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# Familial vascular malformations

## Report of 25 members of one family

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Vascular malformations are described in 25 members of one affected family. Most of these lesions were cavernous hemangiomas, but arteriovenous malformations and capillary hemangiomas were also microscopically observed in some specimens. The five generation pedigree suggests the vascular malformations are genetically determined on the basis of a dominant inherited trait.

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Vascular malformations such as hemangiomas, port wine stains and arteriovenous malformations are usually sporadic events and are very rarely inherited. Only a few very limited familial cases of hemangiomas, nevi flammei, or arteriovenous malformations have appeared in the literature. Familial cases of syndromes which include vascular malformations such as Sturge-Weber, Klippel-Trenaunay-Weber, Bannayan, Riley, Cobb, Bonnet-Dechaume-Blanc, Rendu-Osler-Weber and von Hippel-Lindau disease have been occasionally reported (Shelley & Livingood 1949, Tonning et al. 1952, McIntosh Nicol 1957, Riley & Smith 1960, Trell et al. 1972, Ide et al. 1974, Kaplan et al. 1976, King et al. 1977, Barre et al. 1978, Snead et al. 1979, Foo et al. 1980a, b, Higginbottom & Schultz 1982). Most of the conditions have demonstrated the autosomal dominant mode of transmission.

We have recently studied a family in which multiple vascular malformations, including cavernous hemangiomas, arteriovenous malformations, and capillary hemangiomas, appeared in 25 individuals in five generations in an autosomal dominant pattern. The pedigree is shown in Figure 1.

### Case Reports

*Case IV-5:* A 37-year-old female was born with vascular malformations within the upper lip and on her right foot. At the age of 6 months the lesion on the foot was surgically excised, but recurred within one year. The lesion was completely excised at 12 years (Figure 2). During her lifetime new hemangiomas in different areas developed: in her mouth, tongue and neck. After the birth of her first child a hemangioma appeared in the vagina. This lesion has progressively grown and is now $5 \times 4$ cm. in size. Three years ago excision of the heman-

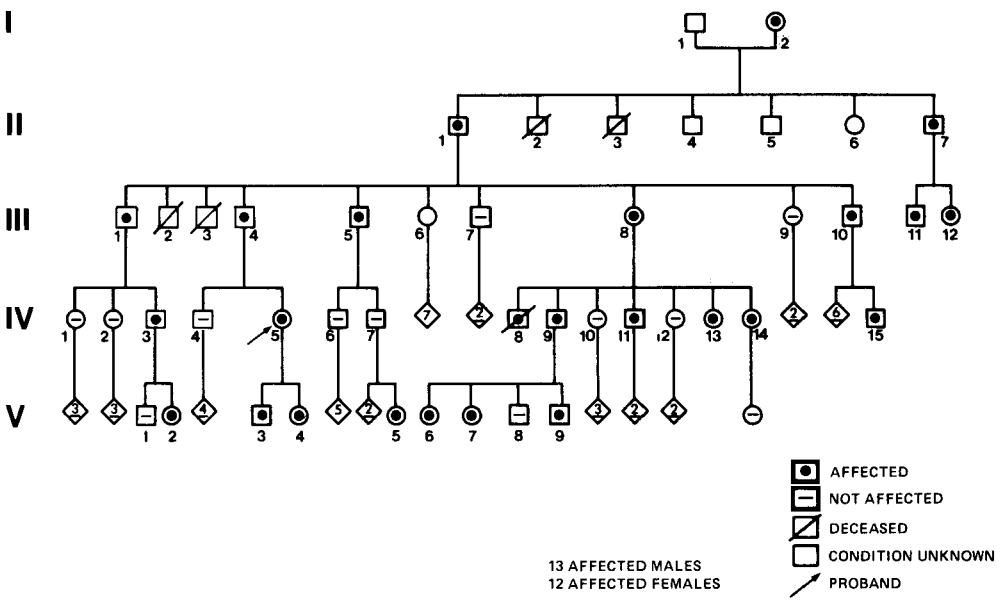


**Fig. 1.** Pedigree of family with congenital vascular malformations in five generations.

gioma of the upper lip (Figure 3) and of a venous aneurysm of the right leg was performed. Histologic diagnosis of the lesion on the foot and lip was cavernous hemangioma with several recent and reorganizing thrombi.

*Case III-4:* The father of the above patient is 68 years old. He has had hemangiomas on both feet since birth (Figure 4). The lesions on his feet were so large that they presented a great impediment to walking as a child and several attempts at subtotal removal were made. Small hemangiomas have spontaneously appeared intermittently during his lifetime: on the forehead, the lower

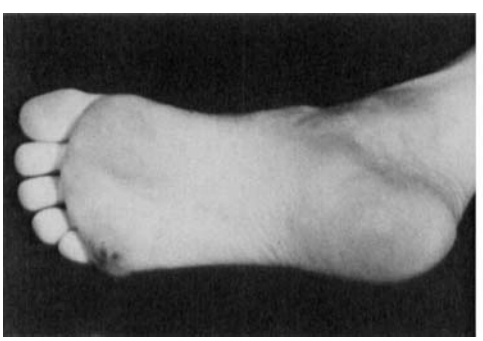

**Fig. 2.** A cavernous hemangioma on the foot of Case IV-5 at age of twelve. The lesion was present at birth and did not proportionately grow over time.

**Fig. 3.** A cavernous hemangioma of the upper lip in patient IV-5. This lesion was not present at birth but appeared at about age 6.

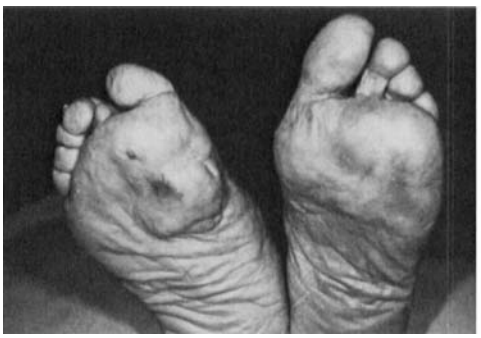

**Fig. 4.** The 68-year-old father of Case IV-5. Cavernous hemangiomas present on the feet at birth and continued to grow proportionately as the patient aged.

lip, the tongue, and on his chin and back. These soft, red tumors are about 1 cm. in diameter and are still present (Figure 5).

*Case V-3:* This 13-year-old, son of the proband, was born with several small (1 cm.) hemangiomas on his left cheek, neck, right index finger and tongue (Figure 6). None of these lesions involuted with time. All were surgically excised. Pathological investigation of the lesion revealed a haphazardly arranged mass of thin-walled vascular channels of cavernous proportion in fibroadipose tissue and skeletal muscle. Many of the vascular spaces contained organizing thrombus.

**Fig. 5.** Patient III-4 developed vascular malformations on his tongue during adolescence, which persisted throughout life.

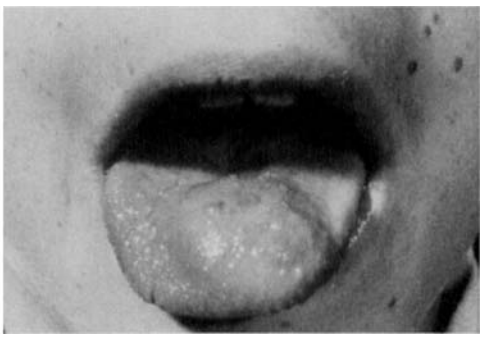

**Fig. 6.** Thirteen-year-old boy (son of proband, Case V-3) with cavernous hemangioma on his tongue. This lesion developed at age one. Multiple other hemangiomas were also present.

*Case V-4:* This seven-year-old girl, the second child of the proband, was born with a soft, $3 \times 2$ cm. sized tumor on the right side of her neck. The lesion was excised when it did not involute and was histopathologically diagnosed as a cavernous hemangioma.

*Case V-2:* This eleven-year-old niece of the proband was born with vascular malformations of her right index finger and has had it subtotally excised multiple times. With a gradual spread of the lesion the finger became non functional (Figure 7). An arteriogram of the right upper extremity revealed a tumor blush of the vascular malformations extending to the base of the metacarpal with no major arterial feeding vessels. At the age of eleven years the right index finger was amputated. Histopathologic examination demonstrated a capillary hemangioma in some parts, cavernous hemangioma with extensive thrombosis and calcification in others, as well as malformed vessels within the fibroadipose tissue. Most of the vessels were thick-walled and lined by a single layer of endothelium. There was also extensive anastomosis of these vessels.

Location of the lesions in other affected

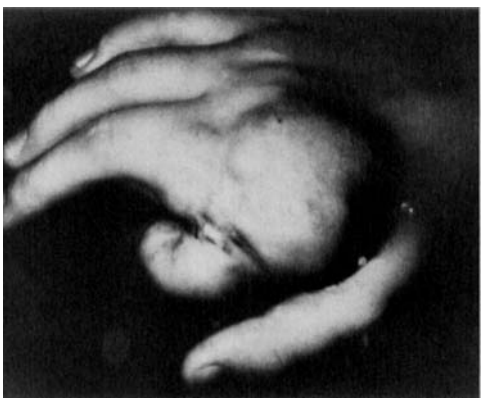

**Fig. 7.** Eleven-year-old girl (Case V-2) with vascular malformations on her right index finger.

members of this family is summarized in Table 1.

## Discussion

Every generation within this family exhibits individuals affected with vascular malformations. Affected individuals usually had some children who are affected. Unaffected individuals had no children who were affected with one exception. A clinically unaffected individual (IV-7) had a child (V-5) with a hemangioma on the foot. This suggests incomplete penetrance of the gene which would not be surprising. In addition, in generations IV and V, where ascertainment is quite complete, there are 15 affected to 20 unaffected individuals. Although this ratio is not statistically different from the 1 : 1 ratio, it may include other cases of incomplete penetrance. However, this clinically unaffected case may well have a lesion which has not been documented since he has not been examined by the authors. In spite of this case, familial distribution was compatible with autosomal dominant inheritance. Thirteen males and twelve females had vascular malformations predominantly in the mucous membranes of the mouth and in the skin and soft tissues. In only two cases (IV-13, IV-5) were hemangiomas known to be within internal organs. One case involved the parenchyma of the breast.

In most cases, the vascular malformations have been notable on the face. Twenty hemangiomas were located in the mouth: on the upper or lower lip, on the tongue, on the mucous site of the cheek and in the larynx including the tonsils. The lesions were found on the forehead in three patients, on the temple in two, and on the chin and eyelid in two others. Four individuals had hemangiomas behind the ear. In five cases similar lesions were noted on the neck. Six others had them on the trunk or abdomen. The extremities were involved in 15 individuals. In five cases these vascular lesions were located on the middle or index finger. In four others they appeared on one or both feet.

It is interesting to note that the location of the hemangioma was almost identical in some cases. For example our proband (IV-5) had lesions on her foot, but they were not quite as large as her father's (III-4). Similar vascular lesions were observed in our proband's cousin (IV-14) and niece (V-5). Four siblings (IV-8, IV-9, IV-11, IV-13) had hemangiomas behind the ear. The hemangiomas on the right middle finger were found in individual (II-1), in his daughter (III-8) and his granddaughter (IV-13). Index fingers were affected in two cousins (V-2 and V-3). Hemangiomas of the lower lip were noted in two siblings (III-5 and III-8) and her granddaughters (V-6, V-9).

Some family members were born with hemangiomas which never regressed and new ones spontaneously developed in different areas during their lifetime (IV-5). In other cases, these vascular lesions appeared during life. In a majority of cases the lesions were small, grew slowly, and were asymptomatic. Only a few cases required significant surgical procedures. Mastectomy was

performed in Case I-2. Case IV-13 had three fourths of the stomach removed at the age of two years. Case III-1 had a tonsillectomy complicated by massive hemorrhage. Three cases (III-4, IV-5, IV-14) had a partial removal of hemangioma of the feet. Amputation of the fourth toe was performed on patient IV-14 and the index finger removed from patient V-2. No one in this family has had any symptoms suggestive of central nervous system involvement.

Histopathological examination in most cases revealed typical cavernous hemangiomas. These malformations were composed of large, lacunar vascular spaces forming compact masses. The walls of these dilated vessels were relatively thin, lined with a single layer of endothelium. No smooth muscle or elastic tissue surrounded the vessels. Fresh or organizing thrombi as well as calcification was often found within the lesions. Great variation both in vessel calibre and thickness of their walls was recognized in affected areas in some other cases. Some vessels ranged from relatively well differentiated arteries and veins to malformed, thick and thin-walled hyalinized vessels apparently neither artery nor vein.

**Table 1**

Summary of affected members of the family with vascular malformations

| Case | |
|---|---|
| I-2 | Mastectomy for large hemangioma of breast. |
| II-1 | Hemangioma distal right middle finger. |
| II-7 | Had hemangioma – location unknown. |
| III-1 | Hemangioma of pharynx including tonsils; hemorrhage during tonsillectomy; other lesions in mouth and cheek since birth; small hemangioma on right shoulder appeared late in life. |
| III-4* | Hemangiomas on feet, tongue and cheek at birth; new ones in mouth, lower lip, forehead, chin and back developed in adolescence. |
| III-5 | Small hemangioma in mouth since birth. |
| III-8 | Hemangioma on cheek, lower lip, right side of neck and right middle finger. |
| III-10 | Hemangioma on the temple. |
| III-11 | Hemangioma on the neck. |
| III-12 | Several hemangiomas on back of leg. |
| IV-3 | Hemangioma on the neck appeared at 15–16 years of age; periumbilical hemangioma developed late in life. |
| IV-5* | Hemangioma on right foot and upper lip since birth; later lesions appeared on left corner of mouth, tongue, neck and vagina. |
| IV-8 | Hemangioma behind left ear since birth. |
| IV-9 | Hemangioma behind left ear and upper lip since birth. Developed forearm lesion at ten years of age; right first toe at 15 years; mouth at twenty years of age. |
| IV-11 | Hemangioma behind left ear. |
| IV-13 | Hemangioma on right ear and in larynx since birth; underwent partial laryngectomy and 3/4 gastrectomy for hemangioma at age two years; new hemangiomas appeared later on forehead (surgically excised), tongue (surgically excised), neck, armpit, right middle finger and back. |
| IV-14 | Hemangiomas on both feet and on left popliteal area since birth. |
| IV-15 | Hemangioma on temple. |
| V-2* | Vascular malformations of index finger since birth; seven attempts at subtotal excision ended in amputation two years ago. |
| V-3* | Hemangioma of tongue, cheek, neck and right index finger since age one. |
| V-4* | Hemangioma on right side of neck since age one. |
| V-5 | Hemangioma on foot. |
| V-6 | Popliteal hemangioma since birth; lesions on lower lip and left wrist and middle of chest since adolescence. |
| V-7 | Hemangioma of left upper eyelid since birth (strawberry type). |
| V-9 | Hemangioma of forehead and neck since birth; lip lesion developed later. |

* Described in text.

Dilatations or aneurysms of these vessels were observed. Thrombosis inside the lumen with stages of organization were also found in veins (IV-5, V-2, V-3). Moreover, in case V-2 with indirect multiple excisions, the lesion consisted predominantly of capillary hemangioma together with features of cavernous hemangioma and arteriovenous malformations.

The presence of several members in one family with vascular malformations should alert the physician to rule out associated intracranial vascular anomalies. The neurological literature contains multiple reports of potentially catastrophic familial central nervous system abnormalities associated with vascular malformations. Cavernous hemangiomas or arteriovenous malformations have been found intracranially in the affected members of several families (Kidd & Cumings 1947, Tonning et al. 1952, Graf 1966, McCormick 1966, Clark 1970, Tay et al. 1971, Laing & Smith 1974, Stoll & Wolfram 1977, Bicknell et al. 1978, Hayman et al. 1982). The actual frequency of these anomalies is unknown since most were asymptomatic and found only at postmortem examination (Russel & Rubinstein 1977, Snead et al. 1979). The presence of familial nevus flammeus and cavernous hemangiomas, associated with intraspinal (Kufs 1928, Tonnie & Lange Cosack 1953, Kaplan et al. 1976, Nova 1979, Foo et al. 1980a,b) or intracranial (Zaremba et al. 1979) arteriovenous malformations has also been reported in a few families. Familial port wine stain, retinal cavernous hemangioma, and central nervous system involvement have been observed by Goldberg et al. (1979). Familial occurrence of congenital diffuse cavernous hemangiomatosis of the skin, mucous membranes, ocular regions and internal organs, have been reported in two infants by Ide et al. (1974). King et al. (1977) have observed arteriovenous malformations in the central nervous system in several generations of a family with hereditary hemorrhagic telangiactasia. Subcutaneous hemangiomas, lymphangiomas, and /or lipomas associated with macrocephaly and intracranial meningiomas have been recorded by Higgenbottom & Schultz (1982) in a family with a Bannayan syndrome. None of the patients in our report have had symptoms which would suggest intracranial involvement. There have been no seizure disorders in any of the generations, nor has there been a death from intracranial catastrophe.

Familial subcutaneous angiolipomas with abdominal chemodectomas have been reported (Lee et al. 1977). A malignant transformation (angiosarcoma) of a cavernous hemangioma in a family with Bean's syndrome has also been described (Sarrat & Sarrat 1980). No associated neoplasm or malignant transformation has been observed in any members of the family which we reported.

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