Von Hippel-Lindau disease in a Newfoundland kindred

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Von Hippel-Lindau disease, an autosomal dominant condition with complete penetrance, has been recognized in a large family that originated in Newfoundland but has some members who live in New Brunswick and Ontario. A collaborative investigation was begun in 1982 to document the number of affected members and the extent of their disease and to improve management of the disease. The condition has been documented in 38 members of the family, 28 living and 10 dead. The most common manifestations are retinal angioma (present in 60% of the gene carriers) and pheochromocytoma (present in 53%). Of the 28 living affected members 14 had been identified before the study began. Only 3 of the 14 patients in whom the disease was subsequently diagnosed presented with symptoms; in the remaining 11 the condition was detected by routine screening. Overall the mean age at the time of diagnosis was 23 years; in the 21 affected members of the fourth generation it was 18 years. The authors outline a regimen of regular screening for members at risk that has evolved as a result of their experience with this family.

La maladie de von Hippel-Lindau se transmet sur le mode dominant autosomique à pénétrance complète. On la trouve dans une vaste famille originaire de Terre-Neuve qui a essaimé quelque peu au Nouveau-Brunswick et en Ontario. Dès 1982 on entreprenait une enquête multicentrique afin de dépister les personnes atteintes, d'établir l'importance de leur maladie et d'améliorer les traitements offerts. On a répertorié 38 personnes dont 28 vivent encore. Il s'agit surtout d'angiomes rétiniens (chez 60% des personnes atteintes) et de phéochromocytomes (chez 53%). Parmi les 28 survivants, 14 étaient déjà reconnus au moment du début de la présente étude. Des 14 sujets chez qui on a posé le diagnostic par la suite, seuls 3 présentaient des symptômes; les 11 autres sont reconnus grâce au dépistage systématique. L'âge moyen au moment du diagnostic est 23 ans; il s'abaisse à 18 ans pour les 21 malades de la quatrième génération. À la lumière de leurs constatations chez cette famille, les auteurs proposent un programme de surveillance des personnes exposées au risque.

Von Hippel-Lindau disease is an autosomal dominant condition with virtually complete penetrance and highly variable expressivity. Carriers of the gene have increased susceptibility to a variety of phakomatous neoplasms of neuroectodermal origin, in particular retinal angioma, cerebellar, medullary and spinal cord hemangioblastoma, pheochromocytoma and renal cell carcinoma (hypernephroma) as well as paraganglioma and cysts of the pancreas, kidney, adrenal gland and other abdominal organs.[1]

Melmon and Rosen[2] reviewed the contributions of von Hippel and Lindau in describing the major manifestations of the disease early in this century. Only pheochromocytoma was included later, by Glushien and colleagues.[3] Clinical and genetic aspects have recently been reviewed by Hardwig and Robertson[4] and by Go and associates,[5] who have reported the largest kindred so far (41 affected members among 220 descendants of a Puerto Rican couple).

In a study of several families,[1] retinal angiomas were the most frequent clinically evident lesions (58% of members affected), followed by cerebellar hemangioblastomas (36%), renal cell carcinomas (28%) and pheochromocytomas (10%). However, the types of tumours and their frequencies vary from one family to another. In one family 12 of 13 members had pheochromocytoma;[6] in another, 10 of 11 members who proved to be

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affected had cerebellar hemangioblastoma.[2] In a third family hypernephroma was the main serious manifestation, occurring in five of six affected members.[7] A follow-up study identified three more affected members, who had renal cysts only.[8]

Von Hippel–Lindau disease has been recognized in a large Newfoundland family. Although some members of the family had been seen by individual physicians in the past, a collaborative investigation was begun in 1982 to document the number of affected members and the extent of their disease and to improve management of the disease. In this family, with 38 affected members, retinal angioma and pheochromocytoma are both common, occurring in 23 (60%) and 20 (53%) respectively of the 38; cerebellar hemangioblastoma, frequent in other families, appears in only 7 members (18%).

The protean manifestations of the condition and the importance of early diagnosis have led us to develop a protocol for periodic review that may be helpful to those who become involved with the medical care of family members at risk.

Genetic features

The family ancestors trace back to the Bonavista Peninsula of Newfoundland; descendants have migrated to other parts of the island, to New Brunswick and to Ontario. The pedigree is presented in Fig. 1. Of the 38 family members affected 10 have died; autopsy findings for 3 have been reported by Rho.[9] Three dead members (I-2, II-1 and II-5) are considered to have been affected on the basis of presumptive historical evidence and affected offspring. Two other members are presumed to have been affected: III-2, who was blind in one eye when accidentally killed at age 29, and IV-29, who had a cerebral hemorrhage and died following "severe toxemia of pregnancy". The clinical findings most likely resulted from pheochromocytoma.

The pattern of inheritance is clearly autosomal dominant with complete penetrance. In the first four generations (generation V is too young to be included) the ratio of affected to unaffected offspring of affected members is 36:28, close to the expected ratio of 1:1. There is no evidence of segregation distortion, the ratio being 18:15 for offspring of affected men and 18:13 for those of affected women. Excluding the five members presumed to have been affected and the members not yet examined does not change these ratios appreciably. There is no case of transmission through an unaffected parent.

X-linked dominant hypophosphatemic vitamin-D-resistant rickets, also present in the family, is inherited independently of the autosomal dominant von Hippel–Lindau trait, as would be expected.

Clinical features

The clinical details of the affected family

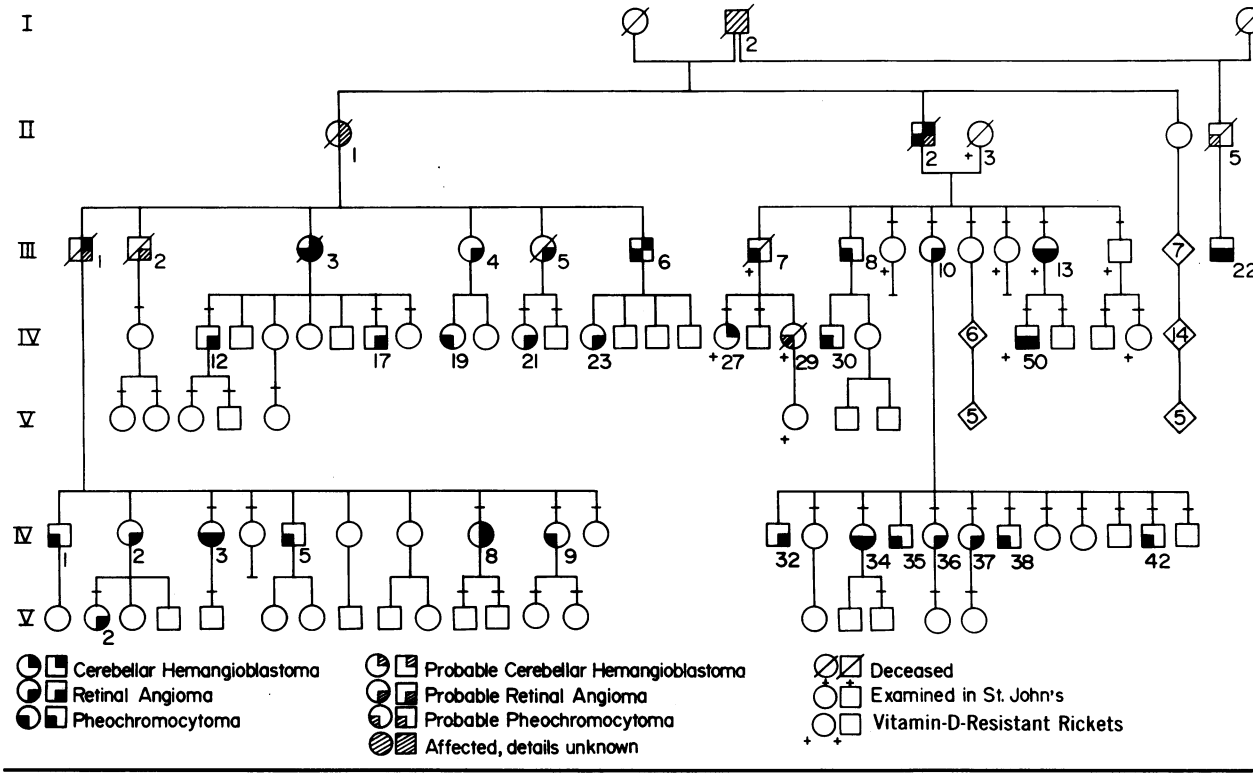

Fig. 1—Pedigree of Newfoundland kindred with von Hippel–Lindau disease.

members were culled from an extensive review of medical and autopsy records of family members in Newfoundland, New Brunswick and Ontario and from examination of 42 of the 44 family members living in Newfoundland and known to be affected or at risk because of an affected parent.* The two not yet examined are a 2-year-old girl, who will be examined when she is 3, and a 70-year-old woman (II-4), apparently free of the disease, who has 26 unaffected descendants. Five children who have a young, asymptomatic parent but an affected grandparent were also examined since the parent might be carrying the gene but not yet have shown manifestations of the disease.

The most common clinical manifestations of von Hippel–Lindau disease in this family and the median age at the time of diagnosis of the various lesions are shown in Table I. Among the 31 affected members for whom the information was available, retinal angioma was the first manifestation in 16 (52%), pheochromocytoma was the first manifestation in 14 (45%) and cerebellar hemangioblastoma was the first and only manifestation in 1 (3%). Since there was no obvious tendency for regular association of the various manifestations, in a member with retinal angioma the chance that pheochromocytoma will develop could be considered to be about 53%, and the chance that cerebellar hemangioblastoma will develop, 18%.

The average age at the time of onset in the cases in which this information was available was 23 years. It is clearly earlier in the later generations; this is almost certainly due in part to the surveillance that has been in progress since 1982. In generation IV the mean age at the time of recognition was 18 years, compared with 33 years in the three previous generations.

Any syndrome with variable expression and variable age at the time of onset presents a serious problem to physicians in terms of identifying the affected people. When the consequences of undetected disease are as serious as in von Hippel–Lindau disease, it is crucial to identify affected people early, when treatment can be successful, and to plan a surveillance system to identify further lesions as they occur. Our recommendations and the experience on which they are based are as follows.

*A table of the clinical details of all the affected members is available on request.

Retinal angioma

In 10 of the 23 members of this family with retinal angioma, the lesions are bilateral. All those who have been followed by us for more than 2 years have had at least one recurrence, and four have had several. Since the angiomas are generally in the periphery, they are asymptomatic in the early stages and can be detected at this readily treatable stage only by means of indirect ophthalmoscopic examination, with the pupils fully dilated.

The retinal angiomas varied in size when first identified from a scarcely visible dilation at the end of the vessel to a raised lesion of one or two disc diameters (Fig. 2). Asymmetry of vessels arising from the disc was sometimes the first clue that an angioma was present in a particular quadrant (Fig. 3). Exudate at the posterior pole of the eye similarly pointed to a leaking angioma in the superior quadrants of the retina (Figs. 4 and 5). Six patients have an angioma on the surface of the optic disc; in patient IV-3 it showed up more clearly with fluorescein angiography than by means of direct inspection (Figs. 6 and 7).

Although there are examples in the literature of small retinal angiomas being followed untreated for extended periods,[10] changes may occur very rapidly, so that the lesion becomes very difficult to eradicate or control. Patients in this family who had a large angioma or multiple angiomas when first seen have had to have repeated laser treatment and cryotherapy to new areas of activity within old lesions. Two patients from the early generations had bilateral blindness, and another eight were unilaterally blind.

We have observed a new retinal tumour, larger than one disc diameter, in a 42-year-old woman (III-10) 1 year after indirect ophthalmoscopic examination had shown the retina to be completely normal. The youngest age at which a retinal angioma was detected was 4 years. Therefore, no age can currently be regarded as exempt, and we suggest that retinal examination be done at least

Table I—Most common clinical manifestations of von Hippel–Lindau disease in 38 affected members of a family in Newfoundland

Lesion	No. (and %) affected: Definitely	No. (and %) affected: Definitely and probably	Age at time of diagnosis, range (and median)
Retinal angioma	19 (50)	23 (60)	4–42 (19)
Pheochromocytoma	18 (47)	20 (53)	11–58 (22)
Hemangioblastoma			
Cerebellar	6 (16)	7 (18)	22–58 (30)
Spinal cord	2 (5)	2 (5)	39, 58 (–)
Hypernephroma	1 (3)	1 (3)	58 (–)

yearly in those known to be at risk and every 6 months in those with any aspect of the disease.

Pheochromocytoma

The lowest age at which pheochromocytoma was diagnosed in this family was 11 years. Bilateral tumours have been documented in 12 of the 20 family members affected, either at the time of initial presentation or as a recurrence in the second adrenal gland. One patient had an extra-adrenal pheochromocytoma (paraganglioma), and in one case the pheochromocytoma was malignant, with metastases.

In the earlier generations pheochromocytoma was detected only after a hypertensive crisis or at autopsy. Two women (IV-9 and IV-34) who were apparently asymptomatic and who were ultimately found to have pheochromocytoma had had "toxemia of pregnancy", which might well have been the first expression of the tumour. The same applies to another woman (IV-29) who had a cerebral hemorrhage following "toxemia of pregnancy". In affected families the diagnosis "toxemia of pregnancy" should arouse suspicion of pheochromocytoma. As well, any evidence of unusual headache, high blood pressure or postural hypotension justifies investigation for pheochromocytoma.

Affected members and those at risk should be seen annually by pediatricians or internists, depending on age. Blood pressure should be taken with the patient lying and standing, and a 24-hour collection of urine should be taken. Since the vanillylmandelic acid (VMA) assay has sometimes given false-negative results, urinary catecholamine or metanephrine assays are now being done. Biochemical evidence of pheochromocytoma requires computed tomography (CT) scanning with a contrast agent to localize the lesion in the adrenal gland or elsewhere. Variable blood pressure or postural hypotension without an increased urinary catecholamine level requires measurement of the plasma catecholamine level. Pheochromocytoma, confirmed by CT scanning, was found in a 22-year-old woman (IV-9) with low to normal VMA and urinary catecholamine levels (Fig. 8); a plasma catecholamine assay was done because of postural hypotension, and a high norepinephrine level was found. To prevent a hypertensive crisis, surgery is recommended when pheochromocytoma is identified, even when there is no significant hypertension.

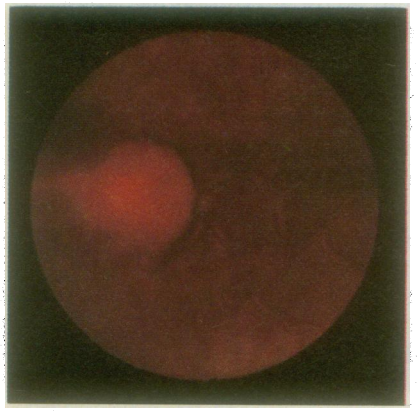

Fig. 2—Retinal angioma in temporal periphery of right eye of patient IV-36.

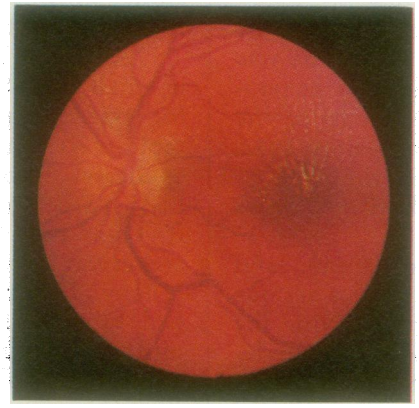

Fig. 4—Exudate at macula in left eye of patient IV-37, evidence of leaking angioma.

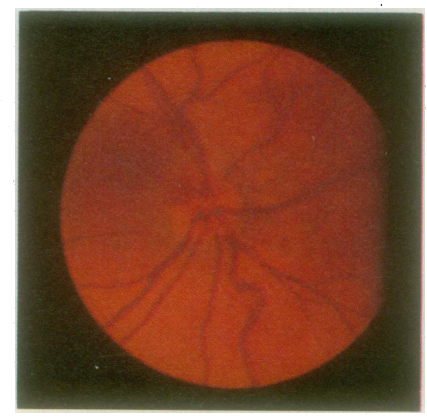

Fig. 6—Capillary angioma on temporal aspect of disc in left eye of patient IV-3 (appears as fanlike vessels). Compare with Fig. 7.

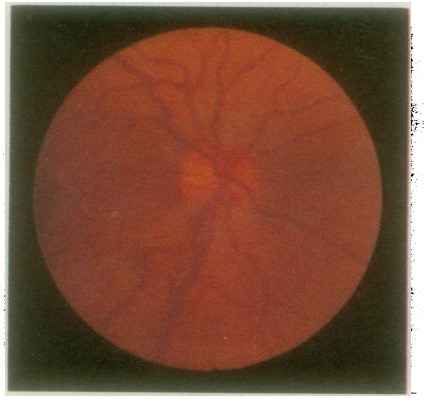

Fig. 3—Asymmetry between upper and lower vessels at disc in right eye of patient IV-36.

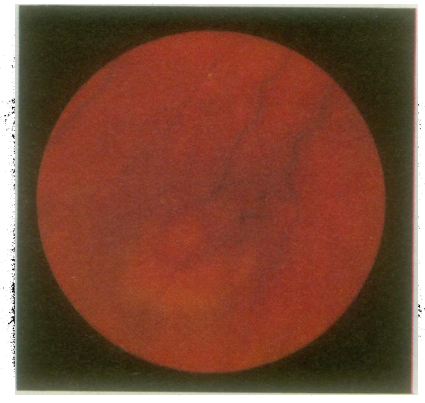

Fig. 5—Retinal angioma in superior periphery of left eye of patient IV-37.

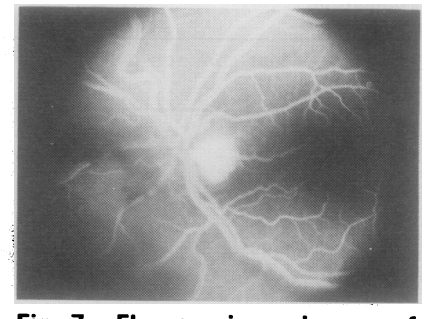

Fig. 7—Fluorescein angiogram of angioma on temporal aspect of disc in left eye of patient IV-3, showing leakage.

Cerebellar hemangioblastoma

CT scanning of the brain in an asymptomatic 23-year-old woman (IV-8) who had previously been treated for retinal angioma showed a cerebellar midline hemangioblastoma whose image was enhanced with a contrast agent; the tumour had not been apparent on a CT scan 6 months earlier. The lesion and a smaller one were defined with angiography. It may be impractical to perform CT scanning of the brain every 6 months, but we think it should be done in the late teens as a base-line study and yearly in those with any other manifestation of the disease. CT scanning of the brain with a contrast agent (Fig. 9) should be performed with particular attention to the posterior fossa but not ignoring other regions. All those at risk, both affected and unaffected, should have an annual neurologic examination; suggestive signs necessitate CT scanning of the brain or spinal cord. Any lesions detected should be further defined with angiography (Fig. 10), and the timing of surgery should be decided by the neurosurgeon.

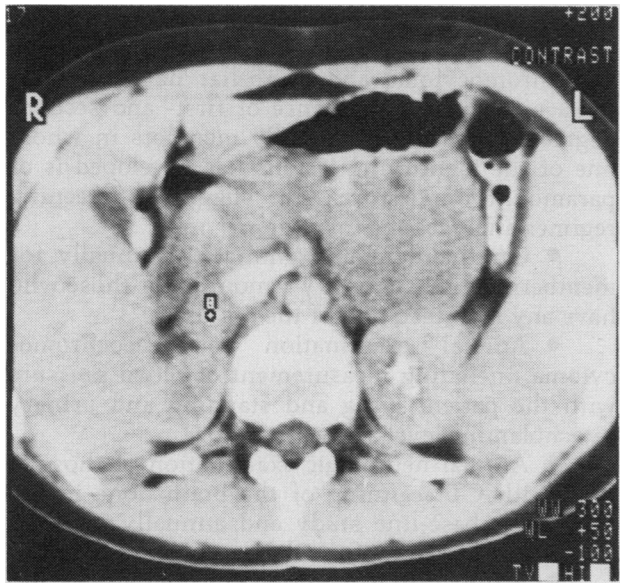

Fig. 8—Computed tomography (CT) scan of upper abdomen of patient IV-9, showing pheochromocytoma of right adrenal gland (+), posterolateral to inferior vena cava.

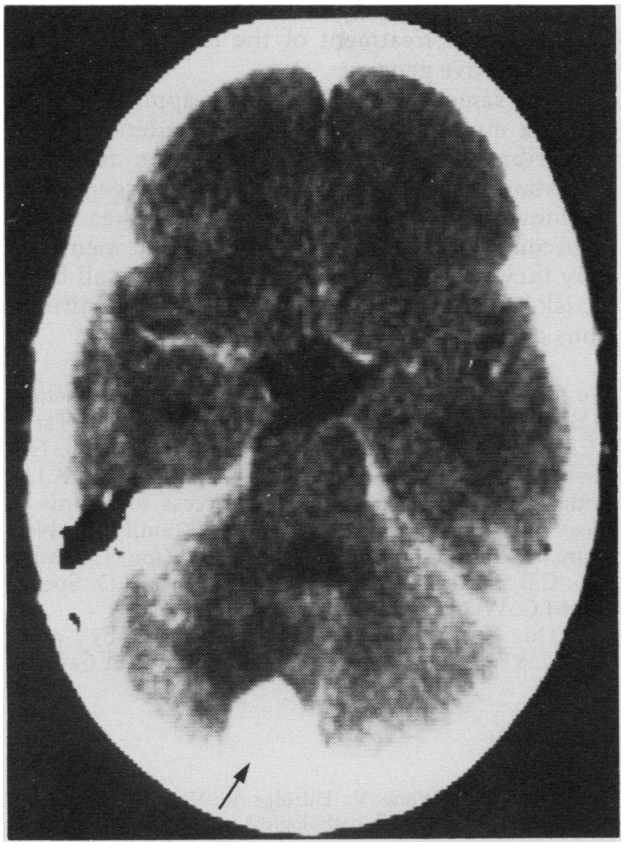

Fig. 9—CT scan of head of patient IV-27, showing enhanced image of lesion in right posterior cerebellar hemisphere.

Hypernephroma

Although hypernephroma has been identified only once in this family, in an elderly, severely affected man, the literature suggests that this tumour, as demonstrated at autopsy, is much more common than is clinically recognized and may have previously been missed in some family members.[1] Screening by annual CT scanning of the abdomen has been recommended in families in which hypernephroma is common,[11] but we feel that the exposure to radiation is not warranted in this family. We recommend annual ultrasonography of the kidneys starting from the teenage years, with a single base-line CT scan done in the mid-20s. Suspicious results of ultrasonography are followed up by CT scanning or laparotomy, as indicated.

Cystic disease

In von Hippel–Lindau disease, cysts are frequently seen in the kidney, liver, pancreas and other abdominal organs; they have been document-

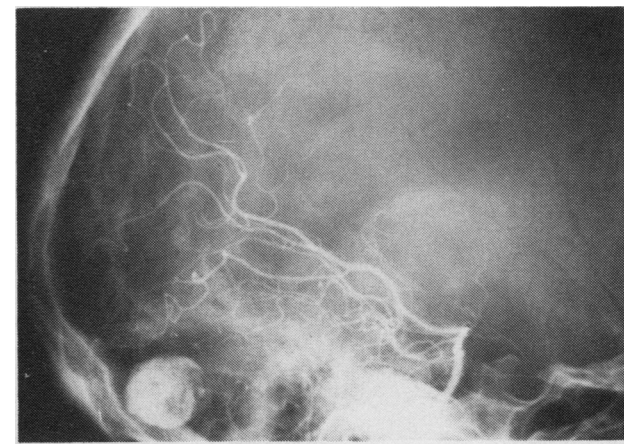

Fig. 10—Left vertebral arteriogram from patient IV-27, showing cerebellar hemangioblastoma 2 cm in diameter.

ed in seven members of this family (Fig. 11). Although the cysts are usually present without symptoms, they are an important diagnostic feature of the disease and may well be the first indication that a person at risk is carrying the gene. Radiologists reading the results of ultrasonography or CT scanning of the abdomen should take particular note of the presence of cysts in any abdominal organs.

Discussion

While the screening program for any particular family should be directed toward the lesions known to be most frequent in that family, the rarer lesions, such as medullary hemangioblastoma, pancreatic adenoma and meningioma, must be kept in mind.

Of the 28 living affected members of this family 14 had been identified before the study began. Among the 14 members identified since then, pheochromocytoma was coincidentally identified in 1 during other medical investigations, 1 member presented with visual loss and was found to have multiple retinal angiomas and retinal detachment, and 1 was investigated because of recurrent high blood pressure and was found to have bilateral pheochromocytomas and bilateral retinal angiomas. The remaining 11 members were asymptomatic, and the diagnosis was made during routine screening: retinal angiomas were found in 6, pheochromocytomas in 4, and retinal angiomas and pheochromocytomas in 1.

The average age at the time of death for the 10 affected members who have died was 37 years. The specific cause of the earliest death is unknown, and one death was accidental. Of the remaining eight deaths seven can reasonably be attributed to hypertension from unrecognized pheochromocytoma or complications of cerebellar or spinal cord hemangioblastoma. In contrast, 10 members in whom pheochromocytoma was diagnosed within the past 10 years and 1 member with cerebellar hemangioblastoma have all had surgery, with good results.

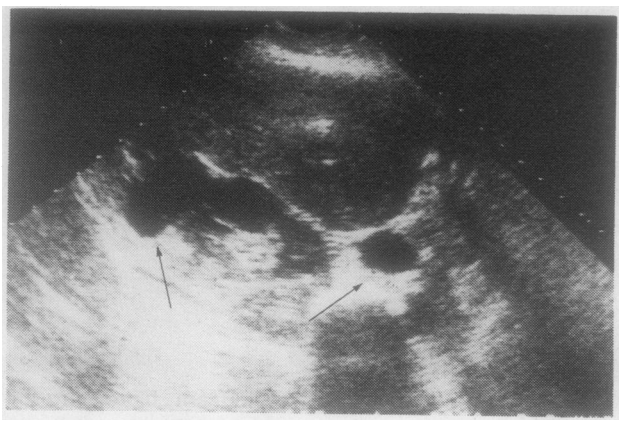

Fig. 11—Ultrasound scan of right kidney of patient III-10, showing multiple cysts.

The family has received extensive genetic counselling and support. In addition, an educational pamphlet has been prepared for circulation to family members explaining the mode of inheritance, the potential risks of the disease and the possible symptoms and outlining the screening program and the recommended treatment. Since family members are at risk for one or more of several lesions — in particular, retinal angioma, pheochromocytoma and cerebellar hemangioblastoma — regular surveillance of first- and second-degree relatives and of family members in whom one of the identifying lesions has developed is of paramount importance. Our suggested screening regimen includes the following:

- Ophthalmologic examination annually for members at risk and every 6 months for those who have any manifestation of the disease.
- Annual examination for pheochromocytoma, including measurement of blood pressure with the patient lying and standing and urinary catecholamine level assay.
- Annual neurologic examination of those at risk, with CT scanning of the brain done in the teens as a base-line study and annually in those with any other sign of the disease.
- Annual ultrasonography of the kidneys and base-line CT scanning of the kidneys in the mid-20s.

The considerable effort necessary to carry out this regimen in what may be a good many family members at risk is offset by the benefits of early diagnosis and treatment of the lesions caused by the destructive gene.

The same approach should be applied to other variable multisystem dominant disorders, such as neurofibromatosis, multiple endocrine neoplasia and Marfan's syndrome, for better management of the families involved. Once a closely linked marker becomes available to identify affected members, only they need to be followed. Until then, all those at risk must be screened for all possible manifestations of the particular disease.

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large size of his infarction the patient drifted into cardiogenic shock and died 2 weeks later.

Comments

The first cardiac pacemakers were external and paced the heart through skin electrodes.[1] However, with the advent of implantable pacemakers, transcutaneous pacing rapidly became obsolete. Recently transcutaneous pacing has been resurrected and has been shown to be useful in the immediate management of severe bradycardia.[2-5] This case report illustrates a new use of transcutaneous pacing — for terminating ventricular tachycardia.

Transvenous rapid ventricular pacing has been shown to be useful in terminating sustained ventricular tachycardia,[6,7] but even synchronous pacing can accelerate the tachycardia or induce ventricular fibrillation.[8,9] The pacemaker we used is a fixed-rate device that has no sensing capability and hence might be more arrhythmogenic. A further limitation might be difficulty in capturing the heart at higher pacing rates.

Further testing of the safety of this method of terminating ventricular tachycardia is warranted in view of both its ease of use and the possible risk of accelerating tachyarrhythmias and inducing ventricular fibrillation.

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