**A General Imaging Approach to Brain Malformations**

Whenever an infant or child is referred for imaging because of either seizures or delayed development, the possibility of a brain malformation should be carefully investigated. If the child appears dysmorphic in any way (low-set ears, abnormal facies, hypotelorism), the likelihood of an underlying brain malformation is even higher, but a normal appearance is no guarantee of a normal brain. In all such cases, imaging should be geared toward showing a structural abnormality. The imaging sequences should maximize contrast between gray matter and white matter, have high spatial resolution, and be acquired as volumetric data whenever possible so that images can be reformatted in any plane or as a surface rendering. The high resolution and ability to reformat will aid in the diagnosis of subtle abnormalities. High-resolution T1-weighted volumetric images are essential for this purpose. High-resolution 2D coronal T2 images remain a workhorse for evaluation of midline structures, hippocampi, and optic nerves. High-resolution 3D FLAIR images may be particularly helpful in evaluating for focal cortical dysplasia. The use of diffusion tensor imaging (DTI) to acquire color fractional anisotropy (FA) maps and perform tractography is useful to better understand the connectivity of the malformed brain, particularly in the brainstem, and may become clinically useful in the near future.

After acquisition of appropriate images, image analysis must take place in an orderly manner. The midline structures (including cerebral commissures, septum pellucidum, nose and rhinencephalon, pituitary gland, optic chiasm, and hypothalamus), the cerebral cortex (cortical thickness, gyral pattern, and cortical gray matter-white matter junction), the cerebral white matter (myelination, presence of nodules or clefts), the basal ganglia, the ventricular system (all ventricles completely present and of normal size and shape), the interhemispheric fissure, and the midbrain hindbrain structures (brainstem and cerebellum) should all be scrutinized in every patient.

Evaluate the midline structures first, as many disease processes of children take place in the midline, including anomalies of the cerebral commissures (corpus callosum, anterior commissure, and hippocampal commissure), midline tumors (suprasellar, pineal, brainstem, and 4th ventricle), anomalies of the cerebellar vermis, and anomalies of the craniofacial junction. Anomalies of the cerebral commissures are the most common brain malformations; more than 130 syndromes involving them have been described. Many of these malformations are associated with anomalies of the hypothalamus, so always look at the hypothalamus and pituitary gland to ensure that the posterior pituitary lobe is in the sella turcica and not in the median eminence of the hypothalamus. The midline leptomeninges are important in commissural development, so be sure to look for other anomalies associated with abnormal midline leptomeninges, such as interhemispheric lipomas and interhemispheric cysts, when the commissures are absent or dysmorphic. Remember that large CSF spaces in the posterior fossa may be a sign of associated anomalies of the cerebellum. The reason for this has only recently been discovered. Several cerebellar growth factors derive from the overlying leptomeninges. Therefore, abnormalities of the cerebellar leptomeninges may result in anomalies of the cerebellum itself, as well as abnormalities of the surrounding CSF spaces. This is the basis for development of the Dandy-Walker malformation; it requires abnormal development of the cerebellum itself and of the overlying leptomeninges. Looking at the midline image also gives an idea of the relative head size through assessment of the craniofacial ratio. In the normal neonate, the ratio of the cranial vault to the face on midline images is 5:1 or 6:1. By 2 years, it should be 2.5:1, and by 10 years, it should be about 1.5:1.

After looking at the midline, evaluate the brain from outside to inside. Start with the cerebral cortex. Is the thickness normal (2-3 mm)? If it is too thick, think of pachygyria or polymicrogyria. Is the cortical white matter junction smooth or irregular? If it is irregular, think of polymicrogyria or cobblestone cortex. Polymicrogyria is seen in many underlying disorders, including congenital cytomegalovirus and genetic syndromes, among others. Cobblestone cortex may be associated with congenital muscular dystrophies, such as muscle-eye-brain disease. Pachygyria that is more severe in the parietal and occipital lobes suggests a mutation of LIS1 or TUBA1A (TUBA1A is also associated with microcephaly), whereas pachygyria that is worst in the frontal lobes suggests a mutation of DCX. Similarly, there are many different polymicrogyria syndromes that depend upon the location of the polymicrogyria. Bilateral frontal polymicrogyria is a different entity than bilateral perisylvian polymicrogyria or bilateral parasagittal parietooccipital polymicrogyria; it is important to be specific in reporting the location of the abnormality. If the cortex is abnormally thin and associated with diminished underlying white matter, one should think of a prenatal injury (infectious or ischemic), particularly if the thinning is focal or multifocal.

After the cortex, look at the cerebral white matter. Make sure myelination is appropriate for age (there are many sources of normal myelination charts, including journal articles and textbooks). Then, look for areas of abnormal myelination within the deep white matter. Diffuse layers of hypomyelination or myelination associated with polymicrogyria should raise suspicion for congenital cytomegalovirus infection. Generalized ipsilateral ↑T1 & ↓T2 signal in the white matter of a neonate with overlying cortical malformation should prompt one to think of hemimegalencephaly, which is often accompanied by ipsilateral hemisphere & ventricular enlargement. Focal cortical dysplasias (FCDs) are often most conspicuous at birth with ↑T1 & ↓T2 in the subcortical white matter. After myelination, FCDs are typically most conspicuous on FLAIR, where one may see a curvilinear cone-shaped abnormality coursing from the cortex to the superolateral margin of a lateral ventricle (known as the transmantle sign). Narrowing the window on FLAIR images increases conspicuity of FCD. Also, look for nodules of heterotopic gray matter in the periventricular or deep white matter. Transmantle gray matter heterotopia typically extends from the cortex all the way to the lateral ventricular wall, whereas periventricular nodular heterotopia is more localized to the immediate subependymal/periventricular region. Heterotopia might be difficult to differentiate from unmystelinated or injured white matter on T1-weighted images, so be sure to look at T2-weighted images or FLAIR images to ensure that the lesion is isointense to gray matter on all sequences.

The basal ganglia are sometimes abnormal in neuronal-migration disorders, as they are formed from neurons generated in the medial and lateral ganglionic eminences, the
same germinal zones that produce GABAergic neurons that migrate to the cerebral cortex. In particular, the basal ganglia tend to be dysmorphic in appearance in patients with subcortical heterotopia. In addition, the hippocampi are often abnormal in cortical-development malformations. In patients with lissencephaly, in particular, the hippocampi are incompletely folded. Sometimes the only structural abnormalities in children with developmental delay are hippocampal; always ensure that they are fully folded and not too round. In the case of longstanding seizures, carefully inspect the hippocampi for asymmetric atrophy and increased signal to suggest hippocampal sclerosis.

Always look at the entire interhemispheric fissure (IHF); if the cerebral hemispheres are continuous across the midline, holoprosencephaly should be diagnosed. In severe holoprosencephalies, the IHF is completely absent, whereas in milder forms of holoprosencephaly, certain areas of the IHF will be absent (anterior IHF in semilobar holoprosencephaly, central IHF in syntelencephaly). Look at the septum pellucidum; absence of the septum is seen in corpus callosum dysgenesis/agenesis and septo-optic dysplasia. When septo-optic dysplasia is identified, look carefully for pituitary abnormalities, most commonly an ectopic posterior pituitary. Additionally, whenever septo-optic dysplasia is suspected, a careful search for associated schizencephaly or polymicrogyria is warranted. If present, a diagnosis of septo-optic dysplasia plus is established. While checking the septum, look at the lateral ventricles to ensure they are normal in size and shape. Abnormally enlarged trigones and temporal horns are often associated with callosal anomalies and pachygyria. Enlarged frontal horns are often seen in bilateral frontal polymicrogyria.

Remember to look carefully at the posterior fossa; anomalies of the brainstem and cerebellum are commonly overlooked. Make sure that the 4th ventricle and cerebellar vermis are normally sized. In newborns, the vermis should extend from the inferior colliculi to the obex, whereas infants and older children should have a vermis that extends from the intercollicular sulcus to the obex. Also, make sure you see normal vermian fissures. If the fissuration of the vermis looks abnormal, refer to an axial or coronal image to make sure the vermis is present; if the cerebellar hemispheres are continuous without a vermis between them, make a diagnosis of rhombencephalosynapsis. Whenever aqueductal stenosis is encountered, look carefully for rhombencephalosynapsis. If the 4th ventricle has an abnormal rectangular shape (with a horizontal superior margin) with a narrow isthmus and small vermis, consider a molar tooth malformation. To confirm this diagnosis, look on axial images for the molar tooth sign of the lower midbrain, consisting of large, horizontal superior cerebellar peduncles extending posteriorly toward the cerebellum, and a longitudinal cleft in the superior vermis. Make sure that the brainstem components are of normal size; in a child, the height of the pons should be double that of the midbrain on the midline sagittal image. Looking at the size of the pons compared to that of the cerebellar vermis can provide an important clue. Because much of the anterior pons is composed of the decussation of the middle cerebellar peduncles, development hypoplasia of the cerebellum is nearly always associated with hypoplasia of the ventral pons. If the pons is normal in the setting of a small cerebellum, it is most likely that the cerebellum lost volume near the end of gestation or after birth. Remember that in a small posterior fossa, intracranial hypotension, or intracranial hypertension can result in descent of the cerebellum below the foramen magnum. Look for causes of a small posterior fossa (clival anomaly, anomaly of the craniovertebral junction), intracranial hypertension (space-occupying mass, hydrocephalus), or evidence of intracranial hypotension (large dural venous sinuses, large pialurary gland, “slumping” brainstem) before making a diagnosis of Chiari 1 malformation. Finally, remember to look at the size of the CSF spaces in the posterior fossa, enlargement of which may be a sign of abnormal leptomeningeal development.

Selected References
Approach to Brain Malformations

**Callosal Dysgenesis**

*Left* Sagittal T1WI MR in a 7 year old with multiple anomalies shows a short, thin, & dysmorphic corpus callosum. Note the poorly formed splenium & rostrum of the corpus callosum. Isolated dysgenesis of the corpus callosum is uncommon, so look carefully for associated anomalies. *Right* Sagittal T1WI MR shows a large pericallosal lipoma & severe associated callosal dysgenesis. Note the enveloping of vessels by the fatty mass, a common finding in large tubulonodular lipomas.

**Callosal Dysgenesis With Pericallosal Lipoma**

**Pachygyria**

*Left* Coronal T2WI MR in a 1 year old with seizures shows marked thickening of multiple gyri and decreased sulcation symmetrically within both frontal lobes, consistent with pachygyria. Ventricles may be enlarged secondary to small brain volume. *Right* Axial T2WI MR in a 4 year old with congenital CMV shows cortical thickening with irregular cortical surface & an irregular GM-WM junction with shallow sulci, consistent with polymicrogyria. Note the white matter abnormalities, findings often seen in congenital CMV.

**Polymicrogyria in Congenital Cytomegalovirus**

**Focal Cortical Dysplasia**

*Left* Coronal FLAIR images in a 3 year old with focal cortical dysplasia (FCD) type 2B with varying contrast windowing. Note how the FCD is much more conspicuous in the image on the right with greater windowing contrast. Windowing is an important means to increasing detection of subtle FCD lesions. *Right* Axial T2WI MR in a 4 year old with callosal agenesis & extensive bilateral periventricular nodular gray matter heterotopia. Malformations of cortical development are common in callosal abnormalities.

**Subependymal Gray Matter Heterotopia**
Approach to Brain Malformations

(Left) Coronal T2WI MR in a 5 year old with septo-optic dysplasia shows absence of septum pellucidum & a very small left optic nerve. Right optic nerve looks grossly normal in size. Asymmetric optic nerve hypoplasia is very common in this diagnosis.

(Right) Axial T1WI MR shows bilateral schizencephaly lined by dysplastic gray matter. The right side is open lip & the left is closed lip. Again note the bifrontal polymicrogyria & absence of the septum pellucidum in this patient with septo-optic dysplasia plus syndrome.

(Left) Axial T2WI MR in a 2 year old with semilobar holoprosencephaly shows absence of the septum pellucidum, fused thalami, & extension of gray matter across the posterior midline. Also note the near absence of the frontal horns & the azygos anterior cerebral artery.

(Right) Axial T2WI MR in a 3 year old with aqueductal stenosis & rhombencephalosynapsis shows absence of the cerebellar vermis with extension of cerebellar white matter tracts across midline.

(Left) Sagittal T2WI in an infant with classic Dandy-Walker malformation shows marked cystic enlargement of the posterior fossa in continuity with the 4th ventricle, hypoplastic cerebellar vermis, & elevation of the torcula Herophili.