Neurovascular Manifestations of Heritable Connective Tissue Disorders

A Review

Wouter I. Schievink, MD; Virginia V. Michels, MD; David G. Piepras, MD

Heritable disorders of connective tissue affecting the arterial wall are recognized in a minority of arterial diseases of the central nervous system. These primary arteriopathies may result from a defect in a single component of the extracellular matrix. The phenotype of each heritable connective tissue disorder is determined by the organ distribution of the affected extracellular matrix protein. Marked phenotypic heterogeneity may complicate the diagnosis of these heritable connective tissue disorders. Nevertheless, recognition of an underlying connective tissue disorder may be of considerable importance. In this communication, we review the neurovascular complications of the four classically recognized heritable connective tissue disorders: Ehlers-Danlos syndrome, Marfan’s syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum, as well as other systemic disorders with potential vascular manifestations: neurofibromatosis and polycystic kidney disease.

Summary of Review: Typical neurovascular complications of Ehlers-Danlos syndrome are carotid-cavernous fistulae, intracranial aneurysms, and cervical artery dissections. Arterial dissections and intracranial aneurysms cause the majority of neurovascular symptoms in Marfan’s syndrome. Neurovascular disease is uncommon in osteogenesis imperfecta, although carotid-cavernous fistula and vertebral artery dissections have been reported. Neurovascular disease in pseudoxanthoma elasticum is characterized by intracranial aneurysms and cerebral ischemia caused by premature arterial occlusive disease. Intracranial occlusive arterial disease is the most common neurovascular manifestation of neurofibromatosis, followed by cervical arteriovenous fistulae and aneurysms and intracranial aneurysms. Intracranial aneurysms are the hallmark of polycystic kidney disease.

Conclusions: Recognition of an underlying generalized connective tissue disorder may be of considerable importance, although marked phenotypic heterogeneity often complicates the diagnosis of these disorders. Conversely, the association of certain neurovascular anomalies with generalized connective tissue disorders and recognition of their basic molecular defect may offer clues to the etiology and pathogenesis of these neurovascular diseases in general. (Stroke. 1994;25:889-903.)

Key Words: cerebral vascular disorders • connective tissue diseases • genetics
TABLE 2. Classification of the Ehlers-Danlos Syndromes

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Manifestations</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Soft, velvety, markedly fragile, hyperextensible skin; easy bruising; marked joint hypermobility; premature rupture of fetal membranes; occasional vascular complications</td>
<td>AD</td>
</tr>
<tr>
<td>II</td>
<td>Moderately fragile, hyperextensible skin; moderate joint hypermobility</td>
<td>AD</td>
</tr>
<tr>
<td>III</td>
<td>Moderately hyperextensible or normal skin; minimal scarring; marked joint hypermobility</td>
<td>AD</td>
</tr>
<tr>
<td>IV</td>
<td>Thin, translucent, extremely fragile skin with normal extensibility, occasionally normal-appearing skin; easy bruising; joint hypermobility, often limited to the digits; vascular complications common; uterine and bowel rupture; pneuomothorax; occasional characteristic facial appearance</td>
<td>AD</td>
</tr>
<tr>
<td>V</td>
<td>Markedly hyperextensible skin; minimal joint hypermobility; skeletal abnormalities</td>
<td>X-LR</td>
</tr>
<tr>
<td>VI</td>
<td>Soft, velvety, marked hyperextensible skin; marked joint hypermobility; ocular fragility and keratoconus; muscle hypotonia; kyphoscoliosis</td>
<td>AR</td>
</tr>
<tr>
<td>VII</td>
<td>Soft, moderately hyperextensible skin; marked joint hypermobility; congenital hip dislocation; short stature</td>
<td>AD</td>
</tr>
<tr>
<td>VIII</td>
<td>Moderately fragile but minimally hyperextensible skin; moderate joint hypermobility; generalized periodontitis</td>
<td>AD</td>
</tr>
<tr>
<td>IX</td>
<td>Formerly known as X-linked cutis laxa, this disorder is now classified as occipital horn syndrome, a disorder of copper transport.</td>
<td>?</td>
</tr>
<tr>
<td>X</td>
<td>Mildly hyperextensible skin; moderate joint hypermobility; petechiae</td>
<td>?</td>
</tr>
</tbody>
</table>

AD indicates autosomal dominant; X-LR, X-linked recessive; AR, autosomal recessive; and ?, unknown.
include joint hypermobility, sometimes limited to the digits; mitral valve prolapse; and spontaneous pneumothorax. A prematurely aged appearance has been described in a subgroup of patients (the so-called "acrogeric" form). Alternatively, other patients have mild involvement of the skin without a characteristic facial appearance.

Microscopic examination of affected vessels reveals disarrangement of collagen fibers and fragmentation of the intima.

Epidemiology and Inheritance

The prevalence of EDS type IV has not been determined, but it is generally considered to be a rare disease that is undoubtedly related, at least in part, to the difficulties in recognizing the phenotype. In a survey by Beighton and Horan of 100 patients with EDS, 4 had type IV disease, whereas 17 of 151 patients with EDS registered at the Ehlers-Danlos National Foundation had EDS type IV.27 The prevalence of all types of EDS combined has been estimated to be as high as 1 per 5000 population.6 Although earlier reports had suggested the possibility of autosomal recessive inheritance,28,29 biochemical and molecular studies have now shown that inheritance is autosomal dominant.5,6 Family history, however, is often noncontributory, since sporadic mutations frequently occur.

Neurovascular Manifestations

Probably the most common neurovascular manifestation of EDS type IV is the spontaneous direct carotid-cavernous fistula.12,20,23,24,26-49 Conversely, among 212 patients with carotid-cavernous fistulae evaluated by Halbach et al,47 4 had EDS type IV, as was the case in 2 of 12 patients with spontaneous carotid-cavernous fistulae treated by Kupersmith et al.45 Most patients with EDS type IV develop their carotid-cavernous fistulae in the third or fourth decade of life.50 Spontaneous direct carotid-cavernous fistulae are high-flow arteriovenous communications that may develop secondary to the rupture of a cavernous carotid artery aneurysm. Direct rupture or transmural dissection of the cavernous segment of the carotid artery also may cause a fistula. Small tears of the cavernous carotid artery occasionally have been detected at postmortem examination in patients with EDS type IV.23,42,48 In general, bilateral carotid-cavernous fistulae and the familial occurrence of carotid-cavernous fistulae are rare, but they are relatively common in EDS type IV, and their occurrence in particular should raise the suspicion of EDS type IV.

An intracranial aneurysm with or without subarachnoid hemorrhage (SAH) is a typical complication of EDS type IV.5 Spontaneous dissections of the extracranial internal carotid or vertebral artery are more recently recognized features of EDS type IV and are probably underdiagnosed.20,46,51,54 The 21-year-old woman with EDS type IV reported by Ruby et al54 was diagnosed with an extracranial internal carotid artery aneurysm, but angiography was most consistent with a dissection, showing an elongated stenosis and a subcranial aneurysmal dilatation. Pope et al48 described a 22-year-old woman with EDS type IV and an extracranial internal carotid artery dissection who had a normal cerebral angiogram. The diagnosis of dissection, which was strongly suspected clinically, could not be confirmed until a magnetic resonance (MR) image was obtained that showed an intramural hemorrhage. Dissections of the cervical arteries also may be iatrogenic and occur after angiography in patients with EDS type IV.42

Cervical artery aneurysms of which the underlying pathogenetic mechanism (saccular, dissecting, or pseudoaneurysm) is unclear have been reported in patients with EDS type IV who presented with a neck mass.55-58 Brearley et al59 reported a 28-year-old woman with EDS type IV who developed an anterior neck hematoma caused by spontaneous rupture of the external carotid artery with extension into the jugular vein, causing a fistula. Ectasia and tortuosity of the cervical arteries without distinct aneurysmal formation are commonly encountered on angiography and may mimic fibromuscular dysplasia.60

Biochemical and Molecular Defects

The basic molecular defect of EDS type IV is an abnormality of type III collagen.5,6,19,51 Collagen type III is a major component of the extracellular matrix of distensible tissues, such as skin, blood vessels, and hollow viscera, explaining the systemic manifestations of the disease.5,6,19,62 Easy bruising associated with EDS type IV is probably a result of a defective interaction between platelets and the vascular subendothelium, which normally is rich in type III collagen.63 The type III procollagen molecule consists of three pro-α1 (I) chains. The gene encoding for the pro-α1 chain of type III procollagen (COL3A1) is located on chromosome 2.5,6 A wide variety of mutations within the COL3A1 gene resulting in a qualitative or quantitative defect of the type III collagen molecule have been recognized.5,6 The diagnosis of EDS type IV can usually be confirmed by fibroblast culture and biochemical studies of collagen metabolism or sequencing analysis of the COL3A1 gene. In addition, a subgroup of patients with EDS type IV, serum levels of the type III collagen amino- propeptide are reduced.64,65

After the initial reports by Pope and colleagues, who, using biochemical techniques, detected collagen type III abnormalities in up to 40% to 50% of otherwise normal patients with intracranial aneurysms,66-68 several investigators have found collagen type III deficiencies in groups of patients with intracranial aneurysms that apparently were not associated with classic EDS type IV.69,70 However, in a recent study of 40 patients with familial and nonfamilial intracranial aneurysms, Kuivaniemi et al71 detected mutations in the COL3A1 gene in only 2 patients. In a separate study, these investigators reported a COL3A1 mutation in 1 additional patient with an intracranial aneurysm.72 These

*See References 16, 20, 31-35, 38, 41, 43, 46, 48, 50, and 51.
COL3A1 mutations did result in a change in the amino acid sequence of the type III procollagen molecule, but the functional consequences of these amino acid substitutions may be insignificant. These recent data suggest that COL3A1 mutations are not common in patients with intracranial aneurysms. Type III collagen defects, which also have been suggested to play a role in the pathogenesis of some spontaneous cervical artery dissections, have not been detected in patients with spontaneous cervical artery dissections without signs of EDS type IV.

Marfan's Syndrome

Marfan's syndrome is characterized by a combination of skeletal, ocular, and cardiovascular abnormalities. The skeletal manifestations of the syndrome were first described in 1896 by the Parisian pediatrician Antoine-Bernard Marfan. Although the variability of the clinical expression is significant, patients with Marfan's syndrome are often easily recognized by the skeletal manifestations, which include tall stature, arachnodactyly or dolichostenomelia, progerism, high-arched palate, kyphoscoliosis, pectus excavatum or carinatum, and joint hypermobility (Fig 1, middle right). Myopia and ectopia lentis are the most common oculomotor abnormalities, although retinal detachment also can occur. Aortic and mitral valve insufficiency, aeurysmal dilatation of the aortic root, and dissection of the aorta are the typical cardiovascular manifestations of Marfan's syndrome. Aneurysms of medium-sized visceral arteries, however, are relatively infrequent. The cardiovascular complications are the cause of death in the vast majority of patients. The most common cause of death in children is severe aortic and mitral regurgitation, and in adults it is acute aortic dissection. Other features of Marfan's syndrome may include dural ectasia, inguinal hernia, and spontaneous pneumothorax. Excessive vascular fragility may be encountered in patients with Marfan's syndrome, but despite this, cardiovascular surgery and endovascular procedures usually can be accomplished successfully. Pathological examination of the arterial wall characteristically reveals the presence of extensive cystic medial necrosis, often with loss of elastic fibers, although similar changes have been found in patients with EDS and in individuals without any discernible features of a generalized connective tissue disease.

Epidemiology and Inheritance

The prevalence of Marfan's syndrome is approximately 1 per 10 000 population. Marfan's syndrome is inherited as an autosomal dominant trait. In approximately 30% of cases, family history is negative and the disease is caused by a new mutation.

Neurovascular Manifestations

The most common neurovascular complications of Marfan's syndrome are probably extension of aortic dissection into the innominate and common carotid arteries, causing cerebral ischemic symptoms, or involvement of spinal arteries, causing paraparesis. These complications may occur in 10% to 20% of patients. Spontaneous dissection limited to the common carotid artery, the extracranial internal carotid artery, or the extracranial vertebral artery also have been reported in patients with Marfan's syndrome. Finney et al observed common carotid artery dissections after ligation of the cervical internal carotid artery and a giant intracranial aneurysm in a patient with Marfan's syndrome; this patient also developed concurrent dissections of the innominate and subclavian arteries. Aneurysms of the extracranial internal carotid artery without evidence of dissection have been described in patients with Marfan's syndrome who presented with an asymptomatic neck mass. Tortuosity and ectasia of the cerebral arteries similar to that seen in EDS type IV is a common finding on angiography.

Intracranial aneurysms associated with Marfan's syndrome are often large and present with mass effect. They most frequently arise from the cavernous segment of the carotid artery. However, patients with Marfan's syndrome with an SAH caused by the rupture of a saccular intracranial aneurysm also have been reported. Steinheuer et al described atrophic changes of the middle cerebral artery with early saccular aneurysm formation in a patient with Marfan's syndrome who died after aortic valve replacement. These authors suggested that the mode of development of intracranial aneurysms in patients with Marfan's syndrome is not different from that in those without Marfan's syndrome. Ter Berg and colleagues described a large Dutch family with eight members affected with intracranial aneurysms and one member, who was not known to have had an intracranial aneurysm, with Marfan’s syndrome. Julien and de Boucaud described a child with Marfan's syndrome and an aneurysm of the vein of Galen. A case of a dissecting aneurysm of the basilar artery associated with Marfan's syndrome was recently reported by Rose and Pretorius.

Pathological changes of cystic medial necrosis have been described in patients with cervical artery dissection or aneurysm who apparently did not have any external stigmata of Marfan's syndrome but who did have a family history of Marfan’s syndrome or similar arterial aneurysmal disease. Whether these patients had coincidental abnormalities or atypical expression of the Marfan syndrome gene defect is unknown.

Biochemical and Molecular Defects

The basic molecular defect of Marfan's syndrome has only very recently been elucidated. The microfibrillar protein fibrillin, which was discovered in 1986, has been shown to be deficient in patients with Marfan’s syndrome. Fibrillin is one of the major components of elastin-associated microfibrils. These microfibrils are found in a wide variety of connective tissues, including the vessel wall and the ciliary zonule of the eye, explaining the clinical manifestations of Marfan's syndrome. The gene encoding for fibrillin (FBN1) has been localized to chromosome 15, and several mutations in this gene have been characterized in patients with Marfan's syndrome. Fibrillin abnormalities can be sought to confirm a diagnosis of Marfan's syndrome or to evaluate patients with, for example, isolated cystic medial necrosis. However, because of the large number of potential mutations in the fibrillin gene, a specific mutation cannot be found in all patients. For families with multiple affected members, linkage analysis using DNA markers that cosegregate with the gene defect can be used for presymptomatic or prenatal diagnosis.
Osteogenesis Imperfecta

Osteogenesis imperfecta is a heterogeneous group of connective tissue disorders characterized by excessive bone fragility. The earliest documented case of OI is attributed to an Egyptian mummy dating from around 1000 BC. Four major types and several subtypes are now recognized on the basis of clinical and genetic characteristics. The classification of OI is summarized in Table 3. OI type I is characterized by blue sclerae (Fig 1, middle left) and frequent fractures during childhood, with little or no deformity. Sclerae are generally normal. Ligamentous and joint hypermobility is variable. OI type II is lethal in perinatal period; extreme bone fragility; marked skeletal deformity; gray or blue sclerae. OI type III is characterized by blue sclerae (Fig 1, middle left) and frequent fractures during childhood, with little or no deformity. Sclerae are generally normal. Ligamentous and joint hypermobility is variable. OI type IV is characterized by mild-to-moderate bone fragility; variable short stature; mild to moderate skeletal deformity; normal sclerae; occasional hearing loss; dentinogenesis imperfecta common.

Neurovascular Manifestations

Neurovascular manifestations of OI have been reported infrequently. De Campos et al described a 25-year-old man with OI who developed a spontaneous direct carotid-cavernous fistula. We have seen a 40-year-old man with OI type I who suffered a brain stem infarct caused by bilateral vertebral artery dissections (unpublished observation). Many patients with OI develop platybasia, and this could compromise blood flow through the vertebral artery; this mechanism was implicated in a 30-year-old man with OI and symptoms of posterior circulation ischemia.

Biochemical and Molecular Defects

The basic molecular defect in virtually all patients with OI of any type is an abnormality of type I collagen. The type I procollagen molecule consists of two pro-α1 (I) chains encoded by the COL1A1 gene and a single pro-α2 (I) chain encoded by the COL1A2 gene. COL1A1 is located on chromosome 17 and COL1A2 on chromosome 7. A quantitative defect of type I collagen caused by a nonfunctioning COL1A1 allele is found in the majority of patients with OI type I in whom a defect has been detected, although qualitative defects caused by mutations in COL1A1 also have been described. Qualitative defects of type I collagen caused by a variety of mutations in COL1A1 or COL1A2 have been detected in most patients with OI types II through IV. Type I collagen is found in bone, ligaments, sclerae, and blood vessels, explaining the systemic manifestations of OI. Although types I and III collagen are equally abundant in blood vessel walls, it is the type III collagen that provides most of the tensile strength, perhaps explaining why vascular complications are not as common in OI as they are in EDS type IV.

Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum is a disorder affecting elastic fibers in the skin, ocular system, and cardiovascular system. The skin manifestations of PXE were first described by the French dermatologist Rigal in 1881. Grenblad, an ophthalmologist, and Strandberg, a dermatologist, both from Stockholm, first recognized the association of the skin lesions with retinal angioid streaks. The characteristic skin lesions consist of round, oval, or linear yellow-orange papules, resembling xanthomas (Fig 1, bottom left). The skin lesions are often associated with laxity and thickening of the skin and preferentially involve flexoral...
areas, such as the neck, axilla, groin, and antecubital and popliteal spaces. Angioid streaks are the characteristic ocular findings and occur in about 85% of affected patients (Fig 1, bottom right).\textsuperscript{142} Angioid streaks are caused by breaks in the thickened and calcified membrane of Bruch. The number and prominence of angioid streaks increase with age. Retinal hemorrhage occurs in about one third of patients.\textsuperscript{137,138,142,143} The cardiovascular changes associated with PXE are those of stenotic, occlusive, or (less frequently) aneurysmal disease primarily affecting medium-sized peripheral arteries.\textsuperscript{137,138,144-149} The aorta is usually spared. Intermittent claudication of the lower extremities, hypertension, and abdominal angina are the most frequent sequelae of the vascular involvement. The arteries in the extremities may become palpably hard, and plain radiographs often reveal arterial calcification. Gastrointestinal hemorrhage may be a presenting symptom of PXE\textsuperscript{137,138,143,150} and is believed to be the result of visceral arterial degeneration or general fragility of the submucosal arteries. Myocardial infarction is not particularly common, although it has been described as early as adolescence in patients with PXE.\textsuperscript{151,152} Occasionally requiring coronary artery bypass procedures.\textsuperscript{152} Mitral valve prolapse is the most common cardiac valvular abnormality of PXE.\textsuperscript{153}

Histological examination of affected arteries reveals fragmentation of elastic fibers with calcification and secondary proliferation of the intima.

**Prevalence and Inheritance**

The prevalence of PXE has been estimated to be around 1 per 100,000 population.\textsuperscript{137,138} PXE is genetically heterogeneous; two autosomal recessive and two autosomal dominant types have been described.\textsuperscript{154,155} One of the autosomal dominant forms appears to be associated with the most significant vascular changes. Pope\textsuperscript{155} reported that in at least half of patients with PXE, inheritance is autosomal dominant, whereas Neldner\textsuperscript{156} reported autosomal recessive inheritance in at least 90% of patients. There is no generally accepted classification of these types of PXE, and in an individual case, one cannot determine the type because of clinical variability even within families.

**Neurovascular Manifestations**

Cerebral infarction caused by (presumed) premature stenotic and occlusive disease of the carotid and vertebral arteries is the most frequently reported neurovascular manifestation of PXE.\textsuperscript{144,146,156-166} Both the intracranial and extracranial vessels may be involved, and the cerebral infarctions are often multiple. Cerebral ischemic symptoms may occur as early as the third decade of life\textsuperscript{159} but usually are not seen until the fifth or sixth decade. Many of these older patients also have hypertension or other risk factors for cardiovascular disease. Cervical spinal cord ischemia associated with PXE has been described by Beurey et al.\textsuperscript{167}

Abnormal anastomotic vessels between the extracranial carotid artery or branches of the external carotid artery and the intracranial carotid artery ("rete mirabile") associated with carotid hypoplasia have been reported in patients with PXE.\textsuperscript{168-170} Such a rete mirabile is considered to be congenital in nature, in contrast to a moyamoya pattern of collateral circulation, which is an acquired condition. In the patient reported by Rios-Montenegro et al.\textsuperscript{168} and Koo and Newton,\textsuperscript{169} rupture of an abnormal vessel of a rete mirabile was believed to be the cause of a spontaneous carotid-cavernous fistula. This patient also had a vertebral artery rete mirabile and similar vascular changes in the spleen.

Josien\textsuperscript{171} reported a 17-year-old boy with PXE who suffered a spontaneous dissection of the cervical vertebral artery. Moki et al.\textsuperscript{172} have mentioned a 40-year-old man with a spontaneous extracranial internal carotid artery dissection who was found to have at least one angioid streak but no cutaneous abnormalities. Their patient may have had a mild form of PXE, although angioid streaks can also be seen in association with EDS, Marfan's syndrome, andOI.

Tortuosity and ectasia of the cervical arteries with or without distinct aneurysmal formation have been described in some patients with PXE.\textsuperscript{166,173}

Several cases of intracranial aneurysm associated with PXE have been reported since the first description in 1951.\textsuperscript{146,174,177} In a group of 100 patients with PXE attending a dermatologic clinic, the only neurovascular complication was aneurysmal SAH.\textsuperscript{176} SAH, however, may not be the most common presenting symptom of intracranial aneurysms associated with PXE, since the intracranial aneurysms have frequently been located within the cavernous sinus, causing ocular motor nerve palsies.\textsuperscript{146,174,175} SAH in PXE has also been reported in a patient with normal cerebral vessels\textsuperscript{178} and in association with a pontine arteriovenous malformation.\textsuperscript{179} Kito et al.\textsuperscript{180} reported a unique case of a 37-year-old woman with PXE who suffered an SAH caused by the rupture of an anterior spinal artery aneurysm at the level of the 10th thoracic vertebra. Kissel et al.\textsuperscript{181} described a family with PXE, two members of which suffered SAHs of uncertain cause at the ages of 13 and 17 years. Several authors have reported patients with PXE who suffered intracranial hemorrhages, without commenting on the etiology.\textsuperscript{144,145,157,181}

**Biochemical and Molecular Defects**

The pathogenesis of PXE appears to involve abnormalities of elastic fibers, but the basic molecular defect of PXE is currently unknown.\textsuperscript{137,138} Proposed candidate genes for PXE include the elastin, fibrillin, and lysyl oxidase genes.\textsuperscript{182}

**Neurofibromatosis**

Neurofibromatosis is currently divided into two distinct types on the basis of clinical and genetic characteristics.\textsuperscript{3,183} The cardinal features of neurofibromatosis type 1 were first described by the German pathologist Friedrich von Recklinghausen in 1882.\textsuperscript{184} Neurofibromatosis type 1 is a progressive systemic disease involving tissues of mesodermal and ectodermal origin. A wide variety of organ systems are involved, including the skin (neurofibromas, café-au-lait spots, and axillary and inguinal freckling) (Fig 2), eyes (Lisch nodules), central nervous system (gliomas and heterotopias), peripheral nervous system (neurofibromas and schwannomas), meninges (dural ectasia), skeleton (scoliosis and sphenoid wing dysplasia), and endocrine system (pheochromocytomas).\textsuperscript{3,183} The
Neurovascular Manifestations

The most commonly recognized neurovascular complication of neurofibromatosis is stenotic or occlusive disease of the intracranial circulation, usually occurring in childhood or adolescence. Although renal artery stenosis with diffuse areas of ectasia or aneurysm formation is the most common vascular lesion associated with neurofibromatosis type 1, significant renovascular hypertension occurs in less than 1% of patients. Coarctation of the abdominal aorta may be associated. Easy bruising and vascular fragility are occasionally reported but are of unknown significance. Vascular integrity usually is not affected, and surgery in patients with neurofibromatosis type 1 is generally not associated with noticeably abnormal arterial or venous friability.

Microscopic examination of affected large and medium-sized arteries reveals intimal smooth muscle cell proliferation, medial thinning, and/or fragmentation of elastic tissue.

Neurofibromatosis type 2 is characterized by bilateral acoustic schwannomas and other tumors arising from the central or peripheral nervous system. Skin manifestations are few or absent. Vascular disease is not a recognized manifestation of neurofibromatosis type 2.

Epidemiology and Inheritance

Neurofibromatosis is a relatively common genetic disorder with a prevalence of approximately 1 per 3000 population. Inheritance is autosomal dominant. In about half of patients the disease is caused by a new mutation.

Polycystic Kidney Disease

Polycystic kidney disease is characterized by bilateral multiple renal cysts and is currently divided into two major groups: autosomal dominant PKD (ADPKD) and autosomal recessive PKD. Vascular complications have been described only in ADPKD, a systemic disease in which manifestations are not limited to the kidneys. Cysts may be found in many parts of the body, including the liver, spleen, pancreas, pineal gland,
and subarachnoid space.\textsuperscript{5,247-250} Cardiovascular manifestations may include mitral valve prolapse, aortic dissection, aortic root dilatation, aortic aneurysm, and aortic coarctation.\textsuperscript{4,247,249,251,252} Colonic diverticulosis, spontaneous colonic rupture, and inguinal hernias appear to be relatively common features of ADPKD.\textsuperscript{4,247} An abnormality of one or more extracellular matrix proteins may explain the multiorgan involvement of ADPKD.\textsuperscript{4,247}

**Epidemiology and Inheritance**

With a prevalence of approximately 1 in 400 to 1000 population,\textsuperscript{249,254} ADPKD is one of the most common genetic diseases. It was formerly known as adult-onset PKD, but as it became apparent that children and even fetuses may be affected, it was called ADPKD, reflecting its inheritance.

**Neurovascular Manifestations**

Rupture of a saccular intracranial aneurysm is probably the best-known extrarenal complication of ADPKD. Since the initial report on this occurrence by Borelius in 1901,\textsuperscript{255} a multitude of case reports and selected series have confirmed the association of ADPKD with intracranial aneurysms, as has been reviewed recently.\textsuperscript{256,257} In comparison with intracranial aneurysms in the general population, there is a male predominance among patients with ADPKD and intracranial aneurysms. The aneurysms rupture at an earlier age\textsuperscript{256,257} but with a similar mortality rate.\textsuperscript{258} Contrary to what may be expected, intracranial aneurysms in ADPKD are rare in childhood and adolescence, as are other complications of ADPKD in this age group.\textsuperscript{258} In approximately one fourth of patients with ADPKD, an intracranial aneurysm is detected at postmortem examination.\textsuperscript{256} Conversely, the prevalence of ADPKD among patients with intracranial aneurysms has been reported to range between 2% and 8%.\textsuperscript{256,258} Recently, several groups have investigated the prevalence of asymptomatic intracranial aneurysms in patients with ADPKD. Wakabayashi et al\textsuperscript{259} found one or more intracranial aneurysms in 7 (37%) of 19 patients with ADPKD who were studied with angiography. Chapman et al,\textsuperscript{260} using angiography or high-resolution computed tomography, were able to detect an intracranial aneurysm in 4 (5%) of 88 patients with ADPKD. Using MR angiography, Poulos et al\textsuperscript{261} found saccular intracranial aneurysms in 8 (9%) of 93 patients with ADPKD. MR angiography was able to detect a saccular intracranial aneurysm in 9 (11%) of 85 patients with ADPKD reported by Huston et al.\textsuperscript{262} The discrepancies between these studies may be explained by the clustering of intracranial aneurysms in some families with ADPKD, differences in the race or age of the patients, and differences in the resolution of the imaging techniques used. ADPKD patients with a family history of intracranial aneurysms\textsuperscript{256,257,252-254} and possibly those with extensive polycystic liver disease\textsuperscript{252,255} may be at an increased risk of harboring an intracranial aneurysm. Although screening for asymptomatic intracranial aneurysms has been advocated for other heritable connective tissue diseases, such as EDS, neurofibromatosis, and Marfan's syndrome, on the basis of frequency, screening is probably indicated only for patients with ADPKD, especially those with a positive family history. MR angiography may be the most useful screening tool at the present time. Persistent fetal carotid-basilar anastomoses are relatively frequent findings in patients with ADPKD and may or may not be related to the presence of an intracranial aneurysm.\textsuperscript{260,266,267} Kulla et al\textsuperscript{264} described a unique patient with ADPKD and both saccular and dissecting intracranial aneurysms. Other cerebrovascular abnormalities noted in patients with ADPKD have included moyamoya disease,\textsuperscript{269} intracranial arteriovenous malformations,\textsuperscript{270,271} and intracranial vascular ectasia.\textsuperscript{256,261,262} Poulos et al\textsuperscript{261} noted extracranial carotid artery aneurysms in 3 of 93 patients with ADPKD whom they studied with MR angiography. The underlying pathogenetic mechanism of these aneurysms is not clear, but the angiographic appearance suggests the possibility of dissection. Guthrie and Maclean\textsuperscript{272} mentioned a patient with polycystic kidney and liver disease who developed a common carotid artery dissection after a tractor accident. Extracranial vertebral artery dissection occurred during angiography in 1 of 32 patients with ADPKD so studied by Chapman et al.\textsuperscript{260}

Arterial hypertension is probably not the primary factor in the development of intracranial aneurysms in patients with ADPKD,\textsuperscript{258} although it may have a contributory role. In ADPKD patients with poorly controlled hypertension, primary intracerebral hemorrhage may be more common than aneurysmal SAH.\textsuperscript{273}

**Biochemical and Molecular Defects**

The gene (PKD1) responsible for the great majority of cases of ADPKD has been localized to chromosome 16.\textsuperscript{4,247,254-256} Mutations at other loci are found in approximately 5% to 10% of ADPKD patients.\textsuperscript{4,247,254-256} The structure and function of the PKD gene product have not been determined, and the nature of the biochemical defect underlying ADPKD remains elusive. Several investigators have suggested that an alteration of the extracellular matrix may be crucial in the pathogenesis of ADPKD.\textsuperscript{4,247,257}

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