

BRIEF REPORT: A FAMILIAL SYNDROME OF ARTERIAL DISSECTIONS WITH LENTIGINOSIS

WOUTER I. SCHIEVINK, M.D.,
VIRGINIA V. MICHELS, M.D., BAHRAM MOKRI, M.D.,
DAVID G. PIEPGRAS, M.D.,
AND HAROLD O. PERRY, M.D.

ARTERIAL dissection occurs when blood enters a vessel wall through an intimal tear and a false lumen of blood is formed within the media.^{1,2} The artery most commonly affected by dissection is the aorta,¹ followed by the renal^{3,4} and extracranial internal carotid^{2,5} arteries.

The pathogenesis of arterial dissection is incompletely understood, but a primary arteriopathy is frequently suspected, especially in younger patients. The possibility of a genetic predisposition to such an arteriopathy is supported by the familial occurrence of arterial dissections⁶⁻⁹ and their association with various heritable connective-tissue disorders.^{10,11} In our experience with cervical-artery dissections, the nature of the arteriopathy is identified in only a small fraction of patients.^{12,13}

Among approximately 240 patients with spontaneous cervical-artery dissections who were seen at the Mayo Clinic between 1970 and 1992, 8 had a documented family history of arterial dissection. We describe two of these patients and their families, whose main clinical features were arterial dissection occurring at an early age and the presence of multiple lentiginosities. The arterial media and melanocytes are derived from neural-crest cells, suggesting that a neural-crest defect may be the underlying abnormality in these families.

CASE REPORTS

Family A

Propositus

A left temporal headache and amaurosis fugax of the left eye followed by dysphasia and right hemiparesis developed in a 33-year-old man (Subject II-8 in Fig. 1). He had undergone surgical repair of an aortic coarctation just distal to the left subclavian artery at the age of 19 years.

On examination, the left and right brachial blood pressures were 150/100 and 155/100 mm Hg, respectively, and ankle blood pressures were 162/100 mm Hg bilaterally. Numerous uniformly sized (approximately 3 mm in diameter) maculae that were dark brown to black were present on the trunk and particularly on the arms and legs (Fig. 2), including the palms and the soles. Areas that were exposed to the sun as well as areas protected from the sun were affected, but the face and mucous membranes were not involved. The skin lesions had developed around the age of two years and had increased markedly in number during adolescence. The skin lesions did not darken with exposure to the sun. There were no café au lait spots. The patient did not have ocular hypertelorism or deafness and was

of normal stature (height, 174 cm; weight, 70 kg). Neurologic examination revealed dysphasia, right hemiparesis, right homonymous hemianopia, and a left carotid bruit. A computed tomographic scan of the head showed an infarct of the left parietal lobe. Electrocardiography showed left ventricular hypertrophy, and echocardiography revealed mild septal hypertrophy. Ophthalmologic examination was normal. Aortography revealed no residual coarctation. Cerebral angiography demonstrated bilateral loops of the cervical internal carotid arteries and a high-grade stenosis due to dissection in the area of the loop of the left internal carotid artery.

The patient was treated with aspirin. Cerebral angiography three months later revealed that the dissection had resolved. Biopsy of a thigh skin lesion confirmed the diagnosis of lentiginosities. No vascular events have occurred and the lentiginosities have faded during 12 years of follow-up.

Family History

There was no evidence of consanguinity in the patient's family, which was of German origin. At the time of his birth, his mother was 31 years of age and his father was 35.

One of his brothers (Subject II-7 in Fig. 1) had died suddenly at the age of 22 years. Autopsy revealed a hemopericardium caused by dissection and rupture of the ascending aorta. Extensive cystic medial necrosis of the aorta was also noted. The remainder of the cardiovascular system was normal. Like his brother, Subject II-7 had numerous hyperpigmented skin lesions mainly affecting the skin of the extremities, as confirmed by examination of photographs. No other relatives had a history of arterial dissection or hyperpigmented skin lesions compatible with a diagnosis of lentiginosities.

Family B

Propositus

An occipital headache and right hemifacial numbness developed in a previously healthy 24-year-old woman (Subject VI-3 in Fig. 1) shortly after a downhill-skiing accident in which she fractured her right radius but sustained no head or neck injury. Neurologic examination showed right hemiparesis and left Horner's syndrome. Angiography demonstrated a dissection of the left cervical vertebral artery, resulting in occlusion. Six and a half years later, six weeks post partum, the patient had a sudden right occipital headache while breast-feeding. Right hemicorporal numbness and transient dysphasia developed shortly thereafter.

On examination, the patient's blood pressure was 125/70 mm Hg. Multiple small (2 to 3 mm in diameter) maculae that were dark brown and uniformly colored were present on the trunk as well as the arms and legs, particularly the fingers and toes. Areas exposed to the sun as well as areas protected from the sun were affected. The face and mucous membranes were not involved, and the skin lesions did not darken with exposure to the sun. These skin lesions had first been noted in childhood and had increased in number until early adulthood. There were no café au lait spots. The patient did not have ocular hypertelorism or deafness and was of normal stature (height, 175 cm; weight, 76 kg). Neurologic examination showed dysarthria, left-beating nystagmus, and truncal ataxia. A computed tomographic scan of the head and examination of the cerebrospinal fluid revealed no abnormalities, nor did ophthalmologic, electrocardiographic, and echocardiographic examinations. Angiography revealed a dissection of the right cervical vertebral artery and the previously identified occlusion of the left vertebral artery. Both carotid arteries were normal. A saphenous-vein graft was placed between the left occipital artery and the left posterior inferior cerebellar artery because multiple episodes of transient quadriplegia had developed despite anticoagulation. At surgery, the left occipital artery was found to be discolored and blue, with a very weak pulse. The artery was opened, and a dissection was found. The artery proximal to the dissection was used for the bypass. The occipital-artery dissection was believed to be related to the operation. Microscopic examination of the resected artery showed an acute medial dissection with focal cystic degeneration of the media. Biopsy of an upper-arm lesion confirmed the diagnosis of lentiginosities.

No vascular events have occurred and the lentiginosities have faded

From the Departments of Neurologic Surgery (W.I.S., D.G.P.), Medical Genetics (V.V.M.), Neurology (B.M.), and Dermatology (H.O.P.), Mayo Clinic, Rochester, Minn. Address reprint requests to Dr. Schievink at the Mayo Clinic, Department of Neurologic Surgery, 200 First St., SW, Rochester, MN 55905.

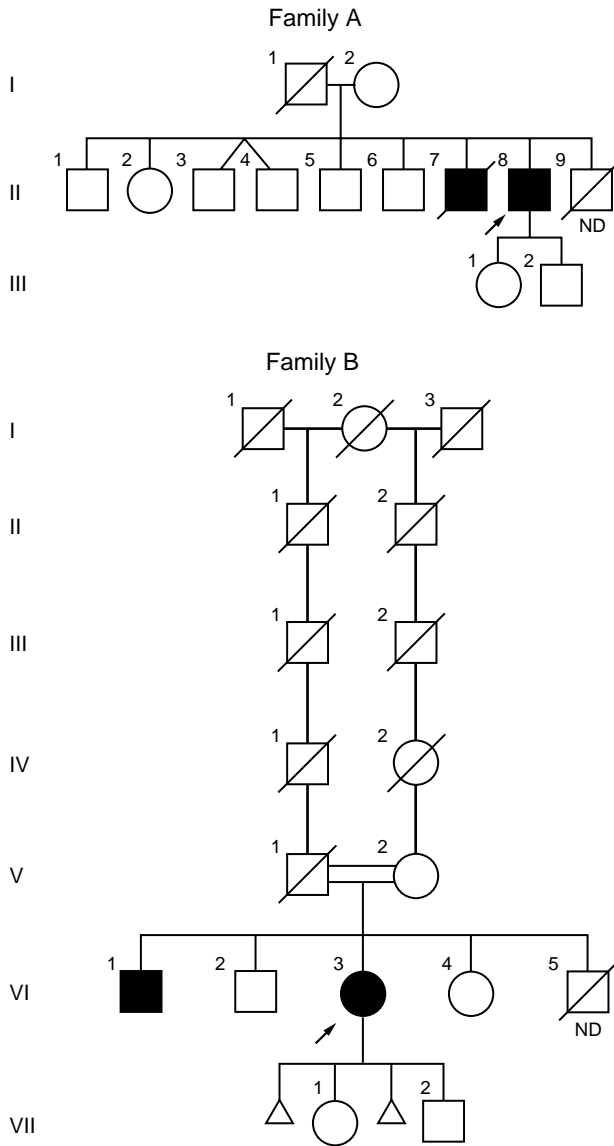


Figure 1. Pedigrees of Family A and Family B.

Circles denote female family members, squares male family members, slashes deceased family members, solid symbols persons with arterial dissection and lentiginosis, arrows propiiti, ND neonatal death, triangles miscarriages, and double horizontal lines consanguineous mating.

during eight years of follow-up. Analysis of the type III procollagen gene¹³ in cultured skin fibroblasts showed no abnormalities.

Family History

The patient's family was of English and Swedish origin. Her parents (Subjects V-1 and V-2 in Fig. 1) were half third cousins (Wright's coefficient of inbreeding, 1/512). Her parents were 33 years of age when she was born.

At the age of 25 years, one of her brothers (Subject VI-1 in Fig. 1) had a severe headache followed by a right hemiparesis. There was no history of trauma. Angiography revealed an area of smooth stenosis of the left extracranial internal carotid artery beginning 2.5 cm from its origin, a finding consistent with the occurrence of dissection. Like his sister, Subject VI-1 has multiple skin lesions that are dark brown to black on his trunk and extremities, especially the lower legs, as

confirmed by examination of photographs. The lesions appeared in childhood.

The patient's father (Subject V-1 in Fig. 1) had a left hemiparesis at the age of 43 years and died suddenly two years later. His medical records were not available. He had no hyperpigmented skin lesions, as confirmed by examination of photographs. No other relatives had a history of arterial dissection or hyperpigmented skin lesions compatible with a diagnosis of lentiginosis.

DISCUSSION

These two families have a constellation of findings consisting of arterial dissections, multiple lentiginosis, and cystic medial necrosis. We consider this syndrome to be genetic in origin. The absence of documented vertical transmission in the families and the history of consanguinity in Family B suggest autosomal recessive inheritance. However, autosomal dominant inheritance with variable penetrance or expression remains a possibility, since we did not directly examine any of the other family members, with possibly more subtle manifestations of the syndrome, and although well documented, the consanguinity in Family B was distant.

The affected members of these families tended to be younger than patients with cervical-artery or aortic dis-



Figure 2. Legs of the Propiitus of Family A, Showing Generalized Lentiginosis.

sections in general.^{1,2,12} Acute dissection of an occipital artery while it was exposed during surgery, as occurred in one of the patients, is unique in our experience. Other features of the arterial dissections in the families, however, such as multivessel involvement, recurrent dissection, and the presence of carotid loops, are regularly encountered in patients with cervical-artery dissections.^{2,12}

The presence of multiple lentiginosities was the most readily apparent clinical finding in the families. Lentiginosities are flat or slightly raised isolated areas of brown-to-black skin pigmentation, approximately 2 to 4 mm in diameter. They usually appear in childhood and increase in number through early adulthood; they may subsequently fade or disappear completely. Clinically, lentiginosities are distinguished from freckles (ephelides) by their darker color, their presence in areas not exposed to the sun, the fact that they do not darken appreciably or increase in number during exposure to the sun, and their relative uncommonness in red-haired and fair-skinned people.^{14,15} Histologically, lentiginosities have an increased number of melanocytes at the dermoepidermal junction and elongation of the rete ridges, whereas freckles have a normal or slightly decreased number of melanocytes and no elongation of the rete ridges.^{14,15} General lentiginosis is a component of several syndromes, some of which have some of the features found in the families we studied. Carney's complex is an autosomal dominant syndrome whose main clinical features are cardiac myxomas and multiple lentiginosities.¹⁶⁻¹⁹ Affected persons also may have cutaneous myxomas, endocrine overactivity, and schwannomas.²⁰⁻²³ This syndrome can be ruled out in the families we studied, because none of the family members had any evidence of cardiac myxoma on echocardiography or autopsy, nor did they have any of the associated features. In addition, the lentiginosities associated with cardiac myxomas often involve mucous membranes,^{16,23} whereas in our patients the mucous membranes were spared. Multiple lentiginosities can also occur in the syndrome of lentiginosis and hypertrophic cardiomyopathy, or LEOPARD (lentiginosities, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and deafness) syndrome.²⁴⁻²⁶ The congenital heart disease associated with this autosomal dominant syndrome includes subaortic stenosis and valvular or infundibular pulmonary-artery stenosis, but aortic coarctation, as was found in one of our patients, is not a recognized feature, and none of the other components of the LEOPARD syndrome were observed in the syndrome we describe. Moreover, spontaneous arterial dissections have not been noted in any of the above-mentioned syndromes, and previous reports on the familial occurrence of arterial dissections have not mentioned the presence of hyperpigmented skin lesions.

In both of the families we studied, cystic medial necrosis was detected on microscopical examination of arterial segments that were available because of surgical resection or autopsy. Cystic medial necrosis is a

nonspecific disorder of the arterial media that is found at autopsy in approximately 2 percent of the population, especially in the elderly.²⁷ In young persons, cystic medial necrosis has been described in various heritable disorders that are associated with arterial dissections, including the Marfan syndrome,²⁸ Ehlers-Danlos syndrome,²⁹ and autosomal dominant polycystic kidney disease.⁹ There was no clinical evidence of any of these disorders in our patients. Cystic medial necrosis has also been described in patients with arterial dissection in the absence of a known phenotypic syndrome, including patients with familial arterial dissections.^{8,30,31} There was no evidence of a mutation in the type III procollagen gene (the underlying defect in Ehlers-Danlos syndrome type IV³²) in the proband from Family B.

An abnormality of cells derived from the neural crest (neurocristopathy) could explain the findings in the families we studied. The neural crest is a transient structure that occurs at a very early stage of embryogenesis.³³ It is divided into two regions, the trunk neural crest and the cranial neural crest.³³ The trunk neural crest gives rise to various types of cells in all parts of the body, including melanocytes.³³ These pigment cells are involved in the pathogenesis of lentiginosities, and this could account for the cutaneous manifestations in the two families. The entire tunica media of the aortic arch and its branches is composed of cells originating in the cranial neural crest,³⁴ which could explain the findings of cystic medial necrosis and the subsequent development of arterial dissection in the two families. After ablating a portion of the cranial neural crest in chick embryos, Rosenquist et al.³⁵ detected marked coarsening and disarray of elastin fibers in the arterial wall, findings similar to the changes of cystic medial necrosis. Aortic coarctation, observed in one of our patients, has also been hypothesized to result from a migration disorder of cells derived from the neural crest.³⁶ Aortic coarctation is associated with aortic dissection and cystic medial necrosis¹ and has also been described in a child with intracranial arterial dissection.³⁷

In conclusion, we describe a familial syndrome of arterial dissection, multiple lentiginosities, and cystic medial necrosis. This syndrome may represent a neurocristopathy.

REFERENCES

- Larson EW, Edwards WD. Risk factors for aortic dissection: a necropsy study of 161 cases. *Am J Cardiol* 1984;53:849-55.
- Mokri B. Dissections of cervicocephalic arteries. In: Meyer FB, ed. *Sundt's occlusive cerebrovascular disease*. 2nd ed. Philadelphia: W.B. Saunders, 1994:45-70.
- Guthrie W, Maclean H. Dissecting aneurysms of arteries other than the aorta. *J Pathol* 1972;108:219-35.
- Edwards B, Stanson AW, Holley KE, Sheps SG. Isolated renal artery dissection, presentation, evaluation, management, and pathology. *Mayo Clin Proc* 1982;57:564-71.
- Schievink WI, Mokri B, Whisnant JP. Internal carotid artery dissection in a community: Rochester, Minnesota, 1987-1992. *Stroke* 1993;24:1678-80.
- Petit H, Bouchez B, Destee A, Clarisse J. Familial form of fibromuscular dysplasia of the internal carotid artery. *J Neuroradiol* 1983;10:15-22.
- Mokri B, Piepgras DG, Wiebers DO, Houser OW. Familial occurrence of spontaneous dissection of the internal carotid artery. *Stroke* 1987;18:246-51.
- Varani E, Magnani G, Magelli C, et al. Aneurisma dissecante dell'aorta: descrizione di casi familiari. *Medicina* 1988;8:293-7.

9. Somlo S, Rutecki G, Giuffra LA, Reeders ST, Cugino A, Whittier FC. A kindred exhibiting cosegregation of an overlap connective tissue disorder and the chromosome 16 linked form of autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 1993;4:1371-8.
10. Schievink WI, Prakash UBS, Piepgras DG, Mokri B. α_1 -Antitrypsin deficiency in intracranial aneurysms and cervical artery dissection. *Lancet* 1994; 343:452-3.
11. Schievink WI, Michels VV, Piepgras DG. Neurovascular manifestations of heritable connective tissue disorders: a review. *Stroke* 1994;25:889-903.
12. Schievink WI, Mokri B, O'Fallon WM. Recurrent spontaneous cervical-artery dissection. *N Engl J Med* 1994;330:393-7.
13. Kuivaniemi H, Prockop DJ, Wu Y, et al. Exclusion of mutations in the gene for type III collagen (COL3A1) as a common cause of intracranial aneurysms or cervical artery dissections: results from sequence analysis of the coding sequences of type III collagen from 55 unrelated patients. *Neurology* 1993;43:2652-8.
14. Mackie RM. Melanocytic naevi and malignant melanoma. In: Champion RH, Burton JL, Ebling FJG, eds. *Textbook of dermatology*. 5th ed. Vol. 2. Oxford, England: Blackwell Scientific, 1992:1525-60.
15. Lever WF, Schaumburg-Lever G. *Histopathology of the skin*. 7th ed. Philadelphia: J.B. Lippincott, 1990:772-4.
16. Rees JR, Ross FMG, Keen G. Lentiginosis and left atrial myxoma. *Br Heart J* 1973;35:874-6.
17. Atherton DJ, Pitcher DW, Wells RS, MacDonald DM. A syndrome of varicous cutaneous pigmented lesions, myxoid neurofibromata and atrial myxoma: the NAME syndrome. *Br J Dermatol* 1980;103:421-9.
18. Rhodes AR, Silverman RA, Harrist TJ, Perez-Atayde AR. Mucocutaneous lentiginos, cardiomucocutaneous myxomas, and multiple blue nevi: the "LAMB" syndrome. *J Am Acad Dermatol* 1984;10:72-82.
19. Bain J. "Carney's complex." *Mayo Clin Proc* 1986;61:508.
20. Schweizer-Cagianut M, Salomon F, Hedinger CE. Primary adrenocortical nodular dysplasia with Cushing's syndrome and cardiac myxomas: a peculiar familial disease. *Virchows Arch A Pathol Anat Histopathol* 1982;397: 183-92.
21. Carney JA, Gordon H, Carpenter PC, Shenoy BV, Go VLW. The complex of myxomas, spotty pigmentation, and endocrine overactivity. *Medicine* 1985; 64:270-83.
22. Young WF Jr, Carney JA, Musa BU, Wulffraat NM, Lens JW, Drexhage HA. Familial Cushing's syndrome due to primary pigmented nodular adrenocortical disease: reinvestigation 50 years later. *N Engl J Med* 1989;321:1659-64.
23. Carney JA. Psammomatous melanotic schwannoma: a distinctive, heritable tumor with special associations, including cardiac myxoma and the Cushing syndrome. *Am J Surg Pathol* 1990;14:206-22.
24. Walther RJ, Polansky BJ, Grots IA. Electrocardiographic abnormalities in a family with generalized lentigo. *N Engl J Med* 1966;275:1220-5.
25. Gorlin RJ, Anderson RC, Blaw M. Multiple lentiginos syndrome. *Am J Dis Child* 1969;117:652-62.
26. Seuanez H, Mane-Garzon F, Kolski R. Cardio-cutaneous syndrome (the "Leopard" syndrome): review of the literature and a new family. *Clin Genet* 1976;9:266-76.
27. Fox B. Cystic medial necrosis. In: Greenhalgh RM, Mannick JA, eds. *The cause and management of aneurysms*. London: W.B. Saunders, 1990:79-87.
28. Roberts WC, Honig HS. The spectrum of cardiovascular disease in the Marfan syndrome: a clinico-morphologic study of 18 necropsy patients and comparison to 151 previously reported necropsy patients. *Am Heart J* 1982; 104:115-35.
29. Rubinstein MK, Cohen NH. Ehlers-Danlos syndrome associated with multiple intracranial aneurysms. *Neurology* 1964;14:125-32.
30. Warnes CA, Kirkman PM, Roberts WC. Aortic dissection in more than one family member. *Am J Cardiol* 1985;55:236-8.
31. Nicod P, Bloor C, Godfrey M, et al. Familial aortic dissecting aneurysm. *J Am Coll Cardiol* 1989;13:811-9.
32. Beighton P. The Ehlers-Danlos syndromes. In: Beighton P, ed. *McKusick's heritable disorders of connective tissue*. 5th ed. St. Louis: C.V. Mosby, 1993: 189-251.
33. Le Douarin NM. *The neural crest*. Vol. 12 of *Developmental and cell biology*. Cambridge, United Kingdom: Cambridge University Press, 1982.
34. Le Lievre CS, Le Douarin NM. Mesenchymal derivatives of the neural crest: analysis of chimaeric quail and chick embryos. *J Embryol Exp Morphol* 1975;34:125-54.
35. Rosenquist TH, Beall AC, Modis L, Fishman R. Impaired elastic matrix development in the great arteries after ablation of the cardiac neural crest. *Anat Rec* 1990;226:347-59.
36. Kappetein AP, Gittenberger-de Groot AC, Zwinderman AH, Rohmer J, Poelmann RE, Huysmans HA. The neural crest as a possible pathogenetic factor in coarctation of the aorta and bicuspid aortic valve. *J Thorac Cardiovasc Surg* 1991;102:830-6.
37. Schievink WI, Mokri B, Piepgras DG. Spontaneous dissections of cervico-cephalic arteries in childhood and adolescence. *Neurology* 1994;44:1607-12.

Massachusetts Medical Society
Registry on Continuing Medical Education

To obtain information on continuing medical education courses in the New England area, call between 9:00 a.m. and 12:00 noon, Monday through Friday, (617) 893-4610 or in Massachusetts 1-800-322-2303, ext. 1342.