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Research Article

von Hippel-Lindau Disease-Associated Pheochromocytoma: Epidemiology, Clinical Characteristics, and Screening and Surveillance Protocols in Japan

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Abstract

von Hippel-Lindau (VHL) disease is an autosomal dominantly inherited syndrome characterized by a predisposition to various neoplastic lesions. To clarify the epidemiology and clinical characteristics of VHL-associated pheochromocytoma (PHEO) in Japan, we have summarized VHL-PHEO characteristics from a nationwide cross-sectional survey for VHL disease on the basis of the epidemiological study program for incurable disease by the Japanese Ministry of Health, Labour and Welfare. The details of the survey included age of onset, sex, living area, treatment modalities, and patient outcome. The incidence rate of PHEO in VHL disease was 15% (62/409). Males and females were equally affected. The mean and median ages of onset were 29.7 and 31.5 years, respectively. The age of onset was distributed between 10 and 75 years and presented two peaks between 15-20 and 35-40 years. Twenty-six (42%) bilateral cases, 8 (13%) extra-adrenal paragangliomas, and 4 (6.4%) malignant cases were observed. Forty-one (65%) patients underwent surgical resection once and 13 (19%) underwent 2 or 3 surgeries, whereas six (10%) were surveyed without surgical treatment. Fourteen of 26 bilateral PHEOs (56%) received steroid replacement therapy following bilateral adrenal surgeries. Four cases died from metastatic PHEOs and one from a severe infection during steroid replacement therapy. None of the patients died of cardiovascular complications due to PHEO crisis. From the current survey results, it is concluded that VHL-PHEO characteristics in Japan are similar to those in Western countries. Based on the above, we propose a screening and surveillance protocol for VHL-PHEO in Japan. Due to its rare incidence and unique characteristics, the continuous survey and registration of VHL-PHEO will remain important to understanding the disease's nature.

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ABBREVIATIONS

VHL: von Hippel-Lindau disease; PHEO: Pheochromocytoma.

INTRODUCTION

Von Hippel-Lindau disease (VHL) (MIM 193300) is an autosomal dominantly inherited disorder characterized by a predisposition to develop multiple tumors and cystic lesions in many organ systems [1,2]. These lesions include retinal angiomas, central nervous system (CNS) (cerebellar, brainstem, and spinal cord) hemangioblastomas, endolymphatic sac tumors, pancreatic neuroendocrine tumors, pheochromocytomas, renal cell carcinomas (RCCs), endolymphatic sac tumors, epididymal cystadenomas in males, and broad ligament cystadenomas in females [1-5]. The disease incidence is estimated at 1 in 36,000-46,000 live births in Western countries, and the disease penetrance is over 90% by 65 years of age [2,6,7].

The gene responsible for VHL is located on the short arm of chromosome 3 (3p25.3); in 1993 the gene was identified as a *VHL* tumor suppressor by a positional cloning approach [8,9]. The *VHL* gene is categorized as a classic tumor suppressor. According to Knudson's two-hit mechanisms, germline mutation in one allele is present in all the cells of affected individuals who inherit the genetic trait. The second *VHL* allele is somatically inactivated in tumors associated with VHL patients [10]. On the other hand, both *VHL* alleles are found to be inactivated by two independent somatic alterations in tumors with non-inherited sporadic occurrence, including clear cell subtype RCC, CNS hemangioblastoma, and pheochromocytoma [11-15].

VHL disease (or the VHL family) is clinically classified into two major categories, depending on the absence or presence of pheochromocytoma as a tumor manifestation [16-18]. Type 1 patients have almost no risk of developing pheochromocytoma, but present other cardinal manifestations. Approximately 80% of VHL families are type 1, while the remaining 20% of families are categorized as type 2, having a high risk of pheochromocytoma. The frequency of pheochromocytoma is 10-20% among all VHL patients, whereas it rises to as many as 70-80% of affected members in the type 2 family. Type 2 is further classified into three subtypes, labeled 2A, 2B, and 2C. Type 2A patients have a low risk of developing RCC, while type 2B patients have a high risk. Both types of patients develop CNS and retinal hemangiomas. On the other hand, Type 2C patients develop pheochromocytomas exclusively [17,19,20]. Genotype-phenotype correlation analyses demonstrated that VHL type 1 families have a variety of mutational types, including missense, nonsense, and frameshift mutations in the highly conserved region and large genomic deletions. These mutations are likely to result in a gross alteration or complete loss of pVHL functions. In contrast, the majority of type 2 families have missense mutations at specific amino acid positions in the pVHL, affecting particular pVHL functions [17-20].

VHL-associated pheochromocytomas (VHL-PHEOs) have been characterized mainly in the Western population; as such, the epidemiology and clinical features in Japanese Asian population have not previously been elucidated. In this study, we first performed nationwide surveillance of VHL patients in Japan. We summarize the current epidemiology and clinical status of VHL-PHEO herein, and we also propose a screening and surveillance protocol for VHL-PHEO patients in Japan.

MATERIALS AND METHODS

Nationwide surveillance of VHL patient in Japan

We performed nationwide, cross-sectional surveillance of VHL patients in Japan. In the first survey, we asked a total of 4,545 medical doctors with specialties in urology (n=1,200), neurosurgery (1,141), ophthalmology (1,149), and pancreatic diseases (1,055) whether they had treated any VHL patients during the 2 years from April 2009 to March 2011. Subsequently, in a second survey, an inquiry-based investigation was carried out with 240 doctors who replied that they had been treating patients diagnosed with VHL. The final response rate was 70.4% for the 2nd questionnaire. In each VHL patient, investigations of all VHL-related diseases were performed, including the onset age of each VHL-related disease, living prefecture, sex, family history of VHL, with or without genetic testing, information on survival and outcome, and the types of treatment modalities. The status of corticosteroid replacement therapy after surgery was also asked for the VHL-PHEO patients. The study protocol was approved by the institutional ethics committee of the Koch University School of Medicine.

RESULTS AND DISCUSSION

Epidemiology

In total, 409 VHL patients were registered by corresponding doctors. Among them, 62 (15%) were suffering from PHEO and considered to be VHL type 2 patients. The distribution of onset age in VHL-PHEO was from 10 to 75 years (median=31.5, mean=29.7±2.0 years), and 2 major age peaks (15-20 and 35-40 years) were observed (Figure 1-A). There was a tendency for the type 2A (without RCC) patients to belong to the younger age peak and type 2B (with RCC) to the elder peak, respectively (Figure 1-B, C).

The involvement of PHEO in bilateral adrenal glands was observed in 26 out of 62 (42%) patients, and extra-adrenal PHEO (paraganglioma) was observed in 8 (13%). There was no difference between the sex distribution (31 cases each in males and females). Malignant PHEOs with distant metastasis were present in 4 cases (6.5%) with ages of onset of 21, 26, 33, and 50 years, respectively.

Treatments and patient outcomes

The frequency of surgical intervention for PHEO was once in 41 patients, twice in 10, and three times in 1. There was no patient registered who underwent 4 or more PHEO surgeries.

Continuous corticosteroid replacement therapies after surgical intervention were carried out in 14 (56%) of 26 patients with bilateral adrenal PHEOs (Table 1). Steroids were not administered, however, for the remaining 12 cases. Of these 12 patients, adrenal-spearing surgery was done in 8, unilateral adrenal surgery plus watchful surveillance of the contralateral tumor in 3, and observation only in 1.

Regarding patient outcomes, 4 patients with malignant PHEO died of metastases; in addition, another patient died of severe cholecystitis during the steroid replacement therapy after bilateral adrenalectomy. However, no patient was reported to have died of
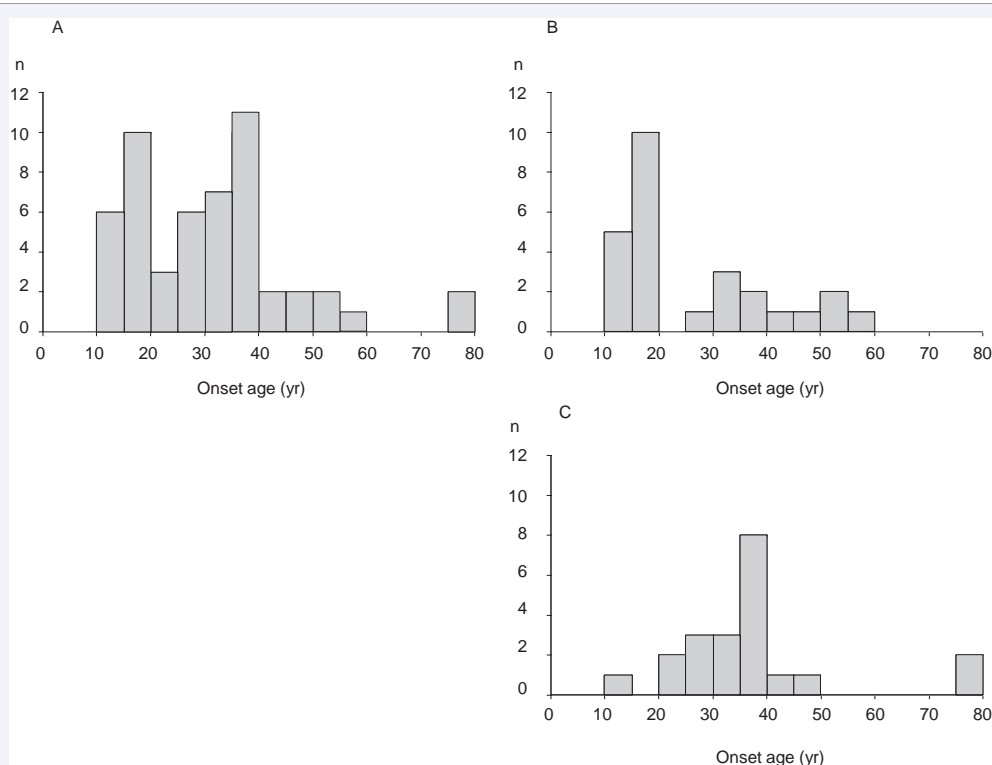
Figure 1 The onset-age distribution of von Hippel-Lindau disease-associated pheochromocytoma in Japan.

Data was available for a total of 52 patients (A), type 2A (without renal cell carcinoma) patients (n=26) (B), and type 2B (with renal cell carcinoma) patients (n=21) (C).

Table 1: Adrenal Surgery and corticosteroid replacement therapy in VHL patient with pheochromocytoma.

Surgery	Number of Patients with/without corticosteroid	
	With	**Without**
Bilateral adrenalectomy	5	0
Unilateral adrenalectomy +contralateral partial adrenalectomy or tumor enucleation	2	7
Unilateral adrenalectomy	1	27
Bilateral partial adrenalectomy or tumor enucleation	0	1
unilateral partial adrenalectomy or tumor enucleation	0	3

cardiovascular complications due to PHEO crisis. At the patient-registration time, a total of 10 VHL-PHEOs were following up, including 4 with the administration of antihypertensive agents and 6 with watchful observation without any treatment due to asyndromic PHEO.

In this study, we first conducted a nationwide surveillance study of VHL patients in Japan. As a result, a total of 409 VHL patients were registered. We then identified the epidemiological and clinical characteristics of VHL patients with PHEO; i.e. VHL type 2, in the Japanese Asian population. Epidemiological characteristics observed in a Japanese patient cohort seem to be basically the same as those reported previously for Western patients, although some older patients (age of onset: range= 10-75 years) and a somewhat higher incidence of malignant PHEO (6.4%) was seen in the Japanese patient cohort compared to the U.S. and European series (age of onset: range 3-60 years and malignant PHEO: 1.6-3.6%) [21,22]. Another interesting point is

that we observed that the VHL type 2A patients (without RCC) tended to have a relatively younger onset age (10-19 years), while type 2B (with RCC) patients tended to have an older age of onset (30-39 years) in the Japanese population.

Previous work has demonstrated that the subset of VHL-associated PHEO shows relatively low hormonal activity compared with other inherited forms of PHEO, including multiple neuroendocrine neoplasia type II (MEN2), paraganglioma syndromes (PGLs), and neurofibromatosis type I (NF1) as well as to PHEO in sporadic occurrence [23-26]. According to the NIH/NCI in the U.S.A. series, among VHL-PHEO patients newly diagnosed by family screening, 35% were asyndromic and non-functioning with a relatively small tumor size [21]. Our surveillance also demonstrated that a substantial number of Japanese VHL-PHEO patients present an asyndromic non-functioning phenotype, and these patients were subsequently followed by observation. Unfortunately, in the current survey, we
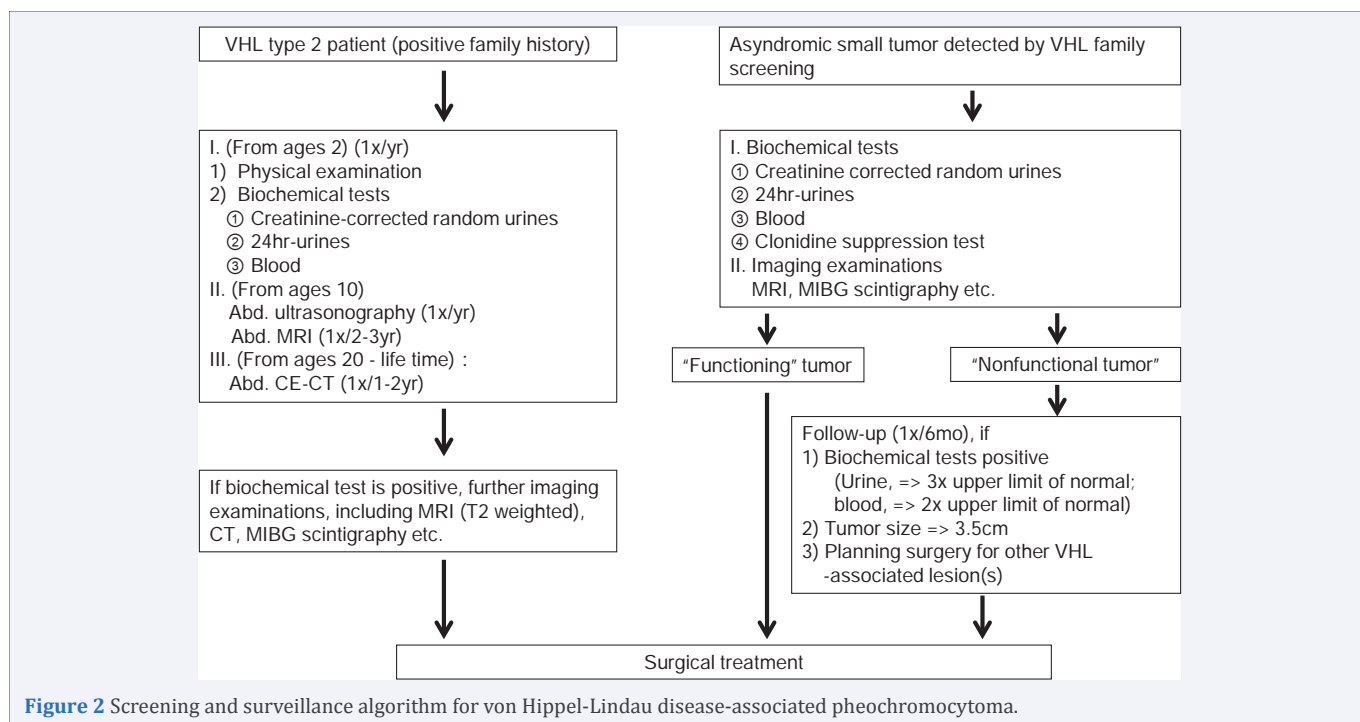
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Figure 2 Screening and surveillance algorithm for von Hippel-Lindau disease-associated pheochromocytoma.

did not collect other detailed information such as the PHEO tumor size and location, tumor doubling time, followup period, exact values of catecholamines, and so on. It is our hope that, in the next survey, additional precise data will be collected to further our understanding of this unique and rare disease condition.

Screening and surveillance protocol for VHL-associated PHEO

Based on previous findings together with the current survey results regarding Japanese VHL-PHEO, we propose the following protocol for the screening and surveillance of the disease (Figure 2). In the type 2 VHL family, annual i) physical examination, ii) biochemical tests, including adrenaline, noradrenaline, dopamine, metanephrine, and normetanephrine, for ① blood and ② urine (24-hr urines or alternatively, creatinine corrected random urine specimens), from age 2. Abdominal ultrasonography (yearly) or plain magnetic resonance imaging (MRI) (1x/2-3yr) should start from age 10. MRI is preferred to computed tomography (CT) in children to avoid radiation exposure during development. From age 20, Abdominal CT with contrast enhancement (CE) (1x/1-2yr) is begun. CT-CE can allow for the screening of other VHL abdominal lesions, including simultaneous screening of the pancreas and kidneys. MIBG scintigraphy is not recommended for screening due to radiation exposure and cost. It should be done to provide a definitive diagnosis for PHEO localization. For a patient who is planning surgery for other VHL lesion(s) or a female patient planning a pregnancy, the absence of a biochemically "functioning" tumor within the 6 month should be confirmed.

Diagnosis and treatment

Diagnosis and treatment for VHL-PHEO is basically the same as that for PHEO in the sporadic form. Surgical resection remains the mainstay of treatment for VHL-PHEO. Due to the relatively early onset age, frequent bilateral occurrences, and

a lifetime multiple surgical operations not only for PHEOs but other organ lesions, adrenal-preserving and minimally invasive surgery such as laparoscopic partial adrenalectomy, should be considered whenever possible [26,27]. Additionally, in cases with asyndromic non-functioning PHEO with relatively small size detected by family screening, watchful observation can be selected with both biochemical and imaging evaluations at 6-month intervals. Surgical treatment is then recommended when i) urine or blood biochemical tests become positive (urine, =>3x upper limit of normal; blood, =>2x upper limit of normal), ii) tumor size becomes =>3.5cm, or iii) planning surgery for other VHL-associated lesion(s).

In conclusion, we conducted a first nationwide survey of VHL-PHEO in Japan. We collected a total of 62 VHL-PHEO patients. The epidemiology in Japanese patients seems to be basically the same as that previously reported in Western patients. In addition, some unique characteristics are also emerging from the current survey. Since the relatively rare incidence and unique nature of disease, prospective continuous registrations as well as a phenotype-genotype correlation study in Japanese VHL will be quite important. We have also for the first time proposed a screening and surveillance protocol for Japanese VHL-PHEO patients. We hope that the protocol will be prospectively validated and updated continuously according to the new diagnostic and therapeutic procedures.

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