7.5 %) at diagnosis. Data on the observation period from the onset of PNET were only obtained for 32 VHL patients in this study, and the median period was 5 years, ranging from 0 to 21 years. We could not obtain the exact data on the observation period from the onset of the VHL for all surveyed patients. PNET was surgically treated in 34 of 53 patients (64.2 %): 29 patients had a single surgery, 3 patients had two surgeries, and 2 patients had four or more surgeries (Table 1). The mean age when surgical operations were performed for 20 patients with PNETs was 36.9 years. The types of surgeries were as follows: 26 patients had partial pancreatectomy or enucleation, 3 patients had total pancreatectomy, and 1 patient had bypass surgery. Two patients received non-surgical therapies: a 33-year-old female patient underwent systemic chemotherapy (dacarbazine plus 5-fluorouracil) after surgical resection of pancreatic tumor for treatment of liver metastasis/relapse, and a 36-year-old male patient repeatedly underwent transarterial chemoembolization. Among the 377 patients in the current study, there were 16 deaths; however, the causes of the death were mostly

Table 1 Characteristics of Japanese patients with VHL-associated PNET

Total patients with VHL	377
Patients with concurrent PNET	53 (14.1 %)
Gender	
Male	20
Female	33
Median age at onset, years (range)	34 (14–55)
Median observation period, years for 32 patients (range)	5 (0–21)
Metastasis	4
Treatment	36
Surgical treatment	34
Number of surgeries performed	
1	29
2	3
≥4	2
Type of surgery	
Partial pancreatectomy or enucleation	26
Total pancreatectomy	3
Bypass surgery	1
Others	2
No information	2
Nonsurgical treatment	
Systemic chemotherapy	1
TACE	1

VHL von Hippel-Lindau disease, *PNET* pancreatic neuroendocrine tumor, *TACE* transarterial chemoembolization

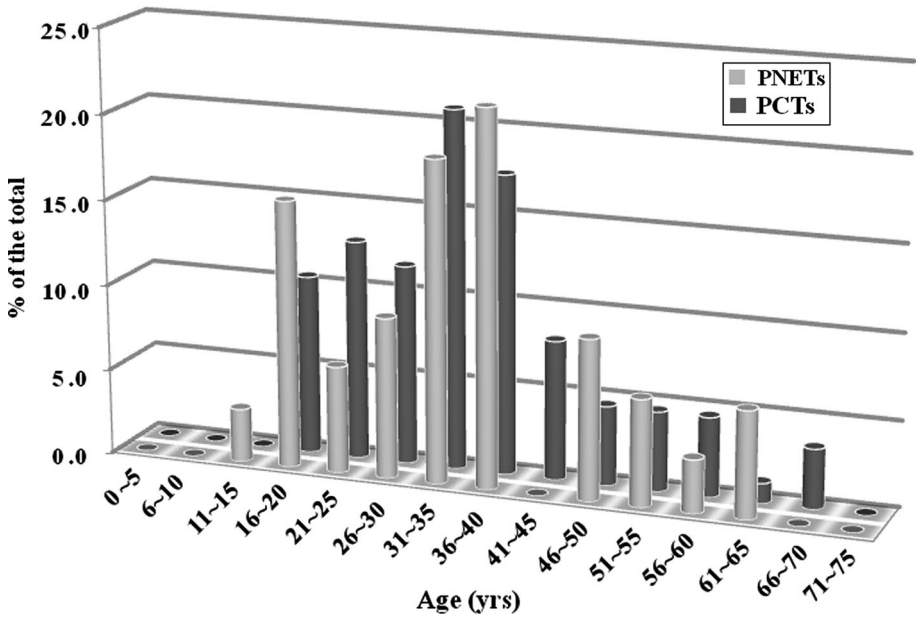

Fig. 1 The onset age distribution of pancreatic endocrine tumors (PNETs) and pancreatic cystic tumors (PCTs) associated with VHL; 254 × 190 mm (96 × 96 DPI)

Table 2 Characteristics of Japanese patients with VHL-associated PCT

Total patients with VHL	377
Patients with concurrent PCT	152 (40.3 %)
Gender	
Male	70
Female	82
Median age at onset, years (range)	33 (15–68)
Surgery or drainage	14
Type of treatment	
Partial pancreatectomy	8
Cystectomy	1
Total pancreatectomy	1
Choledochojejunostomy	1
Cyst paracentesis	1
Biliary stent placement	1
Pancreatic duct stent placement	1

VHL von Hippel-Lindau disease, *PCT* pancreatic cystic tumor

hemangioblastomas of the CNS and renal cancer, and no deaths caused by PNET were observed.

PCT associated with VHL

Among the 377 patients with VHL, 152 had PCT, and the frequency of concurrent PCT was 40.3 % (Table 2). Of the patients with concurrent PCT, 70 were male and 82 were female. The median age at onset was 33 years (range 15–68). The frequency of onset increased from the latter teen years and reached a peak at a range of 30–34 years (Fig. 1). According to data reported in Europe and the USA, concurrent PCT was observed in 7–71 % of patients with VHL [5–7], which is consistent with the data obtained in Japan. In Japan, metastasis of PCT was not observed in any of the patients at diagnosis. In 9.2 % (14/152) of patients, PCT was treated by surgery or drainage (Table 2). In most patients, PCT was routinely checked but not treated. The types of therapies used to treat PCT were: 8 patients had a partial pancreatectomy, 1 patient had a cystectomy, and 1 patient had a total pancreatectomy [8]. Moreover, the following surgical therapies were performed on 1 patient each: cyst paracentesis, choledochojejunostomy, pancreatic duct stent placement and biliary stent placement. None of the reported deaths were related to pancreatic cysts.

Concurrent PNET and PCT with VHL

Among the 377 patients with VHL, 17 (4.5 %) had both PNET and PCT. In other words, 17 of 53 patients (32.1 %) with PNET associated with VHL also had PCT; alternatively, 17 of 152 patients (11.2 %) with PCT associated with VHL also had PNET.

Pancreatic involvement with subtype of VHL

VHL is classified in two subtypes, type 1 concurrent without adrenal pheochromocytoma and type 2 with adrenal pheochromocytoma [2]. In this study, the frequency of type 1 and 2 was 83 % (313/377) and 17 % (64/377), respectively (Table 3). The number of patients with pancreatic involvement including PNET and PCT in each subtype of VHL was 153 in VHL type 1 (153/313; 48.9 %) vs. 35 in VHL type 2 (35/64; 54.7 %) ($P = 0.628$ using

Table 3 Classification of VHL subtypes

	VHL type 1	VHL type 2	Total (*n*)	*P* value
VHL patients	313 (83.0 %; 313/377)	64 (17.0 %; 64/377)	377	
VHL with PNET	29 (9.3 %; 29/313)	24 (37.5 %; 24/64)	53	<0.01*
VHL with PCT	135 (43.1 %; 135/313)	17 (26.6 %; 17/64)	152	0.09
VHL with pancreatic lesion	153 (48.9 %; 153/313)	35 (54.7 %; 35/64)	188	0.628

P value was calculated using 2 × 2 chi-square test

VHL von Hippel-Lindau disease, *PNET* pancreatic neuroendocrine tumor, *PCT* pancreatic cystic tumor

* Significant difference

2 × 2 chi-square test). Especially the number of patients with PNET associated with VHL type 1 and 2 was 29 (29/313; 9.3 %) and 24 (24/64; 37.5 %), which suggested that the patients with VHL type 2 had significantly more PNETs than those with VHL type 1 ($P < 0.01$ using 2 × 2 chi-square test).

Discussion

In most cases, VHL-associated PNET is nonfunctional and asymptomatic [5]. In typical cases, there are multiple tumors, and there is no difference in the intrapancreatic distribution of tumors from the head to tail [5]. Unlike patients with multiple endocrine neoplasia type 1, patients with VHL have no nesidioblastosis or hyperplasia of the islets of Langerhans as the background disease of the pancreatic neoplasm [9].

VHL is classified into two subtypes; type 1 is not associated with adrenal pheochromocytoma and type 2 is [2]. In the previous study, pheochromocytoma was reported to arise in 10–20 % of patients with VHL [2], and in this study we obtained similar results in the Japanese population. Binkovitz et al. [9] suggested the frequent coexistence of PNET and pheochromocytoma. In contrast, Hammel et al. [6] reported that patients with pancreatic lesions had significantly fewer pheochromocytomas than those without pancreatic lesions. Our present data support those of Binkovitz.

Because abdominal surveillance is usually performed from a young age, VHL-associated PNET is often found at an earlier stage than primary PNET [11]. Moreover, distant metastases are only found in 11–20 % of patients at diagnosis [12]. Charlesworth et al. recently published a systematic review of 11 studies (excluding case studies) of VHL-associated pancreatic lesions [5–7, 10, 12–19]. According to their review, 211 (15 %) of the 1,442 patients with VHL also had PNET [12]. Metastasis was observed in 27 VHL patients (12.8 %) with concurrent PNET. In the present study, concurrent PNET and its metastasis were observed in 14.1 and 7.5 % of Japanese VHL patients, respectively. In the present study, the PNET size was not studied. However, according to Libutti et al. [14, 15], the median size of PNETs is larger in patients with metastasis than in patients without metastasis; tumors are 2 cm in patients without metastasis and 5 cm in patients with metastases.

PNET typically grows slowly. Blansfield et al. [18] reported that PNET was the cause of death only in 0.3 % of patients with VHL (633 patients in total) and in 1.9 % of patients with concurrent PNET and VHL (108 patients). In most cases, the cause of death in patients with VHL is CNS hemangioblastoma or renal cancer. Accordingly, the prognosis of PNET associated with VHL is considered to be favorable [18]. Consistently, none of the patients in the present study died from PNET.

Generally, in patients without VHL, PNETs should be treated according to the degree of differentiation and malignancy after evaluating the functionality, disease stage and metastasis of the tumor. As a fundamental rule, surgical resection of PNET is recommended [20]. However, in patients with VHL-associated PNET, surgical treatment should be selected while considering the pathophysiology of VHL. In other words, because many patients with VHL-associated CNS hemangioblastomas or renal cancer have to undergo multiple surgeries [21], we should remind ourselves that the patients may have to undergo many surgeries in their lifetime even though PNET is rarely the direct cause of death [18]. For these reasons, we should choose the surgical treatment option much more carefully in patients with VHL-associated PNET than in those with VHL-unassociated PNET.

Basically, the decision can be made based on the tumor size; Libutti et al. [14, 15] recommended surgery when the tumor size is 3 cm or larger in the pancreatic tail region and 2 cm or larger in the head region. Because of the anatomic constraints in this region and the desire to perform an enucleation rather than a resection of the head of the pancreas, they recommended removing the tumors before they reach a size of 3 cm. Blansfield et al. [18] recommended surgery when the tumor size is 3 cm or larger. They also proposed a tumor doubling time

of <500 days as another factor to be considered when making decisions about the surgical treatment [18]. Therefore, in patients with VHL, surgery is not necessarily the first treatment choice for small PNETs. Moreover, in patients with primary PNET, distant metastases were reported at diagnosis in 64 % of patients in Europe and the USA [22] and in 21 % of patients in Japan [23]. In the present study, distant metastases of VHL-associated PNET were observed in only 7.5 % of patients. The malignant potential of VHL-associated and VHL-unassociated PNETs might differ. However, in this study, we could not obtain the exact data on the observation period for all of the VHL patients, so further survey and analysis are required to conclude whether the prognosis of VHL-associated PNETs is better than that of VHL-unrelated PNETs in Japan. Furthermore, an algorithm for the therapeutic strategy for VHL-associated PNETs needs to be established based on long-term follow-up studies on the prognosis of PNETs in Japanese VHL patients, including the use of molecular-targeted drugs, such as everolimus [24] and sunitinib [25], the efficacy of which has recently been shown for progressive PNET.

On the other hand, serous cystadenoma (SCA) of the pancreas was observed in most patients with VHL-associated PCT with a diagnosed tissue type [5–7]. According to a systemic review by Charlesworth et al. [10], PCT was observed in 47 % of patients with VHL, while SCA was observed in 11 % of these patients. In general, malignant transformation of pancreatic SCA rarely occurs; thus, neither treatment nor follow-up is necessary until the cyst becomes large enough to indicate a clinical symptom, such as a suppressive symptom in relation to neighboring organs [2]. In adult VHL patients, however, a careful differential diagnosis is required between PCT and other cystic lesions of the pancreas (intraductal papillary mucinous neoplasm and mucinous cystic neoplasm) that can potentially transform into malignant lesions. In the present study, 10 patients had a history of resection, including 1 patient who received a total pancreatectomy [8] as well as a cystectomy and partial pancreatectomy. Unfortunately, we have no clinical information on why surgery was selected in these patients. Additional studies are required to establish guidelines for the use of surgical treatments.

In conclusion, this study showed no significant difference in epidemiology between Japanese and non-Japanese VHL patients, suggesting no interspecies difference. To evaluate the prognosis of the pancreatic involvement in Japanese VHL patients and establish the therapeutic strategy, further analysis of VHL pathophysiology and long-term follow-up study of patients is required.

Conflict of interest The authors declare that they have no conflict of interest.

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