

Pediatric and Inherited Neurovascular Diseases

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KEYWORDS

- Pediatric neurovascular diseases
- Inherited neurovascular diseases
- Familial cavernous malformations
- Hereditary hemorrhagic telangiectasia

FAMILIAL CAVERNOUS MALFORMATIONS

Cavernous malformations are congenital vascular lesions affecting blood vessels of the central nervous system (CNS), and account for 20% to 25% of CNS vascular malformations in children.^{1–4} Histologically they consist of sinusoidal-shaped blood vessels with irregular walls that are lined by a single layer of endothelium.⁵ Grossly, cavernomas are collections of sinusoidal vascular channels with an appearance similar to a raspberry and lack intervening brain parenchyma.⁶ Cavernous malformations may occur as sporadic isolated lesions or in a familial form with an autosomal dominant inheritance pattern. In the familial form there are often multiple cavernomas that may arise throughout the CNS. Familial inheritance is a risk factor for aggressive clinical behavior. Familial cavernous malformations occur most frequently in patients of Hispanic origin, although they can be found in any ethnic group.^{4,7–10}

Based on postmortem studies and magnetic resonance imaging (MRI), cavernous malformations have been estimated to affect 0.3% to 0.7% of the general population and represent 5% to 20% of cerebrovascular malformations in all age groups.^{11–13} Reviews of pediatric cavernous malformations estimate that between

3.5% and 26.0% are familial.^{1,11,14} According to several single-institution reviews, the familial form is estimated to represent 75% of patients who present with multiple cavernous malformations, although this number is likely influenced by the screening selection bias of Hispanic patients.^{4,9,15,16}

Familial cavernous malformations are inherited in an autosomal dominant pattern with incomplete clinical penetrance.⁹ Gradient-echo MRI is quite sensitive for detecting these lesions, including small associated subclinical brain hemorrhages. Despite the incomplete clinical penetrance, with gradient-echo MRI the radiologic penetrance is nearly complete.⁹ The probability that standard T2-weighted MRI fails to detect a lesion, given that one existed on gradient-echo MRI, is estimated to be 5% (**Fig. 1**).⁹

Labauge and colleagues⁹ reported on the largest series of familial cavernomas in collaboration with all 28 neurosurgery centers in France. They analyzed 100 symptomatic patients and 278 at-risk relatives without symptoms from 57 indexed families across France. The mean age at clinical onset was 32.6 years (range, 5–74 years). Most patients with familial cavernous malformations had multiple lesions and there was a correlation between the number of lesions and advancing patient age. Surveillance was done using gradient-

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Neurosurg Clin N Am 21 (2010) 427–441

doi:10.1016/j.nec.2010.03.001

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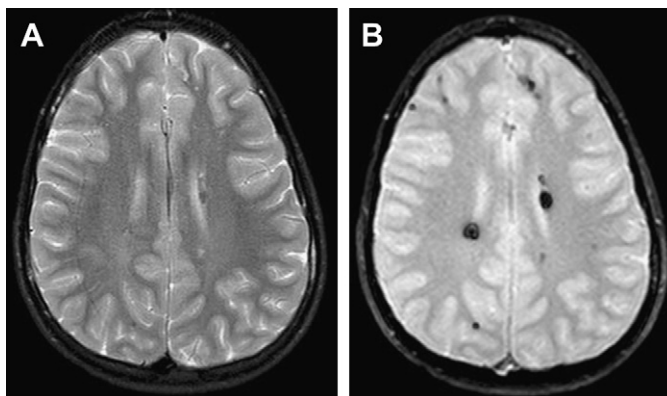


Fig. 1. Axial T2-weighted MRI (A) from a patient with familial cavernous malformations. The T2-STAR sequence (B) is much more sensitive for detection of these lesions.

echo MRI sequences, which had a higher sensitivity for detection of small lesions. The 2 most common presenting symptoms were seizures (affecting 45 of 100 patients) and cerebral hemorrhage (affecting 41 of 100 patients).⁹ Other presenting symptoms included focal sensory and motor neurologic deficits, visual field deficits, and nonmigrainous headaches. The mean age of patient at clinical onset is lower when the initial event is hemorrhage (25.2 years) when compared with all other presenting symptoms (37.8 years).⁹

The natural history of familial cavernous malformations and the optimal radiologic screening protocol has been a topic of debate. Zabramski and colleagues¹³ reported their results after prospectively following 59 members of 6 families by serial interviews, physical examinations, and MRI at 6- to 12-month intervals. Both symptomatic and asymptomatic patients were included in the analysis. Sixty-one percent of patients were symptomatic with seizures (39%), headaches (52%), focal neurologic deficits (10%), and visual field deficits (6%). In these patients, 128 individual cavernous malformations were identified and followed for a mean follow-up period of 2.2 years (range, 1 to 5.5 years). Surveillance MRI revealed new lesions in 29.0% of patients, whereas 10.0% of lesions showed some change in radiographic signal appearance, and 3.9% of lesions changed significantly in size.¹³ The incidence of symptomatic hemorrhage for familial cavernous malformations was 1.1% per lesion per year in that series.¹³ Labauge and colleagues¹⁷ prospectively reviewed the natural history of 33 asymptomatic French patients with relatives diagnosed with familial cavernous malformations. Over a mean period of 2.1 years, 2 patients became symptomatic: 1 with a brainstem hemorrhage, and 1 with a partial seizure. Surveillance MRI found lesion changes in 46% of patients (bleeding in 9.2%,

appearance of new lesions in 30.3%, signal intensity changes in 3.0%, and increased lesion size in 9.1%).

Cavernous malformations in children behave differently compared with adults.¹⁸ Cavernous malformations in children occur at a 4 times lower incidence rate than in adults, but have a more aggressive growth pattern and clinical behavior than in adults.¹ The incidence of a symptomatic hemorrhage from cavernous malformations in children is higher than in adults (27%–78% vs 8%–37%, respectively).^{1,3,11,19,20} In children, a history of the familial form of disease, craniospinal radiotherapy for CNS tumors, and the existence of venous anomalies predicts worse clinical behavior. The existence of multiple cavernous malformations in children is estimated at 12% of cases, whereas up to 80% of patients harboring multiple cavernous malformations exhibit the familial form of disease.^{1,19,21–23} The presence of cavernous malformations with venous anomalies has been reported in as many as 2.1% to 26.0% of patients undergoing surgical treatment.^{24,25} Overall, although much is left to be answered, it is generally agreed that the natural history of cavernous malformations is more aggressive in children than in adults, given their higher hemorrhage rate.

Familial cerebral cavernous malformations are inherited in an autosomal dominant pattern with incomplete clinical penetrance. Linkage analysis of several Hispanic families identified the CCM1 gene on chromosome 7 from q11 to q22 with mutations in KRIT1, which is responsible for familial cavernous malformations.^{26–28} The homogeneity at the CCM1 locus, however, did not represent the expressive phenotype of familial cavernous malformations in patients of non-Hispanic ethnicity. The CCM2 gene on chromosome 7p13-15 (with MGC4607 or malcavernin

mutations) and CCM3 gene at 3q25.2-27 were found after investigation of 20 non-Hispanic white families.^{26,28-31} A fourth CCM locus (CCM4) was identified in 3q26.3-27.2, representing a mutation of PDCD10.^{26,32} The CCM1 protein, KRIT1, participates in regulation of cell adhesion and migration via its interaction with beta-1 integrin.^{26,33,34} This interaction may control endothelial cell behavior. The CCM3 gene (PDCD10) induces apoptosis through modulation of the cell cycle.³⁵ It has therefore been proposed that aberrant apoptosis, by altering the balance between endothelial and neural crest cells within the neurovascular unit, may lead to cavernoma formation. Identification of these and other molecular defects allows clinicians to better screen at-risk families.³⁶ Screening of relatives with multiple or sporadic cavernous malformations continues to be a topic of debate. This question has not yet been convincingly answered by the existing clinical data, although it is generally recommended that first-degree relatives of patients with known familial cavernous malformations have a surveillance brain MRI.

Management of familial cavernous malformations differs from sporadic malformations. Although large multicenter trials have not been performed, many single-center studies show that microsurgery can be performed without significant postsurgical complications to prevent recurrent hemorrhage and control seizure disorders in these patients.^{37,38} The treatment of choice for symptomatic solitary cavernous malformations is often microsurgery; however, for multiple cavernous malformations, as is the case for many patients with familial cavernous malformations, the decision to offer surgery should be entertained with greater caution.^{37,38}

HEREDITARY HEMORRHAGIC TELANGIECTASIA

HHT is an autosomal dominant disorder characterized by arteriovenous malformations (AVMs) of multiple solid organs and telangiectases of the mucous membranes and dermis.³⁹ In the past, this disease has also been referred to as Rendu-Osler-Weber syndrome or Osler-Weber-Rendu syndrome. It is a disease of high penetrance but variable expressivity.⁴⁰ The incidence rate is approximately 1 to 2 individuals per 10,000, with no major ethnic or geographic differences.⁴¹

HHT is classically caused by one of many possible mutations in either endoglin (ENG) or an activin receptorlike kinase 1 (ALK1). ENG is located on chromosome 9 and causes HHT1, whereas ALK1 is located on chromosome 12 and causes HHT2.^{41,42} Both ENG and ALK1 mutations

encode receptor proteins in the transforming growth factor- β (TGF- β) family. ALK1 encodes a type 1 receptor, which is expressed in endothelial cells and highly vascularized tissues. Thus, the ALK1 gene is a positive regulator of angiogenesis. ENG encodes endoglin, which is expressed in endothelial cells, activated monocytes, and tissue macrophages. ENG increases the relative amount of ALK1 in endothelial cells. Therefore, mutations in either ALK1 or ENG will produce a similar phenotype.

Epistaxis is the most common presenting complaint among patients with HHT (Fig. 2). Half of patients report significant epistaxis by 10 years of age and 90% report epistaxis by 21 years of age.⁴³ Gastrointestinal bleeding is the second most common presentation of HHT.⁴⁴ Patients may also present with dermal telangiectasias, but these typically do not appear until later in life. Telangiectases may be found on the oral and nasal mucosa, tongue, lips, nose, fingertips, trunk, arms, nail beds, or conjunctivae.⁴⁵

AVMs of the CNS, lungs, liver, and upper gastrointestinal tract may present at any age. These lesions may present following hemorrhage or as the result of abnormal shunting.⁴¹ Approximately 20% to 30% of patients with HHT harbor pulmonary AVMs. These often present with exercise intolerance, cyanosis, or pulmonary hemorrhage. However, it is critical to note that 30% to 40% of pulmonary AVMs present with thrombotic or embolic events of the CNS such as stroke, transient ischemic attacks, and abscesses. Abscesses have been reported to occur in 5% to



Fig. 2. Anteroposterior external circulation angiogram in a boy with HHT. A nasal vascular malformation is seen. This child presented with epistaxis.

9% of patients with HHT with pulmonary AVMs.⁴⁶ In general, cerebral embolic complications are rare in young children, but become increasingly common in the fourth through sixth decades.⁴⁶ Hepatic AVMs can present with high-output cardiac failure, portal hypertension, biliary disease, or hepatic encephalopathy. Although rare, AVMs have also been described in the spleen, urinary tract, vagina, coronary arteries, or vessels of the eye.

Clinical evaluation along with molecular and DNA testing are currently used when diagnosing HHT. Clinical diagnostic criteria for HHT are as follows⁴⁷:

1. Spontaneous, recurrent epistaxis, especially if nocturnal.
2. Mucocutaneous telangiectasias, especially on the tongue, lips, oral cavity, fingers, or nose.
3. Internal AVMs; commonly pulmonary, cerebral, spinal, hepatic, or gastrointestinal.
4. First-degree relative with HHT (almost all patients have a positive family history).

Three of these criteria are needed to diagnose HHT. The diagnosis is considered “possible” in the presence of 2 criteria, whereas the diagnosis is unlikely when only 1 criterion is present. Molecular diagnosis is available for HHT. If the molecular test is positive, DNA testing is available for further confirmation. Some authors suggest that patients with symptoms strongly suggestive of HHT, as well as those who are asymptomatic with an affected first-degree relative, should be offered molecular genetic diagnosis.⁴¹ A patient with suspected HHT should be referred to a geneticist for a family-based evaluation.

Patients with HHT are at increased risk for harboring cerebrovascular malformations. Fulbright and colleagues⁴⁸ found AVMs in 4.9%

of HHT patients. Maher and colleagues⁴⁶ found in their study of 321 patients with HHT that 3.7% of patients harbored a cerebral AVM, although asymptomatic patients were not screened. In contrast, Willemse and colleagues⁴⁹ reported that 11% of patients with HHT had a cerebral AVM. Differences in AVM incidence among these studies may be attributed to the various screening protocols that were used at those institutions.

These lesions, like AVMs not associated with HHT, may present with hemorrhage, seizures, or other neurologic symptoms. Spinal AVMs occur in 1% of patients with HHT and can present with progressive myelopathy or even radicular pain.⁵⁰ Although AVMs are the most classic CNS lesions associated with HHT, cavernous malformations, dural arteriovenous fistulae, or aneurysms have all been reported in these patients.⁴⁶

The risk of hemorrhage from cerebral AVMs associated with HHT is controversial. The risk of hemorrhage in an unruptured, nonsyndromic AVM is 2% to 4% per year^{51–53}; however, this rate may not be applicable to AVMs in the HHT population for the following reasons. First, pulmonary and gastrointestinal AVMs in patients with HHT grow and change over time; it is possible that cerebral AVMs in these patients behave similarly. Second, most AVMs described in the HHT literature are smaller than 25 mm in diameter (**Fig. 3**). Although some studies suggest an increased risk of hemorrhage in small AVMs among the general population, this has never been demonstrated in patients with HHT.^{46,54} Last, patients with HHT are more likely than the general population to have multiple AVMs and low-flow telangiectasias, which would influence their annual risk of hemorrhage.^{55–57} In a study of 321 patients with HHT, Maher and colleagues⁴⁶ found the likelihood of a patient with HHT presenting with intracerebral hemorrhage from an

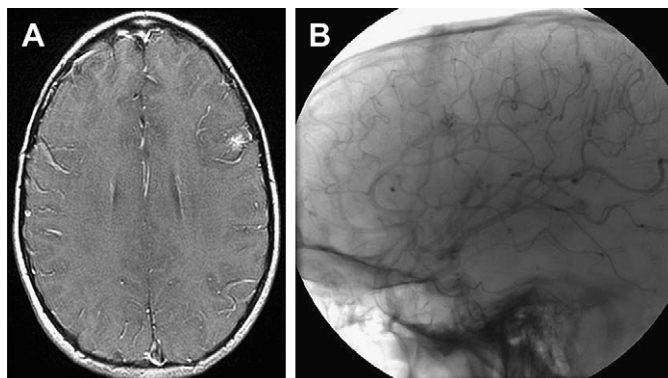


Fig. 3. Axial T1-weighted MRI (A) following contrast administration shows a small AVM that is typical of lesions found in patients with HHT. A follow-up cerebral angiogram (B) shows 3 small AVMs in this patient.

intracranial AVM was very low, occurring in only 2.1% of patients in that large series. This finding is similar to that of Fulbright and colleagues⁴⁸ (0% hemorrhage) and Willemse and colleagues⁴⁹ (1.5% hemorrhage). Taken together, these studies suggest that the natural history of AVMs associated with HHTs is more favorable than that of sporadic cerebral AVMs.

In contrast to the common perception, cerebral AVMs are not the most common cause of neurologic symptoms in patients with HHT. In their study, Roman and colleagues⁵⁸ found that only 36% of 215 patients with neurologic manifestations harbored a cerebrovascular lesion. Most of these lesions were cavernous malformations or venous angiomas; only 7.9% were AVMs. Emboli passing through a pulmonary arteriovenous fistula may result in cerebral abscess or strokes. Untreated or incompletely treated pulmonary fistulas were the most frequent cause of neurologic morbidity in one large series, causing significantly greater morbidity than cerebral AVMs.⁴⁶

Once a patient is diagnosed with HHT, he or she should undergo a multisystem evaluation. An MRI of the brain with and without gadolinium is appropriate for evaluation of cerebral AVMs. Because small AVMs are sometimes difficult to detect on MRI, one may consider a conventional angiogram if the degree of clinical suspicion is high. Patients with HHT should also be evaluated for occult gastrointestinal bleeding. These patients should also be evaluated for the presence of pulmonary AVMs, given that these lesions are a cause of significantly more neurologic morbidity and mortality than cerebral AVMs in patients with HHT. A pulmonary angiogram is the most sensitive test for detection of pulmonary AVMs. A contrast echocardiogram may also be indicated to evaluate for pulmonary shunting. Pulmonary AVMs are usually treated with embolization. The substantial neurologic risk posed by pulmonary AVMs should be taken into account when making treatment decisions regarding these lesions. Treatments for CNS AVMs include surgical resection or stereotactic radiosurgery. In fact, the small size of most AVMs associated with HHT can make them particularly good candidates for radiosurgery. Symptomatic hepatic AVMs are best treated with liver transplantation.⁵⁹ Given the increased risk of bleeding from solid organ AVMs, patients with HHT are generally advised to avoid anticoagulants, including aspirin.

PHACE(S) SYNDROME

PHACE(S) is a neurocutaneous disorder of unknown etiology characterized by posterior fossa

malformations (P), facial hemangiomas (H), arterial and cerebrovascular abnormalities (A), cardiovascular abnormalities (C), and eye abnormalities (E). An “S” is sometimes added for those patients who exhibit ventral congenital defects such as sternal clefting or a supraumbilical raphe.^{60,61} The syndrome has a strong female predominance, but no familial tendency has been demonstrated.⁶² Strict diagnostic criteria for PHACE(S) do not exist. In general, patients are diagnosed with the syndrome if they exhibit the classic cervicofacial hemangioma, as well as at least one extracutaneous anomaly.

Most patients present as infants with large cervicofacial hemangiomas that are not restricted to cutaneous distribution of the trigeminal nerve. These lesions demonstrate a characteristic pattern of rapid neonatal growth, followed by a slow regression.⁶³ A child who presents with a large cervicofacial hemangioma should be evaluated for the extracutaneous manifestations of PHACE(S). The work-up generally includes an echocardiogram to evaluate for cardiac anomalies, as well as an MRI and magnetic resonance angiography (MRA) with and without gadolinium to detect abnormalities of the CNS. If indicated by clinical examination or MRI findings, a conventional angiogram may be considered.

Children with PHACE(S) may harbor congenital malformations of the cerebrum, cerebellum, or cerebral vasculature, including progressive stenosis and occlusion of cerebral arteries. The most common intracranial abnormalities diagnosed in patients with PHACE(S) are posterior fossa lesions ranging from cerebellar hypoplasia to the Dandy-Walker syndrome (Fig. 4). Approximately 43% to 81% of children diagnosed with PHACE(S) have posterior fossa abnormalities.^{60,63} Focal cerebellar lesions tend to occur ipsilateral to the facial hemangioma.⁶³ Poetke and colleagues⁶⁴ found that 81% of patients diagnosed with PHACE(S) also had Dandy-Walker syndrome. Interestingly, another study found that as many as 10% of patients with Dandy-Walker syndrome have a history of infantile hemangiomas, and that 73% of children with both Dandy-Walker syndrome and facial hemangiomas were female.⁶⁵

In a large series of patients with PHACE(S) syndrome, Poetke and colleagues⁶⁴ reported that 12% of patients with PHACE(S) also had intracranial hemangiomas. In their study, the term “intracranial hemangiomas” described extra-axial, meningeal-based, contrast-enhancing masses. These masses were often noted in the cerebello-pontine angle. They demonstrated the same MRI features found in extracranial hemangiomas; that is, isointense on T1-weighted images and

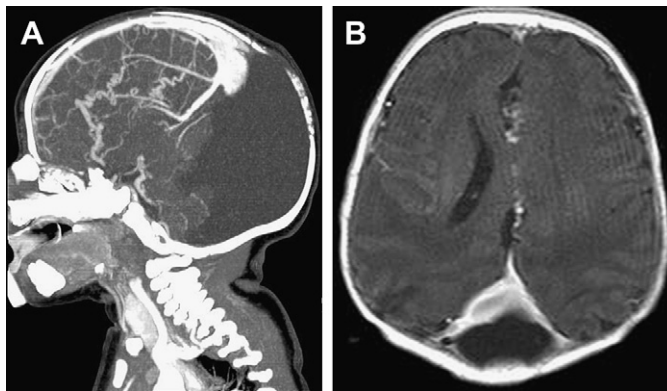


Fig. 4. Sagittal CT angiogram (A) and axial T1-weighted MRI (B) following contrast administration shows cerebral vascular malformations as well as Dandy-Walker malformation in a patient with PHACE(S).

hyperintense on T2-weighted images, suggesting that they are filled with unclotted blood. Intracranial and facial hemangiomas are often ipsilateral and behave in parallel; that is, the intracranial lesion will often demonstrate some involution with steroid therapy administered for the facial lesion.⁶²

Pascual-Castroviejo⁶⁶ first demonstrated in 1978 the relationship between infantile hemangiomas and craniocervical vasculature abnormalities. He described 3 major types of abnormalities: anomalous origin or hypoplasia of major cerebral vessels, persistence of embryonic arteries, especially the trigeminal artery, and “angiomatous” malformations of intra- and extracranial blood vessels including aneurysmal dilations and anomalous arteries mostly located at the carotid siphon and hypothalamus. The most common congenital vascular anomalies associated with PHACE(S) include an aberrant origin or course of major cerebral vessels, arterial absence or agenesis, saccular aneurysms, arterial dysplasia, and persistence of fetal anastomoses.⁶³ Progressive vasculopathy associated with PHACE(S) was first demonstrated by Burrows and colleagues.^{63,67} In that series, progressive arterial obstruction led to ischemic stroke in 4 patients. Less commonly, patients with PHACE(S) can develop moyamoyalike progressive vasculopathy and resultant ischemic strokes. Burrows and colleagues⁶⁷ reported that of the 4 patients in their study with PHACE(S) and ischemic strokes, 3 had moyamoyalike collateral vessel proliferation. Among other studies reporting acute ischemic infarct in patients with a clear diagnosis of PHACE(S), the average age of symptom onset was 8.8 months, with ages ranging from 3 to 18 months. The most common presenting symptoms of infarct in these patients were seizures and hemiparesis.

Focal cerebral dysplasia rarely occurs in association with this syndrome. Lesions reported in patients with PHACE(S) include pachygyria, polymicrogyria, cortical thickening, heterotopic gray matter, and cerebral volume loss. The lesions also tend to occur ipsilateral to the facial hemangioma.^{63,68}

Treating children with PHACE(S) is difficult because they are simultaneously at risk for ischemia as well as hemorrhage. There are no established guidelines for treatment of these patients, but there are many reports describing the use of corticosteroids and aspirin. Burrows and colleagues⁶⁷ suggest that therapies used to treat cutaneous hemangiomas may be helpful in treating the cerebrovascular disease associated with PHACE(S). In their series, 9 of 10 patients with PHACE(S) and ischemic strokes were treated with systemic corticosteroids or interferon therapies, which promote the regression of hemangiomas by modulating the cytokine pathways that regulate angiogenesis. However, one should consider that inhibition of angiogenesis in a patient with moyamoyalike vasculopathy could prevent formation of the collateral circulation necessary to maintain cerebral blood flow, potentially leading to ischemia and infarcts. Strater and colleagues⁶⁹ recommended starting aspirin therapy in patients with PHACE(S) suffering from acute ischemic infarct, as there is at least a 6% risk of recurrent stroke in infants with acute ischemic infarct beyond 6 months of age.

WYBURN-MASON SYNDROME

In 1943, Wyburn-Mason⁷⁰ studied 27 patients with retinal AVMs and found 81% also had intracranial AVMs. The syndrome he described is now known to be a congenital neurocutaneous syndrome of ipsilateral AVMs of the midbrain, vascular

abnormalities affecting the visual pathway (often retinal or orbital AVMs), and facial nevi. The mean age at diagnosis is 23 years for males and 16 years for females.⁷¹ Although there are no strict diagnostic criteria for the syndrome, the presence of all 3 classic features are generally not required for a diagnosis of Wyburn-Mason syndrome.

It is likely that Wyburn-Mason syndrome is the result of an abnormality in the primitive vascular mesoderm that is shared by the developing optic cup and anterior neural tube. Disturbance of these developing tissues before the seventh week of gestation leads to persistence of primitive vascular tissues, affecting both the eye and ipsilateral mesencephalon.⁷¹ Disturbances that occur after the seventh week typically affect only 1 of the 2 structures.⁷² However, bilateral cases of Wyburn-Mason syndrome have been reported and are more difficult to explain developmentally.⁷³

Facial nevi characteristic of Wyburn-Mason syndrome include angiomas affecting the skin in the distribution of the trigeminal nerve. Dayani and colleagues⁷¹ found that 14 of the 27 patients in their study exhibited facial nevi, whereas Theron and colleagues⁷⁴ found that 8 of 25 patients had them. These lesions may also affect deeper structures such as frontal or maxillary sinuses or the mandible. Manipulation of these lesions may lead to significant hemorrhage.

Retinal and orbital AVMs are also associated with Wyburn-Mason syndrome, but are not required for diagnosis. Approximately 30% of Wyburn-Mason patients have retinal AVMs.⁷¹ These lesions commonly present with a progressive or acute decline in visual acuity, proptosis, papillary defects, optic atrophy, and visual field defects. Retinal AVMs are typically more stable than intracranial AVMs.⁷¹ Patients presenting with retinal AVMs should undergo MRI and MRA imaging of the brain and orbit to detect additional AVMs. Changes in retinal AVMs have not been shown to have predictive value in the behavior of cerebral vascular malformations.⁷⁵

The presentation of patients with intracranial AVMs is variable. They are most commonly found in the hypothalamus, thalamus, optic chiasm, and suprasellar area. Many patients are asymptomatic, but among those who experience symptoms, the most common presenting complaints are headaches, retro-orbital pain, and hemiparesis.⁷¹ Patients may also present with developmental delay, irritability, cerebellar dysfunction, or Parinaud's syndrome. Like nonsyndromic AVMs, these lesions may present with spontaneous rupture. The treatment for patients with Wyburn-Mason syndrome is controversial. Occasionally, patients may be managed conservatively, with close observation for

changes in lesions.⁷¹ Surgical, radiosurgical, or endovascular treatment of AVMs can be performed with the same indications, risks, and benefits of AVMs not associated with the syndrome.

KLIPPEL-TRENAUNAY SYNDROME

Klippel-Trenaunay is a congenital syndrome characterized by cutaneous nevi, venous varices, and hemihypertrophy of bones and soft tissues, usually involving one of the extremities. This syndrome may also be associated with lesions characteristic of the Sturge-Weber syndrome, such as leptomeningeal vascular dysplasia; patients with such findings are said to have Klippel-Trenaunay-Weber syndrome.⁷⁶ Klippel-Trenaunay syndrome has also been associated with hydrocephalus, cerebral calcification, AVMs, hemimegalencephaly, and vascular malformations.^{77,78} The syndrome is generally thought to occur sporadically, but some clinical manifestations have been found to cluster in families, suggesting a possible autosomal dominant inheritance pattern.⁷⁹ The cutaneous vascular nevi in Klippel-Trenaunay syndrome include port-wine stains, hemangiomas, or lymphangiomas.

Hemimegalencephaly, a congenital hamartomatous overgrowth of all or part of a cerebral hemisphere with changes in sulcation and pachygyria, is associated with Klippel-Trenaunay syndrome.⁸⁰ When present, hemimegalencephaly occurs on the same side as the cutaneous lesion and bony and soft tissue hypertrophy.^{76,81} Hemimegalencephaly may be asymptomatic or may present with retardation or seizures.⁸² Torregrosa and colleagues⁷⁶ found 18% of patients in their series had cerebral hemihypertrophy. The cause of this abnormality is unknown, but some authors have speculated that it may be attributable to mosaicism resulting in asymmetrical growth of the endo-, meso-, and ectoderm, which must occur before these 3 layers differentiate.^{83,84}

There are approximately 24 reported cases of spinal AVMs associated with Klippel-Trenaunay syndrome in the literature.⁸⁵ Djindjian and colleagues⁸⁶ described 5 cases of Klippel-Trenaunay-Weber syndrome associated with intramedullary AVMs. Retromedullary arteriovenous fistulas and extradural thoracic AVMs have also been reported.^{87,88} Treatment of these lesions does not differ from that for spinal vascular malformations not associated with the syndrome.

SINUS PERICRANII

Sinus pericranii is a rare and usually asymptomatic vascular condition in which there is an abnormal communication between the extracranial and

intradural venous system through diploic veins in the skull. The condition was first described in 1845 by Hecker and again characterized in 1850 by Stromeyer as a “blood bag on the skull, in connection with the veins of the diploe and through these with the sinuses of the brain.”^{89–91} Sinus pericranii is typically diagnosed in childhood and may increase in size. Children often present at birth with a nonpulsatile soft tissue mass. A thrill can sometimes be felt with palpation of the lesion. The anomalous vessels enlarge with crying or when applying a Valsalva maneuver to create increased intracranial pressure, and diminish with compression or elevation of the head.⁹⁰ These lesions are typically located in the midline and frontally, although they can be located anywhere on the skull.⁹²

The differential diagnosis of sinus pericranii is broad and includes subgaleal hematoma, pseudomeningocele, dermoid cysts, epidermoid cysts, hemangiomas, arteriovenous malformations, growing skull fracture, and skin lesions resulting in a subcutaneous soft scalp mass.^{90,93,94} The work-up for these lesions typically begins with skull x-rays, head computed tomography (CT), or brain MRI looking for bony defects or associated cortical changes. Cranial ultrasound with color flow Doppler can demonstrate blood flow between the intradural venous sinuses into the extracranial lesion. Digital subtraction cerebral angiography remains the gold standard for diagnosis; however, CT angiography and magnetic resonance venogram are becoming increasingly useful aids for diagnosis and preventing the need for more invasive testing.

Most patients with sinus pericranii are asymptomatic, but they occasionally experience headaches, nausea, vertigo, local discomfort, mild cardiac failure, and signs and symptoms related to an associated vascular anomaly.^{90,92} There is an association with intracranial venous anomalies, including vein of Galen hypoplasia, vein of Galen malformations, dural sinus malformations, solitary developmental venous anomalies, and intraosseous AVMs.^{92,93,95–97}

Sinus pericranii can arise either as congenital lesions or acquired after trauma. The etiology of congenital sinus pericranii is unknown. Their association with developmental venous anomalies has led some to support a congenital cause from venous hypertension during the embryonic period, thereby altering early intracranial venous development.⁹³ The natural history of sinus pericranii is largely unknown, but prognosis is thought to be favorable as most show no change in size after puberty. Although rare, spontaneous involution of sinus pericranii has been reported in the

literature.^{90,98} The decision to offer surgical treatment is often based on cosmetic concerns. Although uncommon, sinus pericranii can occasionally lead to life-threatening complications from thrombosis or massive scalp hemorrhage.^{90,93,94} Surgical treatment is aimed at prevention of associated complications and restoring cosmesis. Reported surgical options include craniotomy for excision of both the intradural and extracranial lesions, or local scalp incision with plugging of the bony venous channels using bone wax and bone dust.^{90,98–100} Endovascular transvenous embolization for definitive treatment has been described; however, the long-term durability of this technique is unknown.¹⁰¹

VEIN OF GALEN MALFORMATION

Vein of Galen malformations are vascular anomalies of childhood that result from abnormal connections between distal branches of the choroidal and posterior cerebral arteries and the vein of Galen.^{102,103} The development of these lesions occurs between weeks 6 and 11 of gestation, with a persistent embryonic prosencephalic vein of Markowski that drains into the vein of Galen.^{104,105} These lesions may result in high blood flow through the fistula, occasionally resulting in an arterial steal phenomenon, ischemia, and cortical infarction.

There are 2 main classification systems used to describe vein of Galen malformations. Yasargil and colleagues¹⁰⁶ classified them into 4 categories in which types 1, 2, and 3 have no nidus and an artery or arteries directly connect with the vein of Galen. Type 4 malformations are true AVMs, with draining veins through the internal cerebral, basilar, or median atrial vein into the vein of Galen. Lasjaunias and colleagues^{107,108} proposed another classification scheme for vein of Galen malformations, dividing them into choroidal and mural types based on location of the abnormal connection. Choroidal type malformations involve multiple fistulae, which connect with the anterior end of the median prosencephalic vein. The subependymal branches of thalamoperforators or subforniceal, pericallosal, or choroidal arteries supply choroidal type malformations. The fistula is located in the wall of the median prosencephalic vein in mural-type malformations. The posterior choroidal and collicular arteries supply mural-type malformations.

Vein of Galen malformations have an incidence rate of 1 in 25,000 deliveries and represent about 30% to 50% of all vascular malformations in children.^{109–111} With the increasing use of prenatal ultrasound and MRI, in utero diagnosis is becoming

more common.¹⁰² Neonates typically present with macrocephaly, bruits, dilated orbital veins, and high-output heart failure. Infants present with symptoms attributable to hydrocephalus or seizures from focal compression on adjacent CNS structures. Older children and adults present with headaches, cognitive dysfunction, subarachnoid hemorrhage, and focal neurologic deficits.^{110,112} The estimated morbidity and mortality for each hemorrhagic event in the pediatric population is 50% and 5% to 10%, respectively.^{113–115} Neonatal presentation is the most common, encompassing 90% of cases, and carries a worse prognosis.¹⁰⁵ The presence or absence of cortical ischemia and high-output cardiac failure are the most important factors in determining prognosis.¹⁰⁵

Endovascular embolization has become the treatment of choice for vein of Galen malformations.^{114,116} Determining which children to treat and when to offer treatment has been controversial. Lasjaunias and colleagues^{108,117} reviewed their single-institution series of patients with vein of Galen malformations treated over a 20-year period. Of the 371 patients evaluated, 233 were treated with endovascular embolization. In this series, 10.6% of patients died despite or because of treatment. Of the surviving patients, 10.4% survived with severe disability, 15.6% with moderate disability, and 74.0% were neurologically normal. Lasjaunias and colleagues developed a pediatric scoring system to better determine the timing of treatment and when treatment should be withheld in patients with vein of Galen malformations.^{102,108,117} Giebprasert and colleagues¹⁰² suggest that a small subgroup of patients will have a good outcome with conservative management and are unlikely to require surgical intervention. Their criteria for conservative management included mild or well-controlled congestive heart failure; the absence of parenchymal loss, calcifications, hydrocephalus, tonsillar herniation, or evidence of arterial steal on imaging; a high neonatal admission score; and findings suggestive of low-flow shunts (2 or fewer arterial feeding vessels, no deep venous drainage, or no jugular bulb stenosis). Poor prognosis is suggested by severe heart failure with multiorgan failure, or a combination of brain damage, poor clinical status, calcifications on imaging, arterial steal, and an overall poor clinical status. For patients in whom treatment is considered, the timing of treatment remains controversial. Giebprasert and colleagues¹⁰² suggest more urgent treatment if the patient exhibits deterioration of cardiac function, arterial steal, developing hydrocephalus, progressive jugular bulb stenosis, or developmental delay. For all patients, close follow-up is suggested with a brain MRI at least at birth and between 4 to 5

months of age. If the patient remains clinically and radiologically stable, then treatment is offered at 4 to 5 months of age.^{102,105}

BLUE RUBBER BLEB NEVUS SYNDROME

Blue rubber bleb nevus syndrome (BRBN) syndrome is a rare congenital disorder first described by Gascoyen in 1860.¹¹⁸ He took note of the association between cutaneous vascular nevi and gastrointestinal bleeding. Bean¹¹⁹ coined the unique term “blue rubber bleb nevus syndrome” in 1958 to describe the cutaneous vascular malformations that “have the look and feel of rubber nipples.” BRBN primarily involves the skin and gastrointestinal tract. However, vascular lesions may be present in other organs, including lung, pleura, pericardium, heart, liver, spleen, peritoneum, tongue, skeletal muscle, urogenital system, eye, and nasopharynx.¹²⁰ The cutaneous lesions are malformations of venules or capillaries with a cyanotic appearance and an elevated nipplelike center. Gastrointestinal malformations typically involve the small intestines and often bleed causing iron deficiency anemia. CNS involvement of BRBN was first described in 1978 by Waybright and colleagues.¹²¹ Patients with BRBN of the CNS typically present with seizures, developmental delay, or focal neurologic deficits. There have been 8 reported cases in the literature of BRBN with CNS involvement. These lesions are readily seen on brain MRI as multiple enhancing vascular lesions, cortical atrophy, or venous sinus malformations.¹²²

MELAS

The acronym MELAS refers to a syndrome characterized by mitochondrial myopathy (M), encephalopathy (E), and lactic (L) acidosis (A) with strokelike (S) episodes. MELAS is one of the most frequently occurring mitochondrial encephalomyopathies. It is maternally inherited, with onset usually in the first decade of life. Strokelike episodes often occur before the age of 15 years. The clinical course is highly variable, ranging from asymptomatic to progressive muscle weakness, lactic acidosis, cognitive dysfunction, seizures, strokelike episodes, encephalopathy, and death.¹²³ MELAS is associated with many point mutations in mitochondrial DNA, over 80% of which occur in the dihydrouridine loop of the mitochondrial transfer RNA. There is currently no clear consensus on diagnostic criteria for MELAS. It is usually diagnosed by muscle biopsy that demonstrates ragged-red fibers, COX-negative fibers, and abnormally shaped mitochondria with

paracrystalline inclusions. Diagnosis is further confirmed by demonstration of a biochemical respiratory chain defect or one of the known mutations that causes MELAS.¹²⁴ Most affected children meet early milestones normally. They may present later with headaches, recurrent vomiting, seizures, and neurologic deficits resembling ischemic strokes. Many also complain of easy fatigability, short stature, and progressive sensorineural hearing loss.¹²⁵

The strokelike episodes associated with MELAS are recurrent cerebral events that do not conform to discreet vascular territories. These episodes may be transient and nondisabling. Pathogenesis of the strokelike episodes remains unknown, but 2 major theories have been proposed. The first attributes them to mitochondrial angiopathy, with degenerative changes in small arteries and arterioles. The second suggests that these are likely nonischemic events and attributes them to mitochondrial cytopathy characterized by increased capillary permeability, hyperperfusion, neuronal vulnerability, and hyperexcitability.¹²⁶ A specific mechanism for this has been proposed by Iizuka and colleagues¹²⁷: mitochondrial dysfunction in a localized area may cause neuronal hyperexcitability, which then leads to depolarization of adjacent neurons and epileptic activity that spreads to the surrounding cortex. This activity causes increased capillary permeability, leading to the edematous lesions seen predominantly in the cortex on imaging during the strokelike episodes. This is supported by the finding of local cerebral hyperemia that may reflect vasodilation in response to local metabolic acidosis in the area of infarct.¹²⁸

There is no clear treatment paradigm for MELAS, although the results of recent medical therapies have been encouraging. L-arginine is an amino acid that plays an important role in endothelial-dependent vascular relaxation. Koga and colleagues^{129–132} found decreased plasma concentrations of L-arginine in patients with MELAS compared with controls in both the acute phase of strokelike episodes and the period between episodes. Patients treated with L-arginine during the acute phase of strokelike episodes had symptoms that were significantly improved. Oral administration of L-arginine decreased the frequency and severity of strokelike episodes, and improved endothelial function to that of controls at 2-year follow-up.

RADIATION-INDUCED VASCULOPATHY

Intracranial vasculopathy is occasionally seen following radiotherapy to the head and neck.^{133–135}

Vasculopathy following radiation is much more common in small vessels than in medium and large vessels.¹³⁶ A review of 345 patients who underwent therapeutic radiation for a primary brain tumor found that 9.6% had vascular abnormalities on neuroimaging.¹³⁷ Most reported cases presented with vasculopathy many years following radiation treatment, but presentations as early as 15 months after treatment have been described.¹³⁸ Radiation-induced vascular disorders include thrombosis, hemorrhage, aneurysm formation, arterial dissection, moyamoya syndrome, fibrinous exudates, telangiectasias, vascular fibrosis/hyalinization with luminal stenosis, and fibrinoid vascular necrosis.¹³⁹ A large review by Scott and colleagues¹⁴⁰ found that among 345 patients, 10 had vessel ectasia or narrowing, 12 had moyamoya disease, and 3 had hemorrhagic radiation vasculopathy.

Endothelial cells are an actively proliferating site within the brain and are, therefore, one of the most vulnerable to radiation toxicity. Huvos and colleagues¹⁴¹ demonstrated that accelerated atheroma formation, rather than inflammation, is likely the pathologic process induced by radiation in large arteries. Histologic studies of vessels exposed to therapeutic radiation revealed fibrous thickening of the adventitia, intimal hyperplasia, hyaline thickening, and exuberant loose connective tissue production with relative sparing of the media.¹³⁸ Changes are most often noted in small cerebral arteries and white matter, often sparing medium- and large-sized arteries.^{142,143}

Individual risk factors for radiation-induced vascular disease are not well defined but, in general, younger patients are more vulnerable.¹³⁹ Biologic data and case reports suggest that radiation involving the circle of Willis and patients who have neurofibromatosis type 1 may be at increased risk of developing moyamoyalike vascular changes.^{137,140} In a study by Scott and colleagues,¹⁴⁰ among 15 cases of postradiation moyamoya, 8 were treated for hypothalamic-optic gliomas and 4 for craniopharyngioma. The same study also suggests that the development of moyamoya after radiation is both dose- and time-dependent.¹³⁷ This may also prove to be true of other vascular changes associated with radiation.

Guidelines for evaluation and treatment of radiation-induced vasculopathies are not clearly defined. In general, clinical deterioration not explained by tumor recurrence should prompt evaluation by MRI, MRA, or conventional angiography. Treatment varies depending on the specific type and extent of vascular abnormality, but in general, is the same as treatment for similar abnormalities not caused by radiation.

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