Hypothesis: Von Hippel–Lindau disease (VHL) is an autosomal-dominant disorder characterized by benign and malignant tumors involving the central nervous system, kidneys, pancreas, adrenal glands, and paraganglia. Appropriate management of pheochromocytomas and paragangliomas in VHL is evolving as we better understand the genetics and natural course of the disease and master advanced surgical techniques for adrenalectomy.

Design: Retrospective chart review.

Setting: Tertiary referral center.

Patients: A total of 109 patients identified at the Mayo Clinic, Rochester, Minn, with VHL (60 males and 49 females) between January 1, 1975, and June 30, 2000. Seventeen patients (16%) had an identifiable adrenal mass and 3 patients had paragangliomas. Follow-up was complete in all but 2 patients.

Main Outcome Measures: Clinical presentation, preoperative evaluation, surgical management, and outcome.

Results: Three patients with paragangliomas and 13 of 17 patients with adrenal masses underwent surgical resection. Median age at time of diagnosis was 30 years (range, 16–47 years); 8 (40%) were asymptomatic. Fractionated urinary catecholamine and metanephrine concentrations were normal in one third of patients. Computed tomographic scanning identified 20 (83%) of 24 tumors. Adrenalectomies were performed as unilateral or bilateral, open or laparoscopic, and finally, total or cortical-sparing. Seven (50%) of the patients underwent other concurrent abdominal procedures. There were no deaths, with an overall operative morbidity of 2 patients (14%). Only the 2 patients in whom bilateral total adrenalectomies were performed became corticosteroid dependent. No recurrences have been noted to date.

Conclusions: A multidisciplinary approach is imperative for proper examination and monitoring of patients with VHL. Evaluation should begin early in life and always before elective surgery and childbirth. All adrenal masses in patients with VHL should be thoroughly evaluated and most should be resected. Early intervention and advanced surgical techniques better allow for cortical-sparing and laparoscopic procedures. With low recurrence rates, corticosteroid independence can be maintained for prolonged periods.

Arch Surg. 2002;137:682-689
PATIENTS AND METHODS

PATIENTS

By means of the Mayo Medical Index Registry and the Mayo Genetics Department VHL directory, the medical records of 228 patients were reviewed for possible VHL disease between January 1, 1975, and June 30, 2000. All charts were screened on the basis of a known VHL diagnosis, the presence of a first-degree relative with a known VHL diagnosis, or an isolated diagnosis of retinal angioma, CNS hemangioblastoma, or renal cell carcinoma in the setting of multiple renal cysts. Standard criteria were used to identify patients with VHL. These included (1) family history of VHL and 1 major lesion, (2) 2 or more major lesions, or (3) positive genetic testing. Major lesions included renal cell carcinoma, retinal angioma, CNS hemangioblastoma, pheochromocytoma, and paraganglioma.

One hundred nine patients (60 males and 49 females) were identified with a VHL diagnosis by the above criteria. Their medical records were reviewed, including all operative notes, pathology reports, laboratory evaluations, imaging studies, office visits, and outside medical correspondence. All presenting tumors were identified and noted. Seventeen patients (16%) had an identifiable adrenal mass on at least 1 imaging study. Three patients (3%) had paragangliomas: 2 of the inner ear and 1 along the juxtarenal aorta. These histories were then further reviewed for their clinical presentations, preoperative evaluations, diagnostic modalities, delays (if any) in their diagnosis, surgical management, and long-term outcome. Follow-up was complete in 98 (90%) of the patients and was obtained through the medical records or by direct telephone calls to the patients, their first-degree relatives, or their referring physicians. Mean follow-up was 6.8 years (range, 3 months to 37 years).

RESULTS

One hundred nine patients (60 males and 49 females) were identified with VHL. Mean age at time of VHL diagnosis was 29 years (range, 7-66 years). In 17 patients (16%) there was a substantial delay in their VHL diagnosis (range, 1-20 years) from the time of their initial presentation. Family history was available in 95 patients (87%). 62 (65%) of these patients had first-degree relatives with VHL. Fifty-eight patients (53%) had been seen in our Medical Genetics Department and had undergone a pedigree analysis. Twelve patients (11%) had undergone genetic testing, and 5 (5%) had received their VHL diagnosis solely on the basis of positive genetic testing.

**Table 1. Von Hippel-Lindau Tumor Types Seen in 109 Patients**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell carcinoma</td>
<td>50 (46)</td>
</tr>
<tr>
<td>Cerebellar/cerebral hemangioblastomas</td>
<td>83 (76)</td>
</tr>
<tr>
<td>Retinal angiomas</td>
<td>69 (63)</td>
</tr>
<tr>
<td>Pheochromocytomas (adrenal masses)</td>
<td>17 (16)</td>
</tr>
<tr>
<td>Paragangliomas</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Benign renal cysts</td>
<td>66 (61)</td>
</tr>
<tr>
<td>Spinal cord hemangioblastoma</td>
<td>33 (30)</td>
</tr>
<tr>
<td>Pancreatic lesions</td>
<td>47 (43)</td>
</tr>
<tr>
<td>Ovarian cysts</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Epididymal cysts</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Endolymphatic sac tumors</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Hepatic hemangiomas</td>
<td>7 (6)</td>
</tr>
</tbody>
</table>

1982. With the advent of minimally invasive surgery, the challenge lies in the application of laparoscopic and cortical-sparing techniques to this group of patients. The objective would be to avoid lifelong corticosteroid dependence and at the same time offer protection from life-threatening events known to be associated with chromaffin tumors.

Cortical-sparing adrenalectomy can be performed in an open or laparoscopic fashion. Small pheochromocytomas can be approached in an open fashion by either a dorsal lumbotomy or an open anterior approach. In patients with VHL lacking extensive intra-abdominal adhesions, in those not requiring concomitant major pancreatic and renal procedures, and in patients with small unilateral or bilateral pheochromocytomas, the adrenal glands can be approached laparoscopically. Our preferred method is through a lateral transperitoneal approach. The principles for cortical-sparing surgery are the same as for open and laparoscopic techniques. The adrenal gland is exposed but not mobilized. In open cases, careful palpation is performed along with intraoperative ultrasonography to identify the location of the tumor. In laparoscopic cases, more emphasis is placed on visual inspection and laparoscopic ultrasonography, although subtle differences in texture of the gland can be noted with laparoscopic instrumentation. Once the location of the tumor is identified, only that part of the gland is mobilized. This is performed very carefully with clips, electrocautery, and harmonic scalpel. Only arterial tributaries to the involved segment(s) (aortic, renal, and phrenic) are divided. If the main adrenal vein is in this region, it too is divided. Provided the remainder of the gland is left in situ, without mobilization, there are sufficient emissary veins running with the remaining arterial tributaries to maintain adequate venous drainage. When an adequate amount of gland has been mobilized, it can be separated from the segment to be spared by means of a stapling device or harmonic scalpel. Once the specimen is removed, it must be examined by the surgeon and pathologist to ensure an adequate margin around the pheochromocytoma.
tients with CT findings of an adrenal mass (1.0-2.7 cm in size) did not initially undergo further diagnostic workup. One patient was reexamined 4 years later with a symptomatic pheochromocytoma and underwent a successful laparoscopic adrenalectomy. The other 4 adrenal masses were never resected. One of these patients died of unknown causes and the other of a head injury that was assumed to be unrelated. As a result of this study, the other 2 patients were being reexamined, 3 and 7 years after their initial imaging study.

Mean age at time of diagnosis of pheochromocytoma or paraganglioma was 30 years (range, 16-47 years). Seven (41%) of 17 patients were asymptomatic at the time of diagnosis. Another 5 patients (29%) presented with significant cardiac sequelae consisting of arrhythmias and/or cardiomyopathy (Table 2). For 6 patients, the pheochromocytoma or paraganglioma was their first diagnostic VHL tumor. Five (29%) of 17 adrenal masses had bilateral pheochromocytomas. All patients operated on had 24-hour urinary fractionated catecholamines and total metanephrines measured. The urinary excretion of fractionated catecholamines and metanephrines was normal in 4 patients (31%) with pheochromocytomas who underwent operation. All patients underwent abdominal CT scanning; however, only 20 (83%) of 24 pheochromocytomas were identified on CT. Five (31%) of the 16 patients resected underwent additional iodine 123 scintigraphy. The pheochromocytomas missed on CT scan were all identified by 123I scintigraphy.8-10 None of our patients underwent abdominal magnetic resonance imaging as their initial screening. Two patients had non-functioning inner ear paragangliomas; both were diagnosed on screening magnetic resonance imaging for other CNS tumors. The other paraganglioma was identified in the left, juxtarenal, para-aortic region.

<table>
<thead>
<tr>
<th>Patient/ Sex/Age, y</th>
<th>DOS</th>
<th>Symptoms</th>
<th>Operation or Radiographic Findings</th>
<th>Family History</th>
<th>Concurrent Tumors</th>
<th>Postoperative Corticosteroids</th>
<th>Postoperative Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/19</td>
<td>1963</td>
<td>NA</td>
<td>R open total</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>2/M/27</td>
<td>1982</td>
<td>Sweats, HTN</td>
<td>L open total</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>3/M/16</td>
<td>1986</td>
<td>None</td>
<td>Inner ear paraganglioma resection</td>
<td>NA</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>4/F/28</td>
<td>1984</td>
<td>HTN</td>
<td>R open total</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>5/M/24</td>
<td>1986</td>
<td>Palpitations, HTN, sweats</td>
<td>B open total</td>
<td>Yes</td>
<td>Renal</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>6/F/30</td>
<td>1987</td>
<td>Preeclampsia</td>
<td>R open total</td>
<td>No</td>
<td>Renal pancreatic</td>
<td>No</td>
<td>None; died 1990</td>
</tr>
<tr>
<td>7/M/30</td>
<td>1992</td>
<td>None</td>
<td>B open total</td>
<td>Yes</td>
<td>Renal</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>8/M/26</td>
<td>1993</td>
<td>None</td>
<td>R open total</td>
<td>Yes</td>
<td>Renal</td>
<td>No</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>9/M/30</td>
<td>1994</td>
<td>None</td>
<td>Inner ear paraganglioma resection</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>10/M/22</td>
<td>1994</td>
<td>Cardiomyopathy, HTN, arrhythmias</td>
<td>R open total</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>11/M/47</td>
<td>1995</td>
<td>None</td>
<td>L juxtarenal resection for paraganglioma</td>
<td>No</td>
<td>Renal</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>12/F/37</td>
<td>1997</td>
<td>Palpitations, sweats, HTN</td>
<td>R open total/L open cortical-sparing</td>
<td>Yes</td>
<td>Renal, pancreatic</td>
<td>3 mo</td>
<td>None</td>
</tr>
<tr>
<td>13/M/25</td>
<td>2000</td>
<td>Palpitations, HTN</td>
<td>R laparoscopic total</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>14/F/38</td>
<td>2000</td>
<td>Sweats, mood swings</td>
<td>R laparoscopic total</td>
<td>Yes</td>
<td>Renal</td>
<td>No</td>
<td>None</td>
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<tr>
<td>15/F/40</td>
<td>2000</td>
<td>Anxiety, HTN</td>
<td>R laparoscopic cortical-sparing</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>16/M/43</td>
<td>2000</td>
<td>None</td>
<td>B open cortical-sparing</td>
<td>Yes</td>
<td>Renal, pancreatic</td>
<td>&lt;1 mo</td>
<td>None</td>
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<tr>
<td>17/M/65</td>
<td>1997</td>
<td>None</td>
<td>R adrenal mass</td>
<td>Yes</td>
<td>Renal</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>18/M/57</td>
<td>1993</td>
<td>HTN</td>
<td>B adrenal masses</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>19/M/50</td>
<td>1995</td>
<td>NA</td>
<td>R adrenal mass</td>
<td>Yes</td>
<td>Renal</td>
<td>NA</td>
<td>NA; died 1955</td>
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<tr>
<td>20/M/73</td>
<td>1986</td>
<td>NA</td>
<td>R adrenal mass</td>
<td>Yes</td>
<td>Renal</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* DOS indicates date of surgery or date of diagnosis (if not resected); NA, not available; HTN, hypertension; R, right; L, left; and B, bilateral.
† Age at time of diagnosis or surgery.

Table 2. Demographics of Patients With Pheochromocytoma and Paraganglioma*
hildren. These patients may be normotensive23 lies.17-19 Extensive genotyping of the VHL mutations, dur-
be identified in more than 95% of the tested fami-
sis of current testing methods, a
Rosen named this disease for its two pioneers.14
in a landmark article by Cushing and Bailey,13 that the
blastomas and retinal angiomas. It was not until 1928,
observation of an association between CNS hemangio-
were few of the family members were ever screened for the syn-
ties received perioperative replacement doses of meth-
ylprednisolone or hydrocortisone. Both patients were re-
ceiving no steroid replacement at their 3-month follow-up
visit, with normal results of serum cortisol and cortic-
tropin stimulation studies. No metastases were identified in any patients. No recurrences had been noted after a mean
follow-up of 6.8 years (range, 3 months to 37 years) and, specifically, 23.7 months (range, 11-47 months) in the corti-
cal-sparing group.

The earliest report of a patient with VHL dates back to
1894. Ophthalmologist Eugene von Hippel in 1895 and
pathologist Arvid Lindau in 1926 first documented their
observation of an association between CNS hemangio-
blastosomas and retinal angiomas. It was not until 1928,
in a landmark article by Cushing and Bailey,13 that the
syndrome was formally described. In 1964, Melmon and
Rosen named this disease for its two pioneers.14
In 1988, Seizinger and colleagues mapped the VHL
gene to the short arm of chromosome 3. Since then, more
than 140 germline mutations have been identified that
inactivate the VHL tumor suppressor gene.16-19 On the ba-
sis of current testing methods, a VHL gene mutation can be
identified in more than 95% of the tested fami-
lies.17-19 Extensive genotyping of the VHL mutations, dur-
ing the past decade, has demonstrated that the variable
penetration of the different tumors is only partly related
to allelic heterogeneity. Specifically, missense muta-
tions of the gene have been associated with families with
VHL predisposed to pheochromocytomas (type 2 VHL).
Truncated mutations are rarely seen with pheochromocy-
tomas.18-22

Ten percent to 20% of pheochromocytomas are her-
editary.23,24 Recent studies have noted a difference in the
presentation and natural course of familial pheochromocy-
tomas as compared with their sporadic counter-
parts.25-26 The VHL-associated pheochromocytomas tend
to present in younger patients.27 They are often small and
multiple or bilateral.28 Walther et al29 reported up
to 47% bilaterality of pheochromocytomas in their type
2 VHL kindred. These patients may be normotensive23
and asymptomatic26-20 at the time of detection. How-
ever, the quiescent nature of these lesions makes early
screening essential. These lesions can suddenly become
symptomatic and life threatening at the time of surgery
for another VHL tumor, after trauma, or during child-
birth.20,21 This tendency carries with it a significant in-
crease in morbidity and mortality. It is imperative to ad-
here to judicious surveillance protocols that ensure
appropriate detection and follow-up of these tumors.20

In our study (covering a quarter of a century), only
58 patients (53%) were seen through our Medical Ge-
etics Department with formal pedigree analysis and string-
gent periodic monitoring. The other 47% were often seen
only through their primary care provider, neurologist,
urologist, or ophthalmologist. Most of these other pa-
ients lacked reliable, systemic, surveillance screening.
In addition, when seen only in the subspecialty clinics,
few of the family members were ever screened for the
syndrome. All 5 patients whose adrenal masses were not
evaluated were seen directly by a subspecialist for an-
other tumor-related problem. The point of this observa-
tion is not to incriminate a few, but rather to acknowl-
edge that most specialists and primary care physicians
have not successfully functioned as the best gatekeepers
for these patients. These patients need to be monitored
closely by geneticists or internists who are familiar
with this disorder and are aware of the recommended sur-
veillance protocols. It is also extremely important to
coordinate the testing of all other first-degree relatives.

The prognosis of VHL disease has significantly im-
proved in recent years with the implementation of bet-
ter surveillance and more sensitive testing methods.7,33
Also, the advent of genetic testing has helped curtail life-
long surveillance for kindred members lacking specific
VHL mutations. Detailed screening protocols are de-
scribed elsewhere.32 It is important, however, to recog-
nize that in some studies, including this one, urinary cat-
echolamine and metanephrine levels have been normal
in up to 35% of patients with VHL and pheochromocy-
toma.34 Measurement of plasma normetanephrines may
increase the sensitivity of metabolic screening for her-
editary pheochromocytomas (up to 97%).34

Historically, bilateral total adrenalectomies had been
recommended for patients with bilateral familial pheo-
chromocytomas.35 As expected, these were associated with
notable complications, with up to 23% of patients expe-
riencing addisonian crises.36,37 Autotransplantation was
routinely unsuccessful. We know now that the segmental
arterial anatomy (phrenic, aortic, and renal) and the
gland’s dual venous drainage (main adrenal vein and the
venae commitantes—emissary veins) allow for func-
tional cortical-sparing operations.37 In fact, it has been
shown that as little as 10% of well-perfused adrenocor-
tical tissue from a single gland can maintain adequate
corticosteroid function during stress.38,39 On the basis
of this premise, it was logical to devise newer surgical tech-
niques to preserve adrenocortical function. However,
Hamberger et al40 suggested that “cortical-sparing”
adrenalectomy may be associated with subnormal bio-
chemical response to corticosterin.

The first successful open cortical-sparing adrena-
elctomy for bilateral pheochromocytomas was per-
formed in 1965 and reported in 1982.4 Authors have used
the terms cortical-sparing and adrenal-sparing to selec-
tively describe “partial” adrenalectomies, wherein a por-
tion of a single gland or portions of both glands are re-
tained. Since 1982, very few authors have described or

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sparing surgery. Although follow-up is short in these cases, no recurrence has been detected during a mean follow-up of 23.7 months (range, 11-47 months). Corticosteroid independence has been maintained in all of our patients who underwent cortical-sparing and unilateral procedures. We believe that our results, along with those previously reported, support the implementation of laparoscopic and cortical-sparing adrenalectomies whenever feasible for VHL pheochromocytomas. This is in keeping with sound principles of organ preservation adhered to for other VHL-related tumors (renal cell carcinoma and islet cell tumors). We believe, however, that intra-abdominal and retroperitoneal paragangliomas still require open surgery because of their anatomic locations, risk of malignancy, and dense adherence to surrounding structures.

The treatment of patients with VHL has evolved during the past decade as genetic, medical, and surgical expertise has evolved. We strongly support the concept of a centralized, multidisciplinary team approach for the screening, treatment, and follow-up of patients with VHL and their families. Evaluation for pheochromocytomas should begin early in life (age 5 or 6 years) and always before elective surgery or childbirth. At present, we cannot exclude a predisposition to pheochromocytoma (phenotype) on the basis of VHL genotyping. However, advances in VHL genetic testing have the potential to exclude most uninvolved kindred members from lifelong surveillance. More sensitive tests including plasma normetanephrines and [123I] scintigraphy will supplement our diagnostic capability and allow for early detection of small, asymptomatic, and seemingly nonfunctioning tumors. We also believe that, once detected, the majority of adrenal masses in patients with VHL should be resected after appropriate preoperative pharmacologic α- and occasionally β-adrenergic blockade. Early intervention and ad-

Table 3. Published Results of Laparoscopic Cortical-Sparing Adrenalectomies in Patients With von Hippel–Lindau Disease*

<table>
<thead>
<tr>
<th>Source</th>
<th>Institution or Country</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Laterality</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janetschek et al.48,49</td>
<td>Innsbruck, Austria; Freiburg, Germany</td>
<td>1998, 1999, 2000</td>
<td>4</td>
<td>All bilateral</td>
<td>Range, 2 to 24 mo</td>
</tr>
<tr>
<td>Neumann et al.48</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radmayr et al.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walther et al.51</td>
<td>National Cancer Institute, Bethesda, Md</td>
<td>2000</td>
<td>3</td>
<td>1 Bilateral, 2 unilateral</td>
<td>Range, 5 mo to 3 y</td>
</tr>
<tr>
<td>Present series</td>
<td>Mayo Clinic, Rochester, Minn</td>
<td>2001</td>
<td>1</td>
<td>Unilateral</td>
<td>11 mo</td>
</tr>
</tbody>
</table>

*No recurrences were found.

studied this procedure in familial pheochromocytomas. Lee and associates51 in 1996 reported the experience with “cortical-sparing” adrenalectomy for familial pheochromocytomas at The University of Texas M. D. Anderson Cancer Center, Houston. The procedure was performed successfully in 14 of 15 patients: 10 with multiple endocrine neoplasia (MEN) type 2A, 2 with MEN 2B, and 3 with VHL. After a median follow-up of 138 months (range, 10-27 years), only 3 patients (21%) developed recurrence; all were patients with MEN 2. The authors concluded that, with cortical-sparing adrenalectomies, it is possible to reduce complications and maintain corticosteroid independence. However, long-term follow-up and continued surveillance remain essential.

In 1999, Walther and colleagues52 described 13 patients undergoing 14 successful cortical-sparing adrenalectomies for familial pheochromocytomas. Six patients had less than 1 gland remaining. None became corticosteroid dependent at 3-year follow-up, and only 1 developed a new tumor at 152 months. In 1999, Neumann and associates53 presented their results on cortical-sparing adrenalectomies for hereditary and sporadic pheochromocytomas. They successfully completed 37 cortical-sparing operations in 39 patients. Thirteen patients had only partial glands remaining. At follow-up, they had 1 recurrence in a remnant gland of a patient with VHL, 6 years after the initial operation.

The results with open, cortical-sparing adrenalectomy have prompted surgeons to extend the same principles to laparoscopic adrenalectomy. Gagner et al.44 described the first laparoscopic adrenalectomy in 1992. Since then, many surgeons have converted their operative approach from the traditional open (anterior or posterior) procedures to the less morbid laparoscopic approach. These patients tend to have shorter hospital stays, less pain, faster convalescence, and a better cosmetic and functional result.54-57

More recently, there have been 7 reported cases of successful laparoscopic cortical-sparing adrenalectomies in patients with VHL. Table 3. Janetschek et al.50,51 first presented their technique for laparoscopic cortical-sparing surgery in 1997 for an aldosterone-secreting adenoma. A year later, they reported it in 4 cases of familial pheochromocytomas.58 Walther et al.51,59 in a recent article, recommended the use of laparoscopic ultrasound in preparation for minimally invasive cortical-sparing surgery.60 Although follow-up is short in these reported cases, no recurrence has been detected during a 2-year period.61-63 In our series, only 2 patients had bilateral total adrenalectomies. Three of our operations used the “cortical-sparing” or “partial” adrenalectomy technique and 3 were performed laparoscopically. Concomitant intra-abdominal procedures were not performed in the laparoscopic cases. No recurrences, metastases, or new chromaffin tumors have been detected in any of our patients, with a mean follow-up of 6.8 years (range, 3 months to 37 years). In our cortical-sparing cohort, we have seen no recurrence during a mean follow-up of 23.7 months (range, 11-47 months). Corticosteroid independence has been maintained in all of our patients who underwent cortical-sparing and unilateral procedures. We believe that our results, along with those previously reported, support the implementation of laparoscopic and cortical-sparing adrenalectomies whenever feasible for VHL pheochromocytomas. This is in keeping with sound principles of organ preservation adhered to for other VHL-related tumors (renal cell carcinoma and islet cell tumors). We believe, however, that intra-abdominal and retroperitoneal paragangliomas still require open surgery because of their anatomic locations, risk of malignancy, and dense adherence to surrounding structures. The rare malignant pheochromocytoma in VHL should also be managed in an open fashion. In the absence of preoperatively detected metastases, malignancy can only be suspected radiographically by tumors of large size (>8 cm) or tumors demonstrating the loss of surrounding tissue planes.

The treatment of patients with VHL has evolved during the past decade as genetic, medical, and surgical expertise has evolved. We strongly support the concept of a centralized, multidisciplinary team approach for the screening, treatment, and follow-up of patients with VHL and their families. Evaluation for pheochromocytomas should begin early in life (age 5 or 6 years) and always before elective surgery or childbirth. At present, we cannot exclude a predisposition to pheochromocytoma (phenotype) on the basis of VHL genotyping. However, advances in VHL genetic testing have the potential to exclude most uninvolved kindred members from lifelong surveillance. More sensitive tests including plasma normetanephrines and [123I] scintigraphy will supplement our diagnostic capability and allow for early detection of small, asymptomatic, and seemingly nonfunctioning tumors. We also believe that, once detected, the majority of adrenal masses in patients with VHL should be resected after appropriate preoperative pharmacologic α- and occasionally β-adrenergic blockade. Early intervention and ad-
vancements in surgical technique will allow for cortical-sparing and minimally invasive procedures. The absence of adrenomedullary hyperplasia and low malignant potential in VHL, as well as reported low recurrence rates after cortical-sparing surgery, support this approach. These operative techniques have the potential for achieving more rapid recovery with less morbidity while, at the same time, maintaining a prolonged period of corticosteroid independence.

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REFERENCES


Edwin L. Kaplan, MD, Chicago, Ill: I thank Dr Baghai for the insightful comments. Dr Thompson for sending me the manuscript. The authors are to be commended for studying a large series of patients with VHL and for bringing this uncommon disease to our attention.

It must be remembered that not too long ago it was felt that bilateral total adrenalectomy was the operation of choice for hereditary pheochromocytomas because of their propensity to be bilateral and to be multiple in the same gland. It has been clearly shown in the past that in the MEN 2 syndrome, unilateral adrenalectomy is preferable if only one side has a pheochromocytoma, for it permits the child to grow normally without the need for steroid replacement. However, the onus for careful follow-up falls on the physician or surgeon since, later, metachronous pheochromocytomas may occur in the other gland.

As shown in this excellent paper and others, the same is true for patients with VHL. They are young and their lesions may be small, but they can be multiple in the same gland, and bilaterality occurs in 35% to 47% of patients. On the other hand, more than half will remain unilateral and, thus, a unilateral adrenalectomy or partial adrenalectomy is appropriate if only one side is involved.

It should be remembered that if one adrenal gland is removed, the patient does not become adrenal insufficient or require adrenal corticosteroids unless an adrenal tumor producing Cushing syndrome has been removed.

Certainly, if both adrenal glands have to be removed, care should be taken to leave part of one or both adrenal glands in situ to prevent adrenal insufficiency if that is possible. This is a potentially severe disease. One must also have adrenal reserve for times of stress.

We tried 2 cases of autotransplantation early in my career by putting pieces of adrenal cortex in the forearm. They appeared to secrete aldosterone but not enough cortisol. Thus, this technique was abandoned.

Thus, my questions are:
1. Do you really know how much adrenal cortex is necessary for normal function? You state that 10% of the adrenal cortex of one gland is enough. Have you studied this?
2. In the diagnosis of these pheochromocytomas, you state that urinary studies were often normal but that plasma metanephrines or normetanephrines are diagnostic. Could you elaborate on this new test?
3. Do you prepare all of these patients, even when they are asymptomatic, with α- and possibly β-blockers?
4. I agree that laparoscopic removal of pheochromocytomas, especially small favorable ones, is appropriate and that partial adrenalectomy can be performed. However, since the lesions are often small and multiplicity can occur, how can you be certain that all of the pheochromocytomas are removed when a partial resection is performed? For example, do you use ultrasound?

Finally, I know that you did considerable work in trying to find this large quantity of patients. Could you elaborate on the difficulties that you encountered? I enjoyed this paper very much. Thank you.

Gerard V. Aranha, MD, Maywood, Ill: I enjoyed the paper also, Dr Baghai and Dr Thompson. I wanted to ask you a question, though, about the pancreatic part of this syndrome. Let’s say that your CT shows a serous cyst adenoma that has all the characteristics on CT, ie, the central scar, calcifications, etc. How do you handle this situation? Let’s give you 2 scenarios: (1) the cyst is in the body and tail and (2) the cyst is in the head of the pancreas.

Richard A. Prinz, MD, Chicago: This is an excellent paper and has a wealth of information. I have 3 questions.

First, have you done ACTH [corticotropin] stimulation tests on all of the patients who have had cortical-sparing operations and have the responses been any less than in normal control subjects?

Can you share with us the technical aspects of doing cortical-sparing resections, especially when you’re doing this laparoscopically?

Finally, can you generalize cortical-sparing to the MEN 2 patient where bilateral pheochromocytomas are present? Do you do this, and if you don’t, can you tell us why you don’t?

Thank you very much.

Lawrence W. O’Neal, MD, St Louis, Mo: I have done 6 cortical-sparing operations for bilateral pheochromocytoma in MEN 2A and MEN 2B. After temporary cortisone replacement, all of them eventually maintained a cortisol-free existence. In one of them, in the MEN 2B, 20 years after the cortical salvage, her medullary cancer began to secrete ACTH. She developed Cushing syndrome. In the adrenalectomy specimen, there was a small nest of medullary cells.

Thomas Biehl, MD, Seattle, Wash: You alluded to a new anatomical description of the venous drainage of the adrenal gland, dual drainage. I too believe that there is not only one vein, but could you elaborate on what you think the venous drainage truly is from the adrenal gland?

Dr Thompson: Dr Richardson, Dr Thirby, Dr Micheleassi, members, and guests. I stand to thank the Association for the privilege of presenting our paper at this meeting. I would also like to thank all of the discussants, and in particular Dr Kaplan, for the insightful comments.

Dr Kaplan asked how much cortex is necessary to maintain adequate adrenal function. Papers dating from the 1920s and the 1960s have described patient survival, without exogenous steroids, with as little as 10% of adrenal cortex vascularized remaining. There have been a number of more detailed studies that have looked specifically at cosyntropin stimulation testing following partial adrenalectomy. Although some patients demonstrate an impaired response to ACTH stimulation, most patients undergoing cortical-sparing (CS) surgery for familial pheochromocytomas have had normal responses in addition to normal baseline serum cortisol levels. No addisonian crises have been reported to date in these patients undergoing CS surgery.

In our 2 patients who had less than 1 gland or parts of both glands remaining, both had normal ACTH stimulation tests at 3 months. I try to preserve one third to one half of the gland without compromising the margin adjacent to the pheochromocytoma.

Dr Kaplan asked about the assay for plasma metanephrines and normetanephrines. For those of you in the audience familiar with plasma catecholamine studies for epinephrine and norepinephrine, you know that these are notoriously unreliable. Just sticking a needle in someone’s arm can instantly raise plasma levels of epinephrine and norepinephrine. However, the metabolites (metanephrine and normetanephrine) are a sen-
sitive indicator of what has gone on in the prior 24 to 48 hours. It appears that this assay is the most sensitive test for pheochromocytomas and is especially helpful in familial cases when the tumors tend to be small. It is more expensive than doing urinary studies and is, in general, not necessary for sporadic patients with larger tumors. In a large series of sporadic pheochromocytomas, we can detect 99% of patients with positive urinary studies for total metanephrines and fractionated catecholamines. Groups from the Netherlands and NIH with data published in the New England Journal of Medicine have shown that, in familial cases, the screening for plasma metabolites can have a sensitivity rate as high as 97%. The only interfering substance you need to worry about is acetaminophen with this liquid chromatographic method. Tylenol needs to be stopped 5 days before sampling.

Dr. Kaplan asked if we routinely use α-blockade even if the patient is asymptomatic with normal biochemistries. The answer is yes. We obviously use a lower dose of dibenzyline. We have seen patients with small pheochromocytomas that appear to be nonfunctioning. When you begin manipulating the tumor, you may still get dramatic changes in blood pressure.

We do utilize laparoscopic ultrasound, but only in patients with familial tumors, to rule out multiplicity—we therefore have limited numbers in this regard. I have used intraoperative ultrasound for open CS adrenalectomies and it is particularly helpful in determining whether or not you have removed all of the disease on one side or both.

Finally, Dr. Kaplan asked about the 4 unoperated patients. We have had a Medical Genetics Department at Mayo for well over 25 years, and only half of these patients were seen by this dedicated group of physicians. Some of that has to do with the fact that these patients were referred in for a specific problem: ophthalmic, neurologic, or urologic. There were 4 patients in whom adrenal masses were picked up on a CT scan looking at some other pathology, presumably in the kidneys, and were then found to have small adrenal masses. Urinary studies were normal and the patients were subsequently lost to follow-up. In 2 of these patients, we are not sure what transpired. Based on death certificate information, one died of a head injury. Was this an accident or the end result of a hypertensive crisis? In the other patient, now deceased, we have no information. Fortunately, as a result of this study, 2 other patients have been retrieved by the system. It turns out that 1 of these 2 patients, with a unilateral tumor, is on 2 antihypertensive drugs. Both of these patients, after 3 and 7 years, respectively, have had no change in the size of their small tumors and continue to have normal urinary studies. We will, however, pursue plasma metanephrines and normetanephrines and possibly MIBG [123I] scanning if biochemical studies are elevated.

Dr. Aranha asked what to do with a well-defined serous cystadenoma of the pancreas in a VHL patient. I would only operate and resect if it is symptomatic. If there is a question about the nature of the cyst (eg, mucinous neoplasm or a complex cystic islet cell tumor), I would perform endoscopic ultrasound with fine-needle aspiration for mucin stain and cytology.

Dr. Prinz asked about ACTH stimulation testing. In our 2 patients who needed it, it was performed at 3 months, at which time the responses were normal.

The technical aspects of the operation are straightforward. Localization is aided by preoperative imaging and intraoperative ultrasound. We do not necessarily go to the adrenal vein first. If the tumor or tumors are in the region adjacent to the adrenal vein, we will then take the adrenal vein. We try not to mobilize the portion of the gland to be spared. Based on our laparoscopic experience with over 200 adrenalectomies, we know that paired veins (venae comitantes) and other minor emissary veins travel in conjunction with or adjacent to the 3 major arterial branches. If you can leave one third to one half of the gland undisturbed, supplied by its arterial tributary and associated veins, the remnant should survive. We transect the gland using a stapler or harmonic scalpel aided by clips.

In the past we have advocated bilateral total adrenalectomy for MEN 2 patients and more recently unilateral adrenalectomy for early disease confined to 1 gland. I would discourage transection of the MEN 2 gland because of the presence of adenomadelial hyperplasia in MEN 2 patients. In a recent conversation with Dr. Norman Thompson, he described several MEN 2 patients whom he has reexplored from elsewhere, where there has been seeding of the retroperitoneum following adrenal transection. Remember, these patients have a precursor neoplastic lesion not seen in VHL patients. Recurrence rates in the literature are considerably higher than in VHL patients.

ARCHIVES OF INTERNAL MEDICINE

The Fats of Life: The Role of Omega-3 Fatty Acids in the Prevention of Coronary Heart Disease

Charles R. Harper, MD; Terry A. Jacobson, MD

Epidemiological and clinical trial evidence suggests that ω-3 polyunsaturated fatty acids (PUFAs) might have a significant role in the prevention of coronary heart disease. Dietary sources of ω-3 PUFAs include fish oils rich in eicosapentaenoic acid and docosahexaenoic acid along with plants rich in α-linolenic acid. Randomized clinical trials with fish oils (eicosapentaenoic acid and docosahexaenoic acid) and α-linolenic acid have demonstrated reductions in risk that compare favorably with those seen in landmark secondary prevention trials with lipid-lowering drugs. Several mechanisms explaining the cardioprotective effect of ω-3 PUFAs have been suggested, including antiarrhythmic, hypolipidemic, and antithrombotic roles. Although official US guidelines for the dietary intake of ω-3 PUFAs are not available, several international guidelines have been published. Fish is an important source of ω-3 PUFAs in the US diet; however, vegetable sources, including grains and oils, offer an alternative source for those who are unable to regularly consume fish. (2001;161:2185-2192)

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