**Neurovascular Manifestations of Heritable Connective Tissue Disorders**

**A Review**

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

**Background** Heritable disorders of connective tissue are recognized in a small minority of patients with neurovascular diseases. In this report, we review the neurovascular manifestations of four heritable connective tissue disorders: Ehlers-Danlos syndrome, Marfan's syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum, as well as two 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 fistulae 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** • cerebrovascular disorders • connective tissue diseases • genetics

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**Ehlers-Danlos Syndrome**

Ehlers-Danlos syndrome is a heterogeneous group of connective tissue disorders typified by joint laxity, easy bruising, dystrophic scarring, and hyperextensibility of the skin.\(^5\)\(^6\) EDS was first described in 1668 by Job van Meek'\,ren, a surgeon from Amsterdam.\(^3\) At present, nine major types and several subtypes of EDS are recognized on the basis of clinical, genetic, and molecular or biochemical criteria.\(^5\)\(^6\) The classification of EDS is summarized in Table 2. Although the association of EDS with intracranial aneurysms has been described in patients who probably had type I EDS\(^5\) or other underlined forms of EDS,\(^5\)\(^10\) (neuro)vascular complications are the hallmark of EDS type IV, and only this “vascular” type of EDS will be considered in this review.

EDS type IV was first recognized as a distinct clinical entity in 1967 by the British vascular surgeon-in-training Andras Barabas.\(^11\) It is the most life-threatening of all EDS types because of its propensity toward spontaneous rupture, dissection, or aneurysm formation of large and medium-sized arteries in all areas of the body.\(^5\)\(^6\)\(^11\)\(^20\) The arterial complications of EDS type IV are the cause of death in the great majority of patients but usually do not manifest themselves before puberty. Average life expectancy is reported to be approximately 35 years, and survival beyond age 50 is uncommon.\(^6\) However, there is probably a significant bias for more severe cases to be reported, and milder variants are likely to exist in which survival may be longer. Veins are abnormally friable as well, and varicose veins are frequently encountered. The vascular fragility and generalized connective tissue fragility associated with EDS type IV make diagnostic angiography and surgical or endovascular treatment of the vascular anomalies a
hazardous undertaking with an exceptionally high mortality and morbidity. Timely recognition of EDS type IV is therefore of considerable importance. However, the phenotypic expression of EDS type IV is variable, and the external signs are frequently quite subtle. The clinical diagnosis of EDS type IV may therefore be a difficult matter, and a vascular event is often the presenting feature of EDS type IV. In addition to the vascular manifestations, spontaneous rupture of the intestine, often at an early age, and uterine rupture during pregnancy are other catastrophic complications of the disease. Some patients can be recognized by a characteristic facial appearance with expressive eyes, thin nose, thin lips, lobeless ears (Fig 1, top left). The skin is very fragile and thin, almost translucent, allowing the subcutaneous venous pattern to be readily visible, especially over the anterior chest (Fig 1, top right). There is no or only little cutaneous hyperelasticity. Scars are often papyraceous, although keloid formation may also be seen (Fig 1, top right). Easy bruising is common and often of a severe degree. Other features of EDS type IV may be readily visible, especially over the anterior chest and the keloid formation of the right carotid surgical incision. Note the expressive eyes, thin nose, thin lips, lobeless ears, and abnormal scarring of the forehead. Reproduced with permission. Top right, Photograph showing anterior chest and neck of a 20-year-old woman with Ehlers-Danlos syndrome type IV who suffered bilateral carotid-cavernous fistulae. Note the thin skin with a readily visible venous network over the chest and the keloid formation of the right carotid surgical incision. The left carotid surgical incision healed uneventfully. Middle left, Photograph showing deep blue sclerae of a 2-year-old girl with osteogenesis imperfecta. Photograph courtesy of Hymie Gordon, MD. Middle right, Photograph showing body habitus of a 27-year-old man with Marfan’s syndrome. Note the tall stature, dolichostenomelia, and arachnodactyly. His 22-year-old sister, who had no external stigmata of Marfan’s syndrome, suffered a fatal dissection of the cervical internal carotid artery. Photograph courtesy of Hymie Gordon, MD. Bottom left, Photograph showing skin changes of pseudoxanthoma elasticum in the neck of a 27-year-old woman. Note the numerous small, yellow infiltrative papules, which are linearly arranged and have coalesced into elevated plaques. Bottom right, Photograph showing angiod streaks in the fundus of the right eye of a 44-year-old man with pseudoxanthoma elasticum who suffered an ischemic stroke at age 42 years.

TABLE 1. Neurovascular Complications of Heritable Disorders of Connective Tissue

<table>
<thead>
<tr>
<th>Type</th>
<th>Intracranial Aneurysm</th>
<th>Occlusive Arterial Disease</th>
<th>Carotid-Cavernous Fistula</th>
<th>Cervical AV Fistula</th>
<th>Cervical Artery Dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDS</td>
<td>++</td>
<td></td>
<td></td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>MIS</td>
<td>+/+ +</td>
<td></td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>OI</td>
<td>-</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>PXE</td>
<td>+ +</td>
<td>+ +</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NF</td>
<td>+/ + +</td>
<td>+ +</td>
<td></td>
<td>+ +</td>
<td>-</td>
</tr>
<tr>
<td>ADPKD</td>
<td>+ + +</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

AV indicates arteriovenous; EDS, Ehlers-Danlos syndrome; MIS, Marfan’s syndrome; OI, osteogenesis imperfecta; PXE, pseudoxanthoma elasticum; NF, neurofibromatosis; and ADPKD, autosomal dominant polycystic kidney disease.

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>Mildly 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; pneumothorax; 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, markedly 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. The prevalence of all types of EDS combined has been estimated to be as high as 1 per 5000 population. Although earlier reports had suggested the possibility of autosomal recessive inheritance, biochemical and molecular studies have now shown that inheritance is autosomal dominant. 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. Conversely, among 212 patients with carotid-cavernous fistulae evaluated by Halbach et al, 4 had EDS type IV, as was the case in 2 of 12 patients with spontaneous carotid-cavernous fistulae treated by Kupersmith et al. Most patients with EDS type IV develop their carotid-cavernous fistulae in the third or fourth decade of life. 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, 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. The most common site for intracranial aneurysms associated with EDS type IV is the cavernous segment of the carotid artery, and these aneurysms are usually detected after having caused a carotid-cavernous fistula. Intracranial aneurysms associated with EDS type IV characteristically have a very thin wall. SAH of uncertain origin has been reported in several patients suspected of having EDS type IV, including a 5-month-old infant.

Spontaneous dissections of the extracranial internal carotid or vertebral artery are more recently recognized features of EDS type IV and are probably underdiagnosed. The 21-year-old woman with EDS type IV reported by Ruby et al 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 al 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.

Cervical artery aneurysms of 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. Brealey et al 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.

**Biochemical and Molecular Defects**

The basic molecular defect of EDS type IV is an abnormality of type III collagen. 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. 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. The type III procollagen molecule consists of three pro-α(1) (III) chains. The gene encoding for the pro-α(1) chain of type III procollagen (COL3A1) is located on chromosome 2. 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. 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, in a subgroup of patients with EDS type IV, serum levels of the type III collagen amino-propeptide are reduced.

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, 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. However, in a recent study of 40 patients with familial and nonfamilial intracranial aneurysms, Kuivaniemi et al 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. These
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 abnormalities, which include tall stature, arachnodactyly or dolichostenomelia, and joint hypermobility. Myopia and ectopia lentis are the most common ocular abnormalities, although retinal detachment also can occur. Aortic and mitral valve insufficiency, aneurysmal 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 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. 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.

Finnerty et al observed common carotid artery dissections after ligature 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 cervical arteries similar to that seen in EDS type IV is a common finding on angiography.

Intracranial aneurysms associated with Marfan’s syndrome often are 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. 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. 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 now 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.\textsuperscript{113,114} The earliest documented case of OI may be that of an Egyptian mummy dating from around 1000 BC.\textsuperscript{115} The term OI, however, was first coined by Willem Vrolik, an anatomist from Amsterdam, in 1849.\textsuperscript{116} Four major types and several subtypes are now recognized on the basis of clinical and genetic characteristics.\textsuperscript{113,114,117} 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. Stature is generally normal. Ligamentous and joint hypermobility is variable. OI type II is the lethal form of OI and is characterized by blue or grey sclerae and marked skeletal deformity. OI type III is characterized by fractures at birth and progressive growth failure, with frequent fractures and bone deformity. Sclerae are variable in hue. OI type IV is characterized by mild-to-moderate bone deformity and short stature, with normal sclerae. Dentinogenesis imperfecta is an uncommon feature of OI type I but is common in types III and IV. Hearing loss occurs in approximately 50% of patients with OI type I, is common in OI type III, and also can occur in OI type IV.

The cardiovascular manifestations of OI are not well defined. Aortic root dilatation may be the most common vascular abnormality of OI and has been found in all nonlethal types of OI.\textsuperscript{118,119} Other cardiovascular complications may include mitral valve prolapse, aortic regurgitation, and atrial rupture.\textsuperscript{118-123} Aneurysms affecting the coronary\textsuperscript{124} and ulnar arteries\textsuperscript{122} have been described in isolated cases. Easy bruising is common\textsuperscript{113} and may be related to excessive vascular fragility associated with the disease. Excessive vascular fragility has been encountered at the time of surgical procedures,\textsuperscript{120,121,126} and it may also be a factor in the development of extracerebral hematomas in patients with OI.\textsuperscript{127-129}

Epidemiology and Inheritance

The prevalence of OI in all its forms has been estimated to be around 1 per 10 000 population.\textsuperscript{113,114} Inheritance of OI types I and IV is invariably autosomal dominant. The vast majority of OI type II is caused by autosomal dominant new mutations, whereas both autosomal recessive and dominant inheritance have been described in OI type III.

Neurovascular Manifestations

Neurovascular manifestations of OI have been reported infrequently. De Campos et al\textsuperscript{130} 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,\textsuperscript{131-133} 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.\textsuperscript{134}

Biochemical and Molecular Defects

The basic molecular defect in virtually all patients with OI of any type is an abnormality of type I collagen.\textsuperscript{113,114,135,136} The type I procollagen molecule consists of two pro-\(\alpha_1\) (I) chains encoded by the COL1A1 gene and a single pro-\(\alpha_2\) (I) chain encoded by the COL1A2 gene. COL1A1 is located on chromosome 17 and COL1A2 on chromosome 7.\textsuperscript{137} 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.\textsuperscript{138} Although qualitative defects caused by mutations in COL1A1 also have been described,\textsuperscript{133,134,135} 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.\textsuperscript{113,114} 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,\textsuperscript{62} 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.\textsuperscript{137,138} The skin manifestations of PXE were first described by the French dermatologist Rigal in 1881.\textsuperscript{139} Grenblad,\textsuperscript{140} an ophthalmologist, and Strandberg,\textsuperscript{141} a dermatologist, both from Stockholm, first recognized the association of the skin lesions with retinal angiod streaks. The characteristic skin lesions consist of round, oval, or linear yellow-orange papules, resembling xanthomas (Fig 1, bottom left).\textsuperscript{137,138} The skin lesions are often associated with laxity and thickening of the skin and preferentially involve flexural

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Table 3. Classification of Osteogenesis Imperfecta

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Manifestations</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Variable bone fragility; normal stature; little or no skeletal deformity; blue sclerae; hearing loss common; dentinogenesis imperfecta rare</td>
<td>AD</td>
</tr>
<tr>
<td>II</td>
<td>Lethal in perinatal period; extreme bone fragility; marked skeletal deformity; gray or blue sclerae</td>
<td>AD, rarely AR</td>
</tr>
<tr>
<td>III</td>
<td>Severe bone fragility; markedly short stature; progressive skeletal deformity; variable scleral hue, lightening with age; hearing loss common; dentinogenesis imperfecta common</td>
<td>AD or AR</td>
</tr>
<tr>
<td>IV</td>
<td>Mild to moderate bone fragility; variable short stature; mild to moderate skeletal deformity; normal sclerae; occasional hearing loss; dentinogenesis imperfecta common</td>
<td>AD</td>
</tr>
</tbody>
</table>

AD indicates autosomal dominant; AR, autosomal recessive.
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).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.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.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.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.151,152 Occasionally requiring coronary artery bypass procedures.152 Mitral valve prolapse is the most common cardiac valvar abnormality of PXE.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.137,138 PXE is genetically heterogeneous; two autosomal recessive and two autosomal dominant types have been described.154,155 One of the autosomal dominant forms appears to be associated with the most significant vascular changes. Pope155 reported that in at least half of patients with PXE, inheritance is autosomal dominant, whereas Neldner156 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.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 life159 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.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.168-170 Such a rete mirabile is considered to be congenital in nature, in contrast to a moyamoya pattern of collateral circu-
vascular manifestations of neurofibromatosis type 1 are characterized by stenosis, occlusion, rupture, and aneurysm or fistula formation of large and medium-sized arteries.\(^3\) \(^1\) \(^8\) \(^3\) \(^1\) \(^9\) \(^2\) \(^0\) \(^2\) \(^1\) \(^0\) \(^2\) 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.\(^3\) Coarctation of the abdominal aorta may be associated.\(^2\) Easy bruising and vascular fragility are occasionally reported\(^2\) \(^3\) \(^1\) 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.\(^3\) \(^1\) \(^8\) Skin manifestations are few or absent.\(^3\) \(^1\) \(^8\) \(^3\) 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.\(^3\) Inheritance is autosomal dominant. In about half of patients the disease is caused by a new mutation.

**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.\(^3\) \(^1\) \(^8\) - \(^2\) \(^0\) \(^2\) \(^1\) \(^0\) \(^2\) Adult cases are uncommon but not rare. The supraclinoid carotid artery is the most frequently affected segment, and the intracranial posterior circulation is rarely involved. These intracranial arterial occlusions are associated with a moyamoya pattern of collateral circulation in about three fourths of patients. Extracranial stenotic or occlusive disease of the internal carotid or vertebral arteries also has been described. These occlusive lesions are believed to be caused by intimal proliferation.

The most common nonocclusive neurovascular disease associated with neurofibromatosis type 1 is arteriovenous fistula and aneurysm formation of the extracranial internal carotid or vertebral arteries or external carotid artery.\(^2\) \(^1\) \(^0\) \(^2\) \(^3\) These cervical artery anomalies have affected neurofibromatosis type 1 patients of most age groups. They present as an enlarging neck mass or cause a radiculomyelopathy and are not uncommonly mistaken for a spinal or soft tissue neurofibroma or schwannoma. These and other arterial anomalies may be a manifestation of the generalized mesenchymal dysplasia of neurofibromatosis type 1, predisposing the artery to rupture or aneurysm formation. However, Kawakami et al\(^2\) \(^3\) reported a patient with neurofibromatosis type 1 and an arteriovenous fistula of the cervical internal carotid artery that appeared to have been caused by invasion of the arterial wall by a neurofibroma.

Saccular intracranial aneurysms in patients with neurofibromatosis type 1\(^2\) \(^0\) \(^6\) \(^2\) \(^3\) \(^5\) - \(^2\) \(^4\) \(^3\) are often associated with other cerebrovascular anomalies, mainly intracranial occlusive disease. The intracranial aneurysms have been detected as the source of an SAH or as an incidental finding. Several authors have reported neurofibromatosis type 1 patients with fusiform aneurysms of the petrous and cavernous segments of the carotid artery.\(^2\) \(^4\) \(^1\) \(^2\) The fusiform aneurysm described by Muhonen et al\(^2\) \(^4\) had the MR appearance of a dissecting aneurysm.

**Biochemical and Molecular Defects**

The neurofibromatosis type 1 gene has been localized to chromosome 17, and the gene has been cloned.\(^3\) \(^2\) \(^4\) \(^5\) \(^2\) \(^4\) \(^6\) The neurofibromatosis type 1 gene recently has been shown to be a tumor-suppressor gene.\(^2\) \(^4\) \(^5\) \(^2\) \(^4\) \(^6\) Neurofibromin, the product of the neurofibromatosis type 1 gene, is believed to have several additional functions, one of which may be a regulatory role in the growth and development of connective tissues, possibly also vascular connective tissue, through an effect on microtubular function.\(^2\) \(^4\) \(^6\)

**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.\(^4\) Vascular complications have been described only in ADPKD, a systemic disease in which manifestations are not limited to the kidneys.\(^2\) \(^2\) \(^4\) \(^7\) - \(^2\) \(^4\) \(^9\) Cysts may be found in many parts of the body, including the liver, spleen, pancreas, pineal gland,
and subarachnoid space. Cardiovascular manifestations may include mitral valve prolapse, aortic dissection, aortic root dilatation, aortic aneurysm, and aortic coarctation. Colonic diverticulosis, spontaneous colonic rupture, and inguinal herniae appear to be relatively common features of ADPKD. An abnormality of one or more extracellular matrix proteins may explain the multiorgan involvement of ADPKD.

**Epidemiology and Inheritance**

With a prevalence of approximately 1 in 400 to 1000 population, 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, a multitude of case reports and selected series have confirmed the association of ADPKD with intracranial aneurysms, as has been reviewed recently. 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 and but with a similar mortality rate. 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. In approximately one fourth of patients with ADPKD, an intracranial aneurysm is detected at postmortem examination. Conversely, the prevalence of ADPKD among patients with intracranial aneurysms has been reported to range between 2% and 8%. Recently, several groups have investigated the prevalence of asymptomatic intracranial aneurysms in patients with ADPKD. Wakabayashi et al found one or more intracranial aneurysms in 7 (37%) of 19 patients with ADPKD who were studied with arteriography. Chapman et al, using arteriography 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 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. 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 and possibly those with extensive polycystic liver disease 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. Kulla et al 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, intracranial arteriovenous malformations, and intracranial vascular ectasia. Poulos et al 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 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 one of 32 patients with ADPKD so studied by Chapman et al.

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

**Biochemical and Molecular Defects**

The gene (PKD1) responsible for the great majority of cases of ADPKD has been localized to chromosome 16. Mutations at other loci are found in approximately 5% to 10% of ADPKD patients. 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.
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