Twin Vessels in von Hippel-Lindau Disease

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We examined ten patients from three families with von Hippel-Lindau disease and 26 of their at-risk relatives for the presence of twin vessels, defined as a paired retinal arteriole and venule that are separated by less than the diameter of one venule and extend for a distance of more than one disk diameter. They were compared with 36 age- and sex-matched controls. Of the 36 subjects in the study group, 23 had twin vessels compared with two controls ($P < 10^{-6}$). Of the ten patients, nine (14 eyes) had twin vessels; no twin vessels were found in their controls ($P = 5.9 \times 10^{-5}$). Fourteen at-risk relatives and two of their controls had twin vessels ($P = 9.4 \times 10^{-4}$).

THERE ARE THREE patterns of vascularization in the normal human eye: the juxtaposed arterioles and venules of the conjunctiva, the staggered arterioles and venules of the retina, and the sinusoidal venules and arterioles of the choroid.¹ The adult retinal vascular pattern is established several months after birth and matures during the next several years.² The larger arterioles and venules of the retina share a common territory but normally have no close juxtaposition one to another, as do conjunctival or connective tissue vessels.^{1,3}

In retinal angiomas, or von Hippel's disease, there are single or multiple hamartomatous capillary masses in the retina, each supplied and drained respectively by a widely dilated arteriole and venule. In the autosomal dominant hereditary hemangioblastomatosis, or von Hippel-Lindau disease, retinal angio-

mas, hemangioblastoma of the central nervous system, and cysts and benign or malignant tumors in several visceral organs may be present.^{4,5} The diagnosis of von Hippel-Lindau disease is made when either a retinal angioma or a central nervous system hemangioblastoma occurs together with one or more visceral cysts or tumors in one patient or when a single lesion of the von Hippel-Lindau complex is found in a relative at risk.⁴ Eventually, 44% to 64% of the patients with von Hippel-Lindau disease develop one or more retinal angiomas, 52% to 69% develop central nervous system hemangioblastoma, 25% develop renal cell carcinoma, approximately 33% develop renal or pancreatic cysts, 17% develop polycythemia, and 7% develop pheochromocytoma.⁶⁻⁸ In the early stages, most of these lesions are asymptomatic.⁸ Regular screening for lesions of von Hippel-Lindau disease in patients and relatives at risk provides earlier detection and permits better treatment. Regular ophthalmoscopic, neurologic, and internal examinations are therefore indicated, including central nervous system and abdominal computed tomographic scans, abdominal echography, and tests for pheochromocytoma.⁷

Examining members of a family with von Hippel-Lindau disease, one of us noted a strikingly close pairing of retinal arterioles and venules, which we called twin vessels. Twin vessels occurred in patients and at-risk family members. This led us to investigate the significance of this phenomenon to learn if there was an association between the presence of twin vessels and the occurrence of von Hippel-Lindau disease.

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Subjects and Methods

Twin vessels were defined as a pair of vessels, one retinal arteriole and one venule, separated by less than one venule width, that run a parallel course for more than 1 disk diameter; sometimes the vessels may cross each other.

Fig. 1 (de Jong and associates). Sketch of vessels in left eye of Case IV-5, pedigree 1. Arrows indicate twin vessels.

Because crowding of vessels near the optic disk might simulate twin vessels, twin vessels were only scored as such when located at least 2 disk diameters distant from the disk (Figs. 1 through 4).

In three unrelated families with von Hippel-Lindau disease, all patients and at-risk relatives willing to cooperate were examined for the presence of retinal angiomas and twin vessels. They underwent a complete ophthalmic examination, including indirect ophthalmoscopy after pupillary dilation. In selected cases a

Fig. 2 (de Jong and associates). Twin vessels (between arrows) in Case III-4, pedigree 1.

three-mirror Goldmann contact lens was used. When possible, color photographs were taken. Fluorescein angiography was performed in four eyes.

A family history was recorded and all patients and at-risk family members underwent a multidisciplinary screening, according to a previously described protocol.⁶ The screening included neurologic examination and computed tomographic scan of the brain of all patients

Fig. 3 (de Jong and associates). Fluorescein angiogram of twin vessel in at-risk member III-9, pedigree 2. Note that the twin vessel between the black arrows splits and comes together again at the white arrows.

Fig. 4 (de Jong and associates). Angiogram of twin vessel (between arrows) in left eye of control patient of same age and sex as at-risk member II-3, pedigree 1.

and at-risk relatives over 10 years old. Computed tomography of the spinal cord or medulla was indicated only if neurologic abnormalities were found and the computed tomographic scan of the head was normal. Patients and at-risk relatives were also examined for systemic lesions by abdominal echography or computed tomography as well as tests for pheochromocytoma. Data from patients who had died were obtained from their files. From these combined examinations, it was possible to designate patients and at-risk members, according to the previously mentioned definition.

Age- and sex-matched controls with clear media and without retinal vascular disorders were recruited from our ophthalmologic clinic. The first eligible subject examined at the clinic after examination of a member of a von Hippel-Lindau family was used as a control. All subjects gave informed consent for pupillary dilation and indirect ophthalmoscopy, and all were examined by one of us (P.T.V.M.J.). The examiner was not masked to the identity of the subject. For statistical analysis we used Fisher's exact one-tailed test and the chi-square test with Yates' correction factor.

Results

Twin vessels looked like normal retinal vessels except for their adjacent course. The number of twin vessels ranged from one to six per

affected eye (average, two). Twin vessels could be present in all regions of the fundus, including the far periphery. There were never afferent or efferent vessels connected with a visible angioma. The maximum extent of twin vessels was 8 disk diameters. In general, the diameter of the arteriole and venule forming the twin vessel corresponded to the diameter of the vessels in the same retinal area. The diameter between different pairs of twin vessels and sometimes within one twin vessel pair could vary. In this case (Fig. 3), the arteriole was the smaller vessel. On fluorescein angiography the twin vessels showed normal circulation times in comparison with vessels of corresponding diameter in the same region. There was no vascular staining in the late phase and no hemorrhages or exudates in their vicinity. In some eyes the retinal vessels, also nontwin vessels, were radially stretched from the disk towards the periphery without the usual twisted course.

Ophthalmic examination was performed on 36 subjects from three von Hippel-Lindau families and 36 age- and sex-matched controls. Twin vessels were found in 23 subjects (34 eyes) from the affected families and in two controls (two eyes) ($P < 10^{-6}$) (Table).

Thorough ophthalmic, neurologic, and systemic screening of the 36 cooperating members of these three von Hippel-Lindau families yielded ten patients and 26 at-risk relatives (Fig. 5). Nine of the ten patients had retinal angiomas in 13 eyes and nine of the ten pa-

TABLE
RESULTS OF OPHTHALMOSCOPY

FINDING	VON HIPPEL-LINDAU DISEASE		AT-RISK RELATIVES		CONTROLS	
	NO. OF PATIENTS (N = 10)	NO. OF EYES (N = 19)	NO. OF SUBJECTS (N = 26)	NO. OF EYES (N = 52)	NO. OF SUBJECTS (N = 36)	NO. OF EYES (N = 72)
Twin vessels	9*	14 [†]	14 [‡]	20 [§]	2	2
Retinal angiomas	9	13	0	0	0	0
Retinal angioma and twin vessel in same eye	7	10	0	0	0	0
Retinal angioma, no twin vessel in same eye	3	3	0	0	0	0

* $P = 5.9 \times 10^{-5}$ as compared with controls.

[†] $P = 7.6 \times 10^{-6}$ as compared with controls.

[‡] $P = 9.4 \times 10^{-4}$ as compared with controls.

[§] $P = 4.5 \times 10^{-5}$ as compared with controls.

^{||}Numbers do not add. Case II-2, pedigree 1, belongs to both groups.

Fig. 5 (de Jong and associates). Pedigrees of three von Hippel-Lindau families. Top left, pedigree 1. Top right, pedigree 2. Bottom left, pedigree 3. All deceased members except I-1, II-3, and III-1 of pedigree 1 died of von Hippel-Lindau disease. All family members who underwent both ophthalmic, neurologic, and systemic examinations had a computed tomographic scan of the head and echography or computed tomography of the abdomen. Subjects not examined either refused or were too young. Neurologic and systemic findings from patients who died before this study were obtained from their files.

tients had twin vessels in 14 eyes (Table), although twin vessels were not always present in the same eye as the retinal angiomas. Eight of the ten patients had neurologic or systemic lesions, or both, and seven of these eight also had twin vessels.

The only patient without retinal angiomas (Case II-8, pedigree 1) had twin vessels in his left eye and a cerebellar hemangioblastoma. The only patient without twin vessels (Case III-3, pedigree 1) had retinal angiomas and a central nervous system hemangioblastoma.

Three of the nine patients with retinal angiomas (Fig. 5, pedigree 1, II-2 and III-3; pedigree 2, III-4) had one eye with retinal angiomas but no twin vessels.

In Case III-3, pedigree 1, the left eye had been enucleated at age 7 years for neovascular glaucoma secondary to complications of an angioma. This eye is represented in Figure 5 as having no twin vessels, although we cannot tell if this is correct. This was also our youngest patient with retinal angiomas.

The mean age of the patients with retinal

angiomas and twin vessels was 32.4 years, whereas the mean age of the at-risk relatives with only twin vessels was 22.5 years.

In the matched controls of the ten patients, no twin vessels were found ($P = 5.9 \times 10^{-5}$).

Fourteen of the 26 at-risk relatives had twin vessels compared to two of their matched controls ($P = 9.4 \times 10^{-4}$). The youngest at-risk member with a twin vessel was 3 years old.

Discussion

The occurrence of twin vessels in 23 persons of three unrelated families with von Hippel-Lindau disease makes a coincidental vascular anomaly improbable. Twin vessels were observed in nine of the ten patients with von Hippel-Lindau disease. Approximately one half of the examined at-risk relatives had less than 50% chance of having inherited von Hippel-Lindau disease. In the at-risk relatives, however, twin vessels were detected in 14 of

the 26 subjects (54%). Only two of the 36 controls (6%) had twin vessels. These results indicate a significant association between von Hippel-Lindau disease and twin vessels, especially when one considers that the prevalence of von Hippel-Lindau disease is estimated to be 1:230,000.⁹

However, as seen in three eyes, retinal angiomas may occur without twin vessels. Therefore, even in the absence of twin vessels routine ophthalmoscopy of patients and at-risk relatives is warranted.

Twin vessels may be an ocular manifestation of von Hippel-Lindau disease. There could be a common pathogenetic pathway of retinal angiomas and twin vessels, since both originate from mesenchymal cells. Alternatively, a separate gene responsible for the development of twin vessels might be located close to the von Hippel-Lindau mutation, resulting in linkage of both traits in several families. As shown in pedigree 1 (Fig. 5), twin vessels were present in offspring of the monocular patient (III-3) and in offspring of two at-risk relatives (II-4 and III-2); however, these three subjects did not have twin vessels themselves. This could be explained either by the great variability of von Hippel-Lindau disease or by assuming that twin vessels are a separate, dominantly inherited trait with incomplete penetrance. In two other families not described here, isolated central nervous system hemangioblastoma occurred in combination with twin vessels, at present without retinal angiomas or other manifestations of von Hippel-Lindau disease. Further follow-up examinations of these patients will show whether they will develop signs of von Hippel-Lindau disease.

We believe twin vessels are a variant of the normal retinal vascular pattern. They are not pathologic vessels as they have the same diameter as the surrounding retinal arterioles and venules, do not stain or leak on fluorescein angiography, and have no pathologic exudates around them. Twin vessels were observed in patients and at-risk relatives of all ages in this study.

Retinal angiomas are the most common early manifestation of von Hippel-Lindau disease, with an average age at diagnosis of 22 years.⁸ They have been described in a pathologic report of a fetal eye, and growth of a new angioma has been recorded in the seventh decade of life.¹⁰ The youngest patient with a retinal angioma in this study was 7 years old. New angiomas were also found at a relatively advanced age in Patient II-2, pedigree 1 (age 56 years) and Patient II-6, pedigree 1 (age 50 years).

Since the retinal vascular pattern remains stable from the age of 6 months,² we expect that twin vessels remain stable also. Twin vessels are easily detected by ophthalmologic examination and occur in most patients with von Hippel-Lindau disease. A prospective follow-up study of a greater number of patients with von Hippel-Lindau disease and their at-risk relatives is needed to establish a definite association between twin vessels and the occurrence of von Hippel-Lindau disease in an at-risk relative. If such an association can be demonstrated within an individual at-risk family member, the presence of twin vessels could be valuable as an early diagnostic sign of von Hippel-Lindau disease.

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