The phakomatoses are congenital disorders manifesting with central nervous system and cutaneous abnormalities. The structures predominantly affected are those of ectodermal origin, including the skin, nervous system, and eyes. The 4 most common phakomatoses are neurofibromatosis (types 1 and 2), tuberous sclerosis, Sturge-Weber disease, and von Hippel-Lindau disease. Imaging of the brain and spine in these disorders plays an important role in diagnosis, as well as determining the extent of involvement and guiding surgical interventions. This article reviews the application of x-ray computed tomography and magnetic resonance imaging to these disorders, as well as that of newer, “functional” imaging techniques such as positron emission tomography, magnetic resonance perfusion imaging, and spectroscopy.

Neurofibromatosis

NF1
Type 1 neurofibromatosis, also called von Recklinghausen’s disease, is the most common phakomatosis that occurs about 1 in 3,000 to 4,000. It is transmitted as an autosomal dominant trait with the genetic defect localized to chromosome
17q11.2 encoding neurofibromin. Neurofibromin is a tumor suppressor that regulates Ras-guanosine triphosphate activating protein and thereby controls cellular signal transduction. Although it is hereditary, in 50% of the affected individuals, NF1 occurs sporadically because of spontaneous mutation, and, in fact, it is the syndrome with the highest mutation rate. Affected individuals manifest with cutaneous “café au lait” spots, skinfold freckling, and neurofibromas. Lisch nodules, hamartomas of the iris, may also be found. Neurofibromas are benign tumors arising from the nerve sheath and composed of a mixture of Schwann cells, perineurial cells, and fibroblasts. The neurofibromas can be nodular and discrete, or they can be diffuse, plexiform neurofibromas encasing and enlarging multiple nerve fascicles. The plexiform neurofibroma is quite infiltrative and vascular and may occur in the deep spaces of the head and neck causing major disfigurement or in the paraspinal regions, resulting in nerve compression and neurologic deficits (Fig 1). On MRI, these masses are typically T1 hypointense and T2 hyperintense, with a variable contrast-enhancement pattern. There is estimated to be a 10% risk of development of malignant peripheral nerve sheath tumors, often of the plexiform type, in NF1.
patients. Imaging findings of irregular contour and heterogeneous enhancement are suggestive of invasive nature; however, some of the malignant peripheral nerve sheath tumors have a similar appearance to the benign ones. A few studies suggested that F18-deoxyglucose positron-emission tomography (FDG-PET) may be useful in distinguishing the malignant from benign peripheral nerve sheath tumors.8-10 Multiple spinal neurofibromas tend to occur in NF1 patients as tumors in the intradural extramedullary, extradural, or mixed compartments. They have a characteristic feature of a dumbbell shape, expanding the neural foramina (Fig 2) and often exhibiting central dark signal on T2-weighted images reflecting dense collagen formation on histopathology.

Intracranially, NF1 patients have the tendency of developing neoplasms including optic pathway gliomas that are typically of the juvenile pilocytic astrocytoma histology (Fig 3A) as well as astrocytomas in other brain regions (Fig 3B and C). The incidence of CNS tumors in NF1 is about 1% to 5%.11 Among these, the optic nerve gliomas are most common. They are slow-growing tumors that directly infiltrate and enlarge the optic nerve and can involve any portion of the optic pathway including the intraorbital optic nerves, chiasm, optic tracts, lateral geniculate bodies, and optic radiations. The intraorbital and chiasmal optic gliomas may enhance with gadolinium-diethylenetriamine penta-acetic acid (GdDTPA) either avidly or mildly, whereas the extension along the lateral geniculate, optic tracts, and radiations typically shows expansion and T2 prolongation without contrast enhancement. Visual acuity usually declines slowly and is the most common clinical presentation.12

A number of nonneoplastic abnormalities are often encountered in NF1. Mesenchymal dysplasia associated with...
NF1 leads to defective connective tissue, ranging from bony abnormalities such as sphenoid wing dysplasia, vascular abnormalities such as intracranial aneurysm, stenosis, and moyamoya syndrome (Fig 4), to dural dysplasia. Scalloping of the posterior vertebrae may be seen with intraspinal tumors but more typically as an isolated finding related to dural ectasia. Weakness or defect of the meninges in the spine gives rise to characteristic arachnoid cysts or lateral meningoceles, which most commonly occur in the thoracic region (Fig 5). Sphenoid wing dysplasia occurs uncommonly, in about 1% of cases. This can result in pulsatile exophthalmos related to transmission of cerebrospinal fluid pulsations through the bony defect and herniation of the temporal lobe (Fig 6).

With the advent of MRI, it has been found that 60% to 90% of NF1 individuals, without any neurologic symptoms, have lesions on long T2-weighted sequences. These lesions have been coined the name “unidentified bright objects” (UBOs) and are typically found bilaterally in the dentate nuclei of the cerebellum, brainstem, basal ganglia, and thalami in a symmetric or asymmetric fashion (Fig 7). Atypical location may also be found such as in the cerebral white matter. They are not associated with any mass effect or enhancement. On pathology based on autopsy cases, these lesions correspond to vacuolar changes in the myelin sheath. It is of interest that they often decrease in number and size between 7 and 12 years of age, after which they gradually increase and then decrease again. The evolution may also shift in location. It has been noted that UBOs are found in only 29% of NF1 individuals older than 31 years. Even though these lesions do not cause neurologic symptoms, they have been correlated with learning disabilities. At times, UBOs may have an atypical appearance (such as mass-like, associated with apparent mass effect) or location that makes it difficult to distinguish from an astrocytoma. A UBO should never enhance with Gd, yet the typical low-grade glioma (astrocytoma) also does not show any enhancement. In such cases, 1H-MR spectroscopy may be helpful. It has generally been found that the metabolic profile in these UBOs is not very different from that of a normal brain, suggesting that the
“vacuolar changes” simply reflect areas of edema or holes (Fig 8).

**NF2**

In contrast to NF1, there is minimal skin manifestation in individuals affected by NF2, and the prevalence of NF2 is much lower, about 1 in 40,000. NF2 is characterized by bilateral vestibular schwannomas (Fig 9) \(^21,22\) also known as central form of neurofibromatosis or vestibular schwannoma neurofibromatosis. Diagnosis can be made on the basis of (a) bilateral vestibular masses, or (b) a positive family history with either unilateral vestibular mass, or any 2 of meningiomas, gliomas, schwannomas, and congenital cataracts.\(^23,24\) The genetic defect has been localized to chromosome 22q12.2.\(^25,26\) In 50% of the cases, however, the disease occurs as a result of spontaneous mutation.

Because of the prevalence of multiple intracranial and intraspinal neoplasms, NF2 is also known as Multiple Inherited Schwannomas, Meningiomas, and Ependymomas Syndrome.\(^27\) These are readily identified on contrast-enhanced MRI.\(^6\) Schwannomas can be innumerable, showing as enhancing lesions involving multiple cranial nerves as well as within the intradural compartment along the spinal nerve roots (Fig 10) and in the peripheral nerve sheath within the paraspinal regions (Fig 11A). Intraspinal schwannomas tend to grow as large dumbbell-shaped masses expanding the neural foramina, most commonly intradural extramedullary in location but may be located extradurally or occupy both compartments (Fig 11). They are characteristically bright on T2-weighted images, with avid and homogeneous contrast enhancement (Fig 12) and at times a tendency of becoming cystic. In contradistinction to neurofibromas, they do not have a malignant potential. Schwannomas displace but do not infiltrate the adjacent nerve roots; therefore, surgical resection is possible. Multiple meningiomas often occur intracranially in the extra-axial compartment (Fig 13) and occasionally in the intraventricular location (Fig 14). They can also be found in the spine as extramedullary masses. On a CT scan, they are slightly hyperdense, dural based, and may have associated hyperostosis of the adjacent bone. On MRI, they are typically isointense to gray matter on both T1- and T2-weighted images, with avid and homogeneous contrast enhancement. In the general population, meningioma repre-
sents a common extra-axial neoplasm most often encountered in older females, with its growth under the influence of estrogen. When meningioma occurs in a child, the association of NF2 should be considered. Finally, in NF2, there is a tendency of developing multiple ependymomas that typically present as intramedullary enhancing masses in the spine (Fig 15) of the cellular histological type. They are well-circumscribed masses centrally located in the cord, usually exhibiting T1 isointensity and T2 hyperintensity relative to the adjacent parenchyma, and are associated with strong contrast enhancement.

**TS**

Also know as Bourneville disease, TS is characterized by a triad of seizure, mental retardation, and facial angiofibroma (adenoma sebaceum being a common misnomer). Seizures affect more than 75% of TS patients, and there is also a high rate of learning difficulties, cognitive impairment, and behavioral problems. Similar to other phakomatoses, TS manifests as hamartomatous growths in multiple organ systems including skin, heart, eye, kidneys, and lungs, in addition to involvement of the central nervous system. The prevalence is about 1 in 6,000 to 10,000 births, with 60% to 70% cases of sporadic occurrence. It is an inherited disorder with an autosomal dominant trait. Chromosomal abnormality has been localized to 9q34, encoding TSCI or hamartin, and to 16p13.3, encoding TSC2 or tuberin. Both gene products form a cytoplasmic protein heteromeric complex and act as tumor suppressors affecting the regulation of cellular growth, adhesion, and migration.

Intracranial findings clearly show malformations as a result of perturbed proliferation, histogenesis, and migration of neuronal and glial cells. The hamartomatous lesions can be found anywhere from the ependymal surface to the cortex, and are composed of abnormal giant or balloon cells that may exhibit features of astrocytes, neuronal cells, or intermediate forms. These lesions include subependymal nodules, cortical and subcortical tubers, and subependymal giant-cell astrocytoma. All 3 forms are considered the major features in the revised diagnostic criteria from the Tuberous Sclerosis Complex Consensus Conference in 1998, making imaging an important part of establishing the clinical diagnosis. In the revised criteria, 2 major features or 1 major plus 2 minor features are diagnostic; fulfilling 1 major and 1 minor feature is considered probable TS. In addition to these typical findings, white-matter signal abnormalities reflecting “migration lines” can be seen as bands of myelination defect or gliosis.

The MR appearance of these major lesions varies with age. In the perinatal to early infancy periods, they are best seen as T1 bright lesions, including the white-matter lines along the trail of radial glia and migrating neurons (Fig 16). Later in life, the subependymal nodules are often calcified and may be depicted on T1-weighted images as isointensity to mild hyperintensity and mild T2 hypointensity. Cortical and subcortical tubers as well as white-matter migration lines are best seen on long TR sequences, particularly fluid-attenuated inversion recovery (FLAIR).

Subependymal nodules represent disorganized glial and neuronal elements and can be found lining the ependymal margin and protruding into the ventricular system, yielding an appearance of “candle guttering” (Fig 17). Even though these nodules show signal intensity similar to gray matter,
they are slightly hyperintense on FLAIR, probably reflecting increased water content. Not infrequently, these nodules calcify, best seen on CT scans, but also found on MRI, causing dephasing or loss of signal intensity, particularly on susceptibility weighted images. Some of these nodules enhance with GdDTPA without indicating any increased neoplastic potential. There is a 5% to 14% estimated risk of developing intracranial neoplasm–giant-cell astrocytoma (Fig 18) from the subependymal nodule that is located at the foramen of Monro, often resulting in obstructive hydrocephalus. Histologically, this again represents a mixture of varied glioneuronal phenotypes with dysplastic-appearing giant cells. It is a discrete, low-grade neoplasm of World Health Organization class I amenable to surgical resection. Subcortical and cortical tubers similarly represent a disorganized cluster of glioneuronal elements, with variable degrees of differentiation, and have a strong association with epilepsy, particularly manifesting as infantile spasms and generalized tonic-clonic seizures. They typically show areas of hyperintensity on long TR sequences located in the subcortical white matter, with-
out associated mass effect or enhancement.\textsuperscript{38,40,44} They may also calcify (Fig 19). The associated white-matter signal abnormality at times shows a linear or wedge-shaped track extending from the ventricular surface. This is thought to represent the trail of radial glial cells during the migration and proliferation process.

Variable forms of congenital anomaly have been reported in association with TS, ranging from transmantle cortical dysplasia and corpus callosum dysgenesis to findings of schizencephaly and hemimegalencephaly.\textsuperscript{38,47} Infratentorial abnormalities can also be found (Fig 20), including cerebellar folia or nodular white-matter calcifications, cerebellar hemisphere and vermis agenesis or hypoplasia, enlargement of the cerebellar hemisphere, and brainstem and fourth ventricle subependymal nodules and tubers.\textsuperscript{39}

Proton MR spectroscopy of cortical tubers and subependymal nodules show decreased N-acetylaspartate/creatine (NAA/Cr) and increased myoinositol/Cr ratios. This pattern was thought to reflect expression of immature neurons and glia or gliosis as a result of disturbed cell migration and differentiation in TS.\textsuperscript{48,49} In addition to these similar findings, another study correlated the detection of lactate to the regions of epileptic foci on electroencephalography (EEG) in 6 patients.\textsuperscript{50} On diffusion-weighted imaging, cortical tubers show significantly increased apparent diffusion coefficient (ADC) values compared with normal controls.\textsuperscript{51,52} Furthermore, in a study of 4 TS patients who had unifocal interictal spikes on EEG and magnetoencephalography, ADC was significantly higher in the 4 epileptogenic tubers than 18 nonepileptogenic ones, which in turn showed significantly higher ADC compared with that in a normal-appearing cortex.\textsuperscript{53} These findings are yet to be confirmed in a larger series (preferably with correlation of surgical outcomes). However, it would be of significant value if noninvasive imaging techniques can depict the primary epileptogenic focus in those patients being considered for surgical seizure management.

Perfusion-weighted MR images in a child of multiple calcified tubers in the subcortical white matter shows decreased...
overall perfusion compared with adjacent normal-appearing white matter, and in some of the core of the calcified tubers, there is virtually absent perfusion (Fig 21). Perfusion deficit in the tubers is confirmed in multiple prior radionuclide SPECT and PET studies. A more specific radionuclide agent, alpha-[11C]methyl-L-tryptophan ([11C]AMT) assessing serotonin uptake was found to be useful in discriminating the epileptogenic from nonepileptogenic foci in TS patients. Although multiple tubers show decreased glucose metabolism on FDG-PET, there was a differential pattern of [11C]AMT uptake; the tubers with increased uptake had a high correlation with the epileptogenic foci detected on ictal EEG. Moreover, resection of the high [11C]AMT-uptake tubers allowed achievement of seizure-free outcome in children with TS, suggesting that AMT-PET can provide an excellent test for presurgical patient selection and seizure localization.

**SW**

SW, also known as trigemino-encephalo-angiomatosis, is characterized by a cutaneous port-wine stain typically in the ophthalmic division of the trigeminal nerve distribution and intracranial leptomeningeal angiomatosis ipsilaterally. There are often ocular abnormalities as well, including congenital glaucoma and choroidal angioma, affecting the same side as the cutaneous capillary angioma. SW is relatively rare, occurring in about 1 in 40,000. Although there are familial cases, thus far no genetic link has been identified, and SW is thought to occur sporadically. Common neurologic manifestations in affected individuals include seizure, developmental delay, cognitive impairment, visual field defect, headache, and stroke-like symptoms.

The presence of facial port-wine stain at birth raises the suspicion of the diagnosis, but port-wine stain itself is a common cutaneous finding, and only 8% of individuals with port-wine stain have intracranial involvement that is characteristic of SW. Clinically, the expression of SW is variable. In 1992, Roach provided a classification scheme based on the varying degrees of involvement as follows: type 1, classic and the most common form, manifesting both facial and leptomeningeal angioma with or without glaucoma; type 2, facial angioma and possible glaucoma, without intracranial involvement; and type 3, leptomeningeal angioma but no facial angioma or ocular manifestation of disease.

Conventional MRI and CT scans have been useful in aiding the diagnosis of SW and showing the extent of intracranial involvement. A CT scan best shows the classic tram-track calcification of the cortex (Fig 22A), whereas MRI with contrast provides the most sensitive means of depicting lepto-
meningeal enhancement that is considered the hallmark of the disease (Fig 22B), in addition to cortical atrophy. The leptomeningeal angiomatosis represents embryonic venous plexus that is normally present during 4 to 8 weeks of fetal life. The failure of regression and lack of development of normal cortical veins results in ineffective venous drainage, venous stasis and hypertension, and subsequent ischemia of the underlying brain. In the early stage of disease, involvement is most frequently seen in the parietal and occipital lobes, sometimes followed by temporal and frontal lobes resulting in hemiatrophy of the brain. Bilateral involvement occurs in about 15% of cases. Post–contrast T1-weighted FLAIR images have been advocated to better depict leptomeningeal disease. It was found that these images show leptomeningeal enhancement with greater conspicuity compared with the conventional post–contrast T1-weighted spin-echo images, probably by suppressing the vascular signals (Fig 23). In addition to pial angiomatosis that shows enhancement, there are frequently choroidal glomi and transmedullary venous angiomatosis that likely form a collateral venous drainage pathway because the cortical venous system is dysplastic. These transmedullary veins and surface angiomatosis can be exquisitely depicted using long echo time susceptibility weighted gradient-echo MRI or high-resolution MR venography (Fig 24). This sequence uses the intrinsic contrast of venous blood that is rich in deoxyhemoglobin that appears dark in the background of the brain parenchyma because of T2* dephasing effect. By use of this particular sequence, there has been a report of earlier detection of evolving leptomeningeal angiomatosis in an infant with SW before it is evident on post–contrast T1-weighted images.

Nuclear medicine studies including PET and SPECT have traditionally been used to assess functional hypoperfusion in SW as a result of anomalous venous development. Cerebral perfusion imaging using Technetium-99m hexamethylpropyleneaminoxime SPECT have shown hypoperfusion in the area of vascular malformation that is at times more extensive compared with abnormalities depicted on CT scans and MRI. It is suggested that functional measures may be more sensitive for the early diagnosis of the disease because several cases showed that the perfusion (estimated by using SPECT) and metabolism (assessed by using FDG-SPECT) alterations were evident before the development of structural anomalies.

Figure 20 Wedge-shaped cerebellar hamartomas shown on (A) T2 and (B) FLAIR images in a 7-year-old girl with TS.

Figure 21 Dynamic contrast-enhanced susceptibility weighted MR perfusion in tuberous sclerosis. Multiple calcified subcortical tubers are best depicted on susceptibility weighted (T2*-weighted gradient echo) sequence, whereas non-calcified tubers are seen on FLAIR. The right-hand panel of signal intensity versus time plot shows decreased perfusion within the subcortical tubers (white box and plot) or nearly absent perfusion (yellow box and plot). (Color version of figure is available online.)

Figure 22 A 15-year-old boy with SW. (A) A noncontrast-enhanced CT scan shows tram-track calcification of the left parieto-occipital cortex. (B) A post-GdDTPA T1-weighted MR image shows leptomeningeal enhancement in the similar region.
abnormalities. Reductions in perfusion and glucose metabolism also corresponded to the patterns of neurologic deterioration in these patients. In addition, a relationship was shown between seizure frequency, lifetime number of seizures, and hemispheric area of asymmetric cortical metabolism. More recently, perfusion deficits in SW have also been examined by using dynamic contrast MR perfusion technique (Fig 25), similar to that typically used in evaluating acute cerebral infarction. This allows a simple yet comprehensive examination in the same MR study that is used to delineate structural abnormality in SW patients, to avoid the risk of ionizing radiation, and to provide information on abnormalities caused by either the arterial or venous phase.

Proton MR spectroscopy depicts abnormalities of metabolites, providing an independent functional assessment of these patients. Typically in older SW children corresponding to the region of cerebral atrophy, a decreased NAA is identified suggesting neuronal dysfunction or loss (Fig 26). At the early stage of disease and (eg, during the first few years of life), however, the NAA level has been found to be normal, whereas choline is slightly elevated, perhaps reflecting abnormal development or myelination.

VHL

Also known as retinocerebellar angiomatosis, VHL is inherited as an autosomal dominant trait with variable penetrance. The incidence is about 1 in 36,000. The abnormality has been localized to chromosome 3p25-p26, which encodes a tumor suppressor as a regulator of hypoxia-inducible genes. Although most affected individuals inherit the abnormality, 20% are caused by a spontaneous mutation. The symptoms usually manifest in the second to third decade of life. In VHL, patients present with congenital capillary angiomatous harmatomas in the CNS, including cerebellar

Figure 23  Post-GdDTPA FLAIR images in a 2-year-old boy with SW show enlarged choroid glomi on both sides as well as leptomeningeal enhancement in the bilateral occipital regions. Also noted in this case is the left frontal osseous thickening.

Figure 24  Susceptibility weighted image, or 3-dimensional blood oxygen level dependent (BOLD) venography, shows abnormal leptomeningeal angioma along the right temporal lobe in a 17-year-old male with SW. This sequence prominently depicts numerous small cortical and deep veins in the brain.

Figure 25  A dynamic contrast enhanced susceptibility weighted MR perfusion in a 4-year-old girl with SW. Corresponding to marked cortical atrophy and leptomeningeal angiomatosis in the left parietal lobe, there is marked hypoperfusion (shown as prolonged mean transit time, MTT) and venous stasis (magenta box and plot). The MTT scale is in seconds (range 0 to 40), with increasing MTT representing slower flow. In the y-axis, delta R2* represents the change of the inverse transverse relaxation time T2*. (Color version of figure is available online.)
Figure 26  Magnetic resonance spectroscopic imaging (MRSI) of the same girl as in Figure 25. Corresponding to atrophic left parietal lobe, there is reduction of all metabolites (Cho, choline), in part reflecting volume averaging with adjacent CSF. In addition, the NAA is markedly diminished reflecting neuronal loss or dysfunction.

Figure 27  A 23-year-old woman with VHL presenting with headache. (A) Axial T2-weighted and (B) post-GdDTPA T1-weighted images show a left cerebellar cystic mass with an enhancing mural nodule, associated with surrounding vasogenic edema, compression of the left dorsolateral pons, and effacement of the fourth ventricle. (C) Axial T2-weighted and (D) post-GdDTPA T1-weighted images at the level of the C1-2 junction show another mixed cystic and solid mass in the right aspect of the cord. Both tumors were hemangioblastomas.

Figure 28  A 30-year-old man with VHL. (A) A post-GdDTPA sagittal T1 weighted image shows multiple enhancing hemangioblastomas in the cerebellum and within the cord. (B) An axial T2-weighted image shows a peripherally located intramedullary cystic hemangioblastoma expanding the cord. Multiple cystic masses are present in the kidneys. (C) Magnified view of the conus shows a cystic hemangioblastoma with a central enhancing solid nodule and another small solidly enhancing one in the proximal filum.
hemangioblastomas (44%-72%), spinal hemangioblastomas (13%-50%), and retinal angiomas (25%-60%). Outside the CNS, there is also multlsystem involvement including renal cysts that have a high incidence of developing into clear-cell renal cell carcinomas, pancreatic cysts and neuroendocrine tumors, pheochromocytomas, and epididymal or broad ligament papillary cystadenomas.

In the CNS, hemangioblastoma occurs most frequently in the cerebellum. It arises from endothelial origin and is very vascular. Initially, hemangioblastoma shows solid enhancement and appears pial based and is therefore peripherally located in the cerebellum. When large, its appearance is most often cystic with an enhancing mural nodule (Fig 27), and the natural history of progression shows a faster rate of cystic expansion than growth of the causative solid tumor, eventually resulting in pressure effect and clinical symptoms. At times, hemorrhage or prominent serpiginous vascular flow voids can be found associated with the tumor. Although solitary cerebellar hamangioblastoma can occur in any individual, multiplicity suggests the syndrome of VHL. Small tumors are often seen as solidly enhancing nodules that may be difficult to distinguish from metastatic disease.

Hemangioblastoma also occurs in the brainstem with a similar appearance, and in the spine as intramedullary lesions. Because of the peripheral, pial-based location, at times, it is difficult to classify tumor location as intramedullary or extramedullary. Focal expansile T2 hyperintense mass with solid enhancement (25%) or cystic with an enhancing nodule is the typical appearance (Fig 28). There may also be associated syrinx within the cord.

Although rare, endolymphatic sac tumors occur with higher frequency in VHL individuals, affecting about 10% of patients. This is a very vascular and locally aggressive tumor that arises from the endolymphatic sac, which often causes lytic erosion of the petrous temporal bone resulting in sensorineural hearing loss, disequilibrium, and aural fullness (Fig 29).

**Summary**

In summary, neuroimaging plays an important role in the diagnosis of the phakomatoses. Conventional, morphologic imaging techniques such as CT scans and MRI document CNS involvement including lesion size, distribution, and location; newer “functional” imaging techniques (for instance based on perfusion or metabolism) offer further insights into disease pathophysiology.

**References**


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