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## Von Hippel-Lindau Disease: Radiologic Screening for Visceral Manifestations<sup>1</sup>

The visceral manifestations of von Hippel-Lindau (VHL) disease can cause significant morbidity and mortality. The authors prospectively screened 37 persons from a single kindred. Twenty-five subjects underwent abdominal ultrasound (US), contrast material-enhanced abdominal computed tomography (CT), and nonenhanced abdominal magnetic resonance (MR) imaging. Eight subjects younger than 16 years of age underwent abdominal US and MR imaging only. Scrotal US was employed in 25 male patients. Eleven subjects had renal cysts or tumors. Contrast-enhanced CT depicted renal abnormalities in 10 of these subjects, US in seven, and MR imaging in nine. Among 12 subjects with pancreatic cysts or tumors, CT showed pancreatic abnormalities in all 12, US in nine, and MR imaging in nine. Three subjects (mean age, 34.5 years) had renal tumors, and three had pancreatic masses. Scrotal US revealed epididymal cystadenomas in seven subjects; two of these tumors were surgically verified. A combination of contrast-enhanced CT and scrotal US in male patients appears to be the best way to screen for visceral manifestations of VHL disease.

**Index terms:** Abdomen, CT, 70.1211 • Abdomen, cysts, 70.312 • Abdomen, MR studies, 70.1214 • Abdomen, US studies, 70.1298 • Adrenal gland, neoplasms, 86.31 • Epididymis, 847.32 • Kidney, cysts, 81.31 • Kidney neoplasms, 81.32 • Pancreas, cysts, 77.31 • Pancreas, neoplasms, 77.31 • Scrotum, US studies, 849.1298

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VON HIPPEL-LINDAU (VHL) disease is a dominant hereditary disorder that produces benign angiomas of the eye and central nervous system (CNS), as well as cysts and neoplasms of the kidneys, pancreas, adrenal glands, and epididymis (1). Screening of asymptomatic patients at risk for VHL disease is expensive and time-consuming, yet there are at least two important justifications for a comprehensive screening program. First, the identification of patients with VHL disease allows accurate genetic counseling (2). Second, early detection of frequently asymptomatic, potentially vision- and/or life-threatening sequelae of VHL disease in family members may enhance both the length and the quality of life (3-5).

A thorough screening program should ideally include evaluation of the eyes, brain, spinal cord, and abdomen. We previously demonstrated that magnetic resonance (MR) imaging of the brain and spinal cord with gadolinium diethylenetriaminepentaacetic acid enhancement is the single most effective means of diagnosing CNS manifestations of VHL dis-

ease (6). In this article we focus on the detection of visceral manifestations of VHL and compare the findings at abdominal computed tomography (CT), ultrasound (US), and MR imaging in a large family. Further, we examine the often-overlooked role of scrotal US.

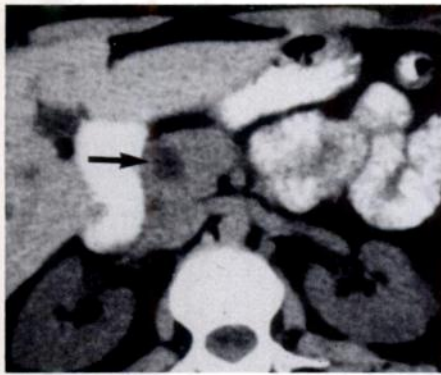
### SUBJECTS AND METHODS

Thirty-seven of 44 persons in a single family who were known to have VHL disease participated in this study. Seven members (one affected, six at risk) were contacted but declined to participate. In 11 subjects (the first 11 in Table 1), VHL lesions had been demonstrated before entry into this study (eight had treated eye lesions, two had undergone prior partial nephrectomy, and one had undergone adrenalectomy). In each case a complete history was obtained, and a physical examination was performed. Unless contraindicated or refused, the screening program consisted of an ophthalmologic examination after pupillary dilation in conjunction with fluorescein angiography; cerebral, spinal, and abdominal MR imaging; contrast-enhanced CT of the head; and CT of the abdomen before and after administration of contrast material. Participants younger than 16 years did not undergo CT.

MR imaging of the abdomen was performed with a 0.5-T system (Vista; Picker International, Highland Heights, Ohio). T1-weighted axial and coronal images were obtained through the abdomen (spin echo [SE] 500/20 [repetition time msec/echo time msec], 192 × 256 matrix, six acquisitions, 10-mm thickness, 50-55-cm field of view). CT was performed with 10-mm sections both before and after the intravenous bolus administration of contrast material (iopamidol [Isovue; Squibb Diagnostics, Princeton, NJ]). The contrast material was administered with a mechanical injector (Medrad, Pittsburgh) at a rate of 1 mL/sec. CT was performed with a 9800 scanner (GE Medical Systems,

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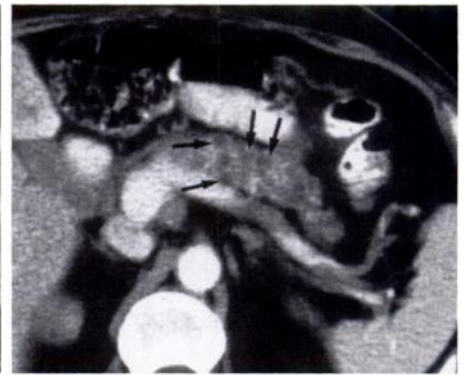
**Abbreviations:** CNS = central nervous system, SE = spin echo, VHL = von Hippel-Lindau.



1.



2.



3.

**Figures 1-3.** (1) CT scan of a 34-year-old man (patient 05-035) demonstrates a single cyst in the head of the pancreas (arrow). He also had cerebral hemangioblastomas and retinal angiomas. (2) CT scan of a 34-year-old woman (patient 05-043) shows multiple pancreatic cysts and a focus of calcification in the tail of the pancreas (arrow). (3) CT scan of a 49-year-old woman (patient 04-029) demonstrates multicystic changes throughout the pancreas (arrows), replacing most of the normal parenchyma. Despite this appearance, she had normal exocrine function.

Milwaukee) in the dynamic mode, so that two images (3.5 seconds each) were followed by a 7-second "breather." Sonograms were obtained with 3-5-MHz transducers for abdominal studies (Wide VU [Diasonics, South San Francisco, Calif] or 128 [Acuson, Mountain View, Calif]) and with a 5-MHz small parts transducer (Acuson) for scrotal imaging. Angiography was performed in seven subjects for the evaluation of specific abdominal abnormalities (renal mass in five, pancreatic mass in one, both in one). Each examination was reviewed prospectively and independently.

We obtained surgical confirmation of visceral imaging findings in five subjects, but the rest of the findings were not surgically verified.

## RESULTS

Twenty-five of the 37 subjects underwent all three abdominal studies, and the data from those studies form the basis of this comparative analysis. Summaries of the visceral manifestations of VHL disease and imaging results are found in Tables 1 and 2. One subject was examined with US alone, and another was not examined, at parental request.

Of the 25 adult subjects who underwent CT, MR imaging, and US, 18 were eventually given a diagnosis of VHL disease, based on the criteria proposed by Melmon and Rosen (1). These criteria specify that patients with VHL disease must have (a) a close relative with a documented hemangioblastoma in the CNS and (b) at least one lesion of the Lindau complex (ie, CNS hemangioblastomas, retinal angiomas, multiple renal cysts, renal adenocarcinoma, pancreatic cysts, cystadenocarcinoma, islet cell tumor, pheochromocytoma, or epididymal cystadenoma). Visceral

**Table 1**  
**Summary of Patient Findings**

Patient No.	Age (y)	Renal Cysts*			Pancreatic Cysts*			Other Abnormalities†			
		CT	US	MR	CT	US	MR	Adrenal	Epididymis	CNS	Eye
06-018	16	1 (0)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	N	NA	Y	Y
05-043	34	5 (0)	4 (0)	5 (0)	15 (0)	4 (0)	8 (0)	N	NA	Y	Y
05-032	37	0 (0)	0 (0)	0 (0)	2 (0)	2 (0)	0 (0)	N	NA	Y	Y
04-029	49	0 (1)	0 (1)	0 (1)	20 (0)	10 (0)	1 (0)	N	NA	Y	Y
05-049	31	20 (1)	20 (1)	12 (1)	4 (0)	0 (0)	4 (0)	N	N	Y	P
05-035	34	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	1 (0)	N	NA	Y	Y
05-048	28	2 (0)	0 (0)	1 (0)	1 (0)	0 (0)	1 (0)	N	N	Y	Y
05-039	31	2 (1)	1 (1)	3 (1)	15 (1)	15 (0)	15 (0)	N	N	Y	Y
05-040	26	24 (0)	20 (2)	20 (1)	2 (0)	2 (0)	2 (0)	Y	Y	Y	Y
05-005	25	1 (0)	0 (0)	0 (0)	8 (1)	5 (1)	1 (1)	Y	Y	Y	P
04-030	60	1 (0)	0 (0)	1 (0)	4 (1)	2 (0)	0 (0)	N	Y	N	P
04-047	62	2 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	N	N	N	Y
05-016	30	2 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	N	Y	N	N
04-033	53	2 (0)	2 (0)	0 (0)	3 (0)	3 (0)	4 (0)	N	N	Y	N
05-008	19	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N	Y	Y	Y
05-006	22	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N	Y	Y	P
05-045	34	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	N	Y	N	P
05-003	21	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	N	N	N	N
05-027	38	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N	N	Y	N
06-003	20	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N	NA	N	NA
05-037	31	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N	N	N	N
05-004	24	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	N	NA	N	N
05-041	30	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N	N	N	N
04-037	53	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N	NA	N	N
05-007	27	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N	NA	N	P

\* Number of masses in parentheses.

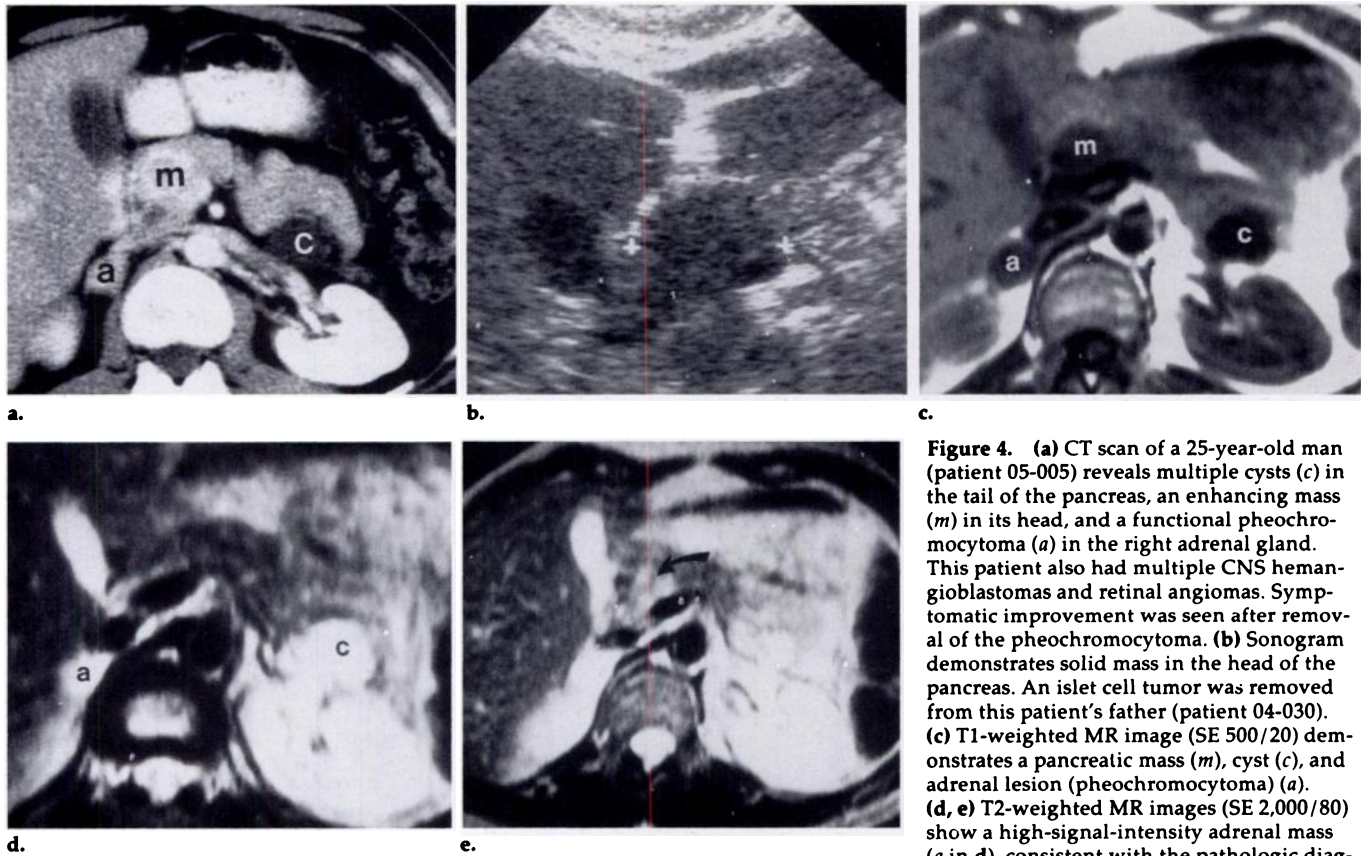
† NA = not applicable (female patients), Y = yes, N = no, P = probable.

manifestations of VHL disease (including scrotal abnormalities) were found in 17 subjects and were the only expression of the disease in three (Tables 1, 2). CT demonstrated all 14 cases of pancreatic or renal manifestations; three cases each were missed at abdominal US and MR imaging.

Three of the eight subjects younger than 16 years who underwent comparative MR imaging and US were given an ultimate diagnosis of VHL disease with ocular and/or CNS findings. No visceral manifestations were demonstrated in this group.

## Pancreatic Disease

Cysts were evenly distributed throughout the pancreas, from the uncinate process to the pancreatic tail (Fig 1). Pancreatic cystic lesions were often associated (eight of 12 subjects) with several small foci of calcifications on CT scans (Fig 2). In three subjects the pancreas was virtually replaced by cysts too numerous to count (Fig 3). One of these subjects had pancreatic insufficiency with diabetes mellitus and steatorrhea. Three subjects had pancreatic masses; two masses were seen only with CT,



**Figure 4.** (a) CT scan of a 25-year-old man (patient 05-005) reveals multiple cysts (c) in the tail of the pancreas, an enhancing mass (m) in its head, and a functional pheochromocytoma (a) in the right adrenal gland. This patient also had multiple CNS hemangioblastomas and retinal angiomas. Symptomatic improvement was seen after removal of the pheochromocytoma. (b) Sonogram demonstrates solid mass in the head of the pancreas. An islet cell tumor was removed from this patient's father (patient 04-030). (c) T1-weighted MR image (SE 500/20) demonstrates a pancreatic mass (m), cyst (c), and adrenal lesion (pheochromocytoma) (a). (d, e) T2-weighted MR images (SE 2,000/80) show a high-signal-intensity adrenal mass (a in d), consistent with the pathologic diagnosis of pheochromocytoma. Although the pancreatic cyst (c) is seen in the tail in d, the mass is better seen in e (obtained at a lower level) as a poorly defined area of increased signal intensity.

**Table 2**  
Renal and Pancreatic Findings at CT, US, and MR Imaging

CT	US		MR Imaging	
	Positive	Negative	Positive	Negative
Renal*				
Positive (n = 12)	7	5	10	2
Negative (n = 13)	0	13	3	10
Total (n = 25)	7	18	13	12
Pancreatic†				
Positive (n = 12)	9	3	8	4
Negative (n = 13)	0	13	3	10
Total (n = 25)	9	16	11	14

\*  $P < .025$  for correlation with US,  $P < .05$  for correlation with MR imaging.  
†  $P < .05$  for correlation with both US and MR imaging.

and a third was seen with CT, MR imaging, and US (Fig 4). Confirmatory angiography was performed in two cases of pancreatic mass. To date, only one of the solid masses has been surgically removed, although a pancreatic islet cell tumor had been previously removed from one subject. Pancreatic cysts were discovered as early as age 16 years in one family member.

CT demonstrated all pancreatic abnormalities, including cysts, in 12 subjects. US and MR imaging each demonstrated pancreatic abnormalities in nine patients. Limitations of MR imaging included its inability to distinguish cysts from fluid-filled adjacent bowel or to demonstrate calci-

fications. Image degradation due to motion artifact interfered with image quality. Pancreatic US failed to depict the pancreatic body and tail adequately in half of the subjects due to overlying bowel. The pancreatic tail was the only portion of the pancreas affected by VHL disease in five of the 12 subjects.

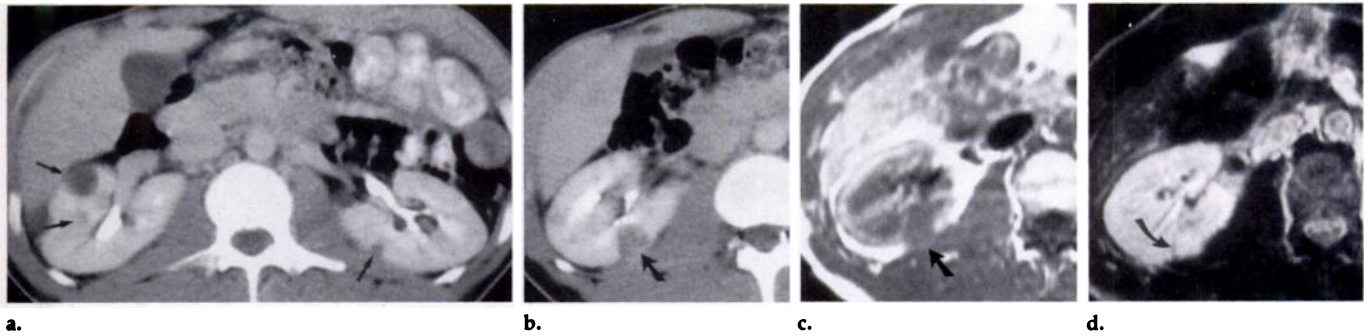
### Renal Lesions

Renal abnormalities were detected in 10 subjects and were accompanied by pancreatic involvement in eight (Table 1). Isolated renal cysts (five or fewer per kidney) occurred in eight subjects (aged 16–62 years; mean, 38 years). Multiple renal cysts (more

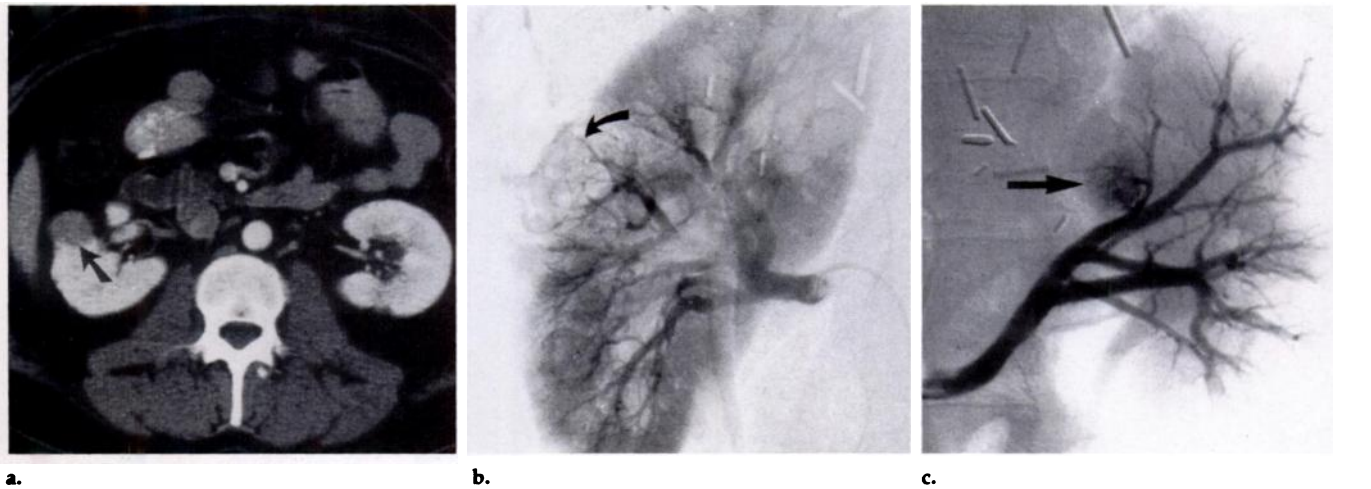
than five per kidney) occurred in two subjects (aged 26 and 31 years). Solid masses were discovered in four subjects (aged 26–49 years; mean, 34 years) and were associated with additional renal cysts in three of four subjects (Fig 5). Solid masses were always accompanied by pancreatic disease. One subject underwent a preoperative angiogram that revealed a contralateral renal mass not detected with CT, US, or MR imaging (Fig 6). The findings at surgery confirmed that both solid lesions were renal carcinomas. However, numerous additional lesions preoperatively classified as cysts on the basis of findings obtained with the three modalities were discovered to have tumor foci within their walls (Fig 6). CT demonstrated all cases of renal disease, US demonstrated disease in seven subjects, and MR imaging demonstrated it in nine.

### Adrenal Lesions

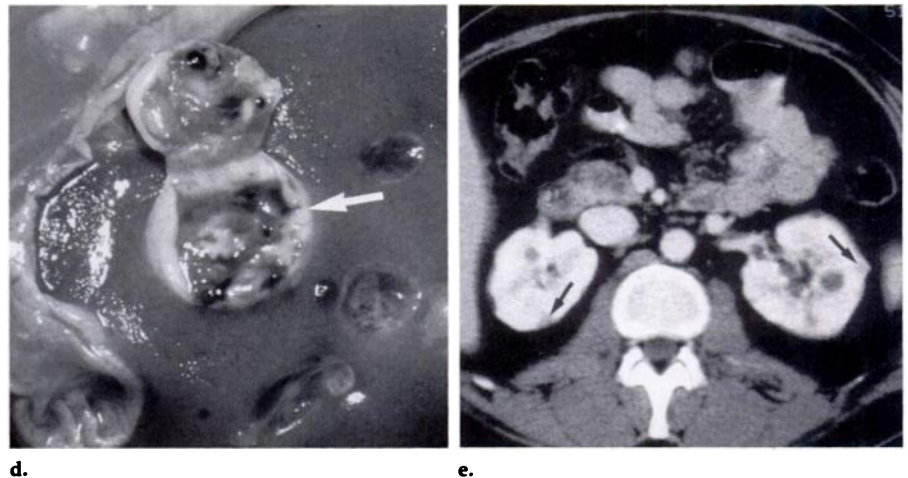
Only one subject (aged 26 years) in this study had a pheochromocytoma (Fig 4). Historically, another subject (patient 05-040) in this family had



**Figure 5.** (a) CT scan of a 31-year-old man (patient 05-049) demonstrates multiple bilateral renal cysts (arrows). (b) CT scan obtained at a lower level demonstrates a solid renal mass measuring 2 cm in diameter (arrow). (c) On a T1-weighted MR image (SE 500/20), the signal intensity of the mass is equivalent to that of the medulla (arrow). (d) T2-weighted MR image (SE 2,000/80) demonstrates high signal intensity within the solid lesion (arrow), nonspecific for the diagnosis of renal carcinoma.



**Figure 6.** (a) CT scan of a 31-year-old man (patient 05-039) shows a solid renal mass in the right kidney (arrow). US and MR findings confirmed the presence of this lesion. (b) Preoperative angiogram demonstrates a mass with neovascularity (arrow). (c) Preoperative angiogram demonstrates the tumor blush of a 1-cm contralateral renal mass (arrow) not detected with noninvasive techniques. (d) Surgical resection of both kidneys yielded solid tumors. In addition, multiple cysts contained mural foci of renal carcinoma (arrow); one from the right kidney is illustrated. (e) CT scan depicts several small atypical cystic lesions (arrows) in the periphery of the kidneys, which proved at surgery to harbor renal carcinoma.



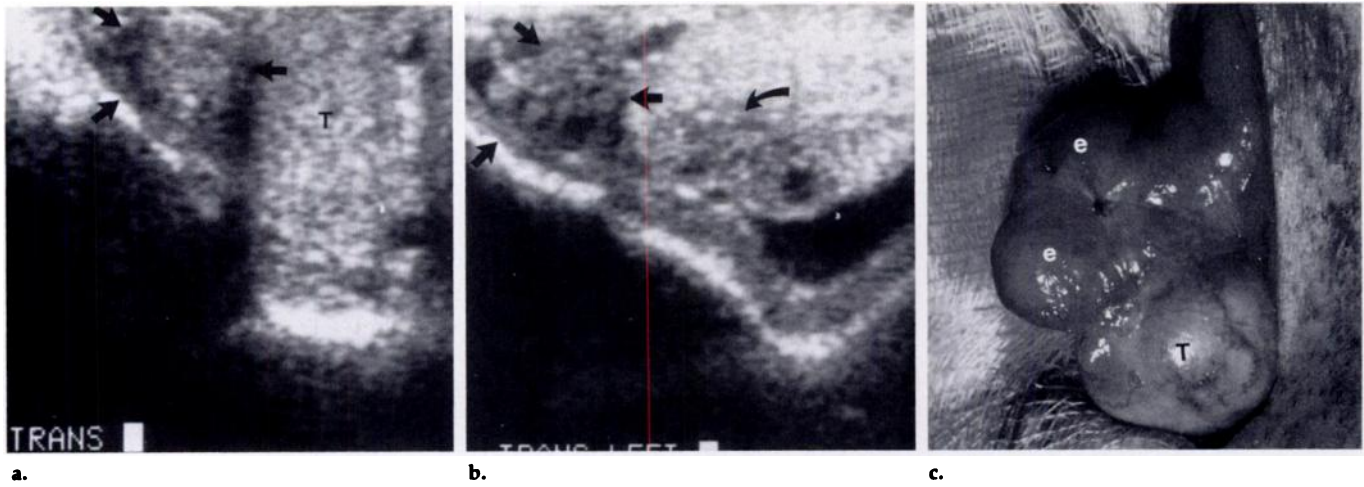
undergone removal of bilateral pheochromocytomas at age 22 years. All three modalities demonstrated the adrenal mass, which measured 3 cm in diameter. The T2-weighted image (2,000/80) demonstrated high signal intensity relative to liver, with a signal-intensity ratio of 3.5.

### Scrotal Abnormalities

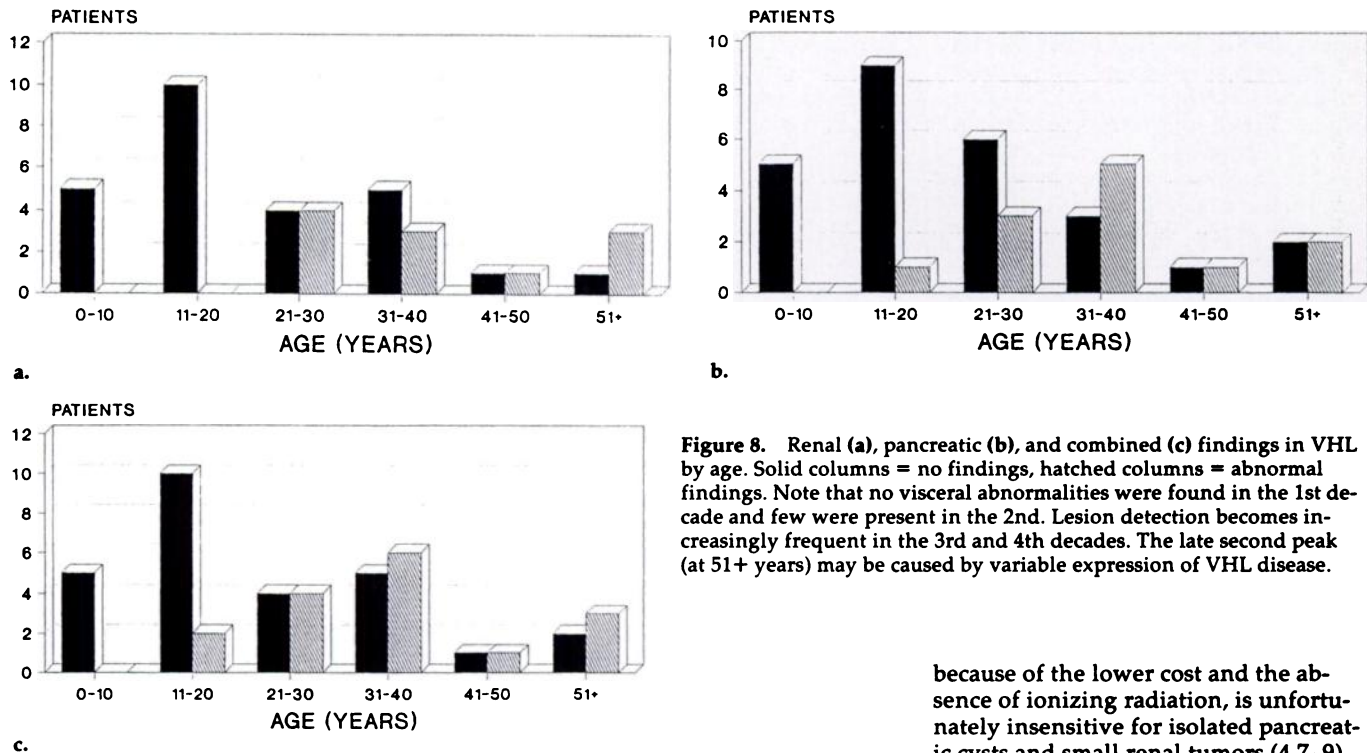
Scrotal US was performed in 25 subjects, aged 4–62 years. The findings were positive in seven subjects

(28%) (aged 19–60 years; mean, 33 years), representing 58% of the affected male subjects in this study. The youngest subject with an epididymal lesion was 19 years old. Epididymal involvement was the only visceral manifestation of VHL disease in three subjects, although CNS lesions or ophthalmologic findings were also present. Epididymal masses were predominantly cystic with some solid components (Fig 7) and were usually located in the epididymal head. The solid component ranged in size from

1 to 2.5 cm and contained cysts ranging from 3 mm to 1.5 cm. Although all lesions were palpable, it was often difficult to establish with physical examination alone whether they were in the testicle, epididymis, or spermatic cord. Lesions were bilateral in two cases and were firm at palpation in all cases. The surgical findings confirmed the presence of papillary cystadenomas in two instances (Fig 7). Cystic dilatation of the rete testis was also found in one case (Fig 7).



**Figure 7.** Manifestations of epididymal cystadenomas in VHL disease. (a) Transaxial sonogram of a 25-year-old man (patient 05-005) [Fig 4] demonstrates a palpable solid mass (arrows) in the head of the right epididymis, measuring 15 × 21 mm. The normal epididymal head was not seen. (b) Sonogram of the father of patient 05-005 (patient 04-030), a 60-year-old man with asymptomatic scrotal enlargement, reveals an epididymal mass (straight arrows) with cystic elements. Hypochoic region in testicle (curved arrow) prompted surgical exploration, which revealed cystic dilatation of the rete testis within the mediastinum testis. (c) Intraoperative photograph demonstrates enlarged epididymal mass (e) in patient 04-030. T = testicle.



**Figure 8.** Renal (a), pancreatic (b), and combined (c) findings in VHL by age. Solid columns = no findings, hatched columns = abnormal findings. Note that no visceral abnormalities were found in the 1st decade and few were present in the 2nd. Lesion detection becomes increasingly frequent in the 3rd and 4th decades. The late second peak (at 51+ years) may be caused by variable expression of VHL disease.

## DISCUSSION

Screening in families affected by VHL disease permits timely genetic counseling and early identification of potentially life-threatening sequelae. A screening program should minimally include evaluation of the eyes, CNS, and abdomen. Ophthalmologic screening should begin in the 1st decade of life to preserve sight in affected persons. Accurate, noninvasive imaging of the CNS and abdomen should begin in the early or middle teens. As shown in Figure 8, signs of VHL disease involving the viscera do not occur before the

late teens. However, a number of lethal abdominal malignancies, including renal carcinoma, pheochromocytoma, and pancreatic carcinoma can occur in the late teens and early 20s. The presence of apparently inconsequential lesions, such as pancreatic or renal cysts and epididymal cystadenomas, may place patients at higher risk for subsequent malignancy.

This study demonstrates that contrast-enhanced CT of the abdomen and scrotal US are the best currently available techniques for identifying visceral signs of VHL disease. Abdominal US, although attractive as a screening tool

because of the lower cost and the absence of ionizing radiation, is unfortunately insensitive for isolated pancreatic cysts and small renal tumors (4,7-9). Children younger than 16 years who are at risk for VHL disease may be screened with abdominal US, since less cooperation is needed and there is no exposure to radiation or contrast media. Abdominal MR imaging has a limited role in screening for VHL disease because of its relative insensitivity in the detection of renal and pancreatic lesions, its propensity for false-positive results, and its expense.

Pancreatic complications of VHL disease include pancreatic cysts, serous cystadenomas, solid nonfunctional islet cell tumors, and adenocarcinomas (5). The earliest signs of pancreatic VHL are small discrete cysts, occasionally ac-

accompanied by focal calcifications. As the patient ages, more cysts may develop, gradually replacing pancreatic parenchyma and occasionally giving rise to pancreatic insufficiency with steatorrhea or diabetes (10). In severe cases, normal parenchyma may become difficult to define and may even be confused with a tumor. Solid masses of the pancreas in the family in this study were associated with severe multicystic disease of the remainder of the pancreas. Such masses usually represent non-functional islet cell tumors, although pancreatic adenocarcinoma may also occur (5). Pancreatic lesions were detected slightly earlier than renal lesions in this family (Fig 8).

Renal tumors occur in approximately 25% of patients with VHL disease and are among its most lethal manifestations, accounting for 20%–50% of deaths (5,11). These tumors can be bilateral and multiple in up to 60% of cases (5). They are usually accompanied by severe pancreatic cystic disease. Four of 11 patients with renal cysts in our study had solid renal masses. The average age at detection of renal carcinoma was 34.5 years (range, 26–49 years). This is significantly below the average age at detection of sporadic nonfamilial renal cancers, which typically arise in the 6th decade (12). In addition to solid masses, multiple renal cystic lesions were seen (4,8,9). Foci of early carcinoma or adenomatous hyperplasia were often present in the cyst wall, despite a benign appearance on imaging studies (13,14). Such cysts may eventually give rise to solid tumors as cystic components of otherwise solid masses (13). Thus, all renal cysts in VHL disease must be considered potentially premalignant lesions. Preoperative angiography has proved invaluable for diagnostic confirmation and for identification of additional lesions (Fig 6). Surgical treatment is controversial, ranging from multiple enucleation to bilateral nephrectomy (5,14).

Pheochromocytomas are relatively common, occurring in 5%–60% of patients with VHL disease, which reflects differing familial patterns (4–6,15,16). Urinary and plasma catecholamine levels are used to screen for the diagnosis. However, imaging studies such as CT are essential for tumor localization, because pheochromocytomas may be bilateral or, more rarely, extraadrenal. MR imaging has been used in the diagnosis of pheochromocytomas, because of their characteristically high signal intensity on T2-weighted images (17).

Epididymal cystadenomas most often

arise in the head of the epididymis and are composed of cystic nodules with papillary excrescences arising from the cyst wall (12,18,19). Although reported in only one-fourth of males with VHL disease (19), abnormalities were found in 58% of affected males in our study, probably because such abnormalities were specifically sought with scrotal US. Epididymal cystic and solid masses were found in seven subjects; in all but one case the masses were associated with other manifestations of VHL disease. The presence of epididymal abnormalities is especially helpful in confirmation of a diagnosis of VHL disease when only one or two other findings are present. However, epididymal abnormalities should not be used as the sole criterion for diagnosis, because up to 30% of healthy volunteers will have sonographic evidence of small epididymal cysts (20). For this reason, it is important to correlate the US results with the physical examination findings and the results of other studies. The value of MR imaging in this diagnosis has not been established. The youngest patient with an epididymal mass was 19 years old, and his father had a similar lesion. The counterpart lesion in females, cystadenoma of the broad ligament (21) and ovary, was not observed in this family. The malignant potential of such lesions is not known but is considered low (12). For this reason, a conservative nonsurgical approach seems justified.

The optimal radiologic screening strategy in persons at risk for VHL disease (ie, primary relatives of patients with the diagnosis) has not yet been determined. We use abdominal US and contrast-enhanced MR imaging of the brain and spine as a baseline in persons aged 11 years or older (6). In those aged 16 years or older, we add contrast-enhanced abdominal CT to the screening evaluation. Given its high yield, low cost, and simplicity, scrotal US is a valuable addition to the screening program for male patients. Abdominal US remains useful as a secondary tool in helping distinguish cystic from solid renal lesions, although this determination is made difficult by the large number of lesions frequently encountered. It should be reemphasized that many cystic-appearing renal lesions contain foci of renal cancer. Although a negative radiologic/ophthalmologic screening examination is strong presumptive evidence against the diagnosis of VHL disease, it cannot be said with certainty that manifestations of VHL will not occur later, because of the variable penetrance of this disease. Figure 8 suggests a possible second peak in older patients, raising the possibility that the

disease may develop at a later age or at a much slower rate in some persons. Although this study did not address the issue of medical follow-up, it is apparent that patients with VHL disease require frequent evaluation. The optimal frequency and form of such follow-up must be determined in longitudinal studies. ■

## References

- Melmon KL, Rosen SW. Lindau's disease. *Am J Med* 1964; 36:595–617.
- Yuen J, Lamiell JM, Hsia YE. Impact of a late-onset autosomal dominant precancerous disease on the knowledge and attitudes of a larger kindred. *Birth Defects* 1984; 20:135–146.
- Green JS. Von Hippel-Lindau disease in a Newfoundland kindred. *Can Med Assoc J* 1986; 134:133–146.
- Levine E, Collins D, Horton WA, Schimke RN. CT screening of the abdomen in von Hippel Lindau disease. *AJR* 1982; 139:505–510.
- Lamiell JM, Salazar FG, Hsia YE. Von Hippel-Lindau disease affecting 43 members of a single kindred. *Medicine* 1989; 68:1–29.
- Filling-Katz MR, Choyke PL, Patronas N, et al. Radiologic screening for von Hippel-Lindau disease: the role of Gd-DTPA enhanced MR imaging of the CNS. *J Comput Assist Tomogr* 1989; 13:743–755.
- Amendola MA, Bree RL, Pollack HM, et al. Small renal cell carcinomas: resolving a diagnostic dilemma. *Radiology* 1988; 166:637–645.
- Pyhtinen J, Suramo I, Lohela P, et al. Abdominal ultrasonography and computed tomography in von Hippel-Lindau disease. *Ann Clin Res* 1982; 14:172–176.
- Levine E, Weigel JW, Collins DL. Diagnosis and management of asymptomatic renal cell carcinomas in von Hippel-Lindau syndrome. *Urology* 1983; 22:146–150.
- Fishman RS, Bartholomew LG. Severe pancreatic involvement in three generations in von Hippel-Lindau disease. *Mayo Clin Proc* 1979; 54:329–331.
- Fill WL, Lamiell JM, Polk NO. The radiographic manifestations of von Hippel-Lindau disease. *Radiology* 1979; 133:289–295.
- Peterson RO. Urologic pathology. Philadelphia: Lippincott, 1986; 89.
- Solomon D, Schwartz A. Renal pathology in von Hippel-Lindau disease. *Hum Pathol* 1988; 19:1072–1079.
- Malek RS, Omess PJ, Benson RC, Zincke H. Renal cell carcinoma in von Hippel-Lindau syndrome. *Am J Med* 1987; 82:236–238.
- Neumann HP. Basic criteria for clinical diagnosis and genetic counselling in von Hippel-Lindau disease. *Vasa* 1987; 16:220–226.
- Jennings AM, Smith C, Cole DR, et al. Von Hippel-Lindau disease in a large British family: clinicopathologic features and recommendations for screening and follow-up. *Q J Med* 1988; 66:233–249.
- Reinig JW, Doppman JL, Dwyer AJ, Johnson AR, Knop RH. Adrenal masses differentiated by MR. *Radiology* 1986; 158:81–86.
- Dershaw DD. Sonography of epididymal cystadenoma. *Urol Radiol* 1985; 7:119–120.
- Tsuda H, Fukushima S, Takahashi M, Hirokawa Y, Hayashi R. Familial bilateral papillary cystadenoma of the epididymis: report of three cases in siblings. *Cancer* 1976; 37:1831–1839.
- Leung ML, Gooding GAW, Williams RD. High resolution sonography of scrotal contents in asymptomatic subjects. *AJR* 1984; 143:161.
- Gersell DJ, King TC. Papillary cystadenoma of the mesosalpinx in von Hippel-Lindau disease. *Am J Surg Pathol* 1988; 12:145–149.