Congenital malformations of the brain

This article describes some of the commonly encountered malformations of the brain. It is important to be aware of the characteristic clinical and radiological features of these conditions to enable correct diagnosis and proper management.

This article will describe some of the commonly encountered malformations of the brain. Around 1% of newborns have congenital malformation of the CNS and these cause significant mortality and morbidity (Kumar et al, 2004; Osborn et al, 2004). Only those malformations which are incompatible with life or cause obvious facial or other deformity are diagnosed in utero or at birth. Many other congenital malformations of the brain may present later in childhood. It is important to be aware of the characteristic clinical and radiological features of these conditions to enable correct diagnosis and proper management.

Background

CNS development is a complex process, involving many cycles of development and remodelling, which begins in early fetal life. The human brain undergoes a variety of developmental anomalies, which vary from mild to so extremely severe that they are incompatible with life. This article presents the most common ones encountered in general clinical and imaging practice, rather than those malformations that are not compatible with life.

Knowledge of the basic principles underlying CNS embryology is useful for understanding CNS malformations. Initially, neural plates are formed which thicken into neural folds. These then fuse to form the neural tube. Closure of the neural tube occurs between day 20 and day 28. In the early stages, the brain is a hollow tube without gyri, fissures or sulci. The tube then bends, thickens and develops surface features. The brain remains smooth before 18 weeks and the normal structures appear after this at predictable intervals. The process of migration starts at week 7 – the embryonic cells migrate outward from the region of the basal ganglia (germinal matrix) to the site of the eventual cortex in successive waves which are responsible for the normal cortical layering (six layers). They follow along the process of other cells (radial glia), which extend from the ventricle to the surface of the brain.

CNS malformations may be caused by chromosomal abnormalities and single gene defects or by imbalances of factors that control gene expression during development. Some malformations are caused by multiple genetic and environmental factors acting in concert (multifactorial aetiology).

There are numerous classifications for congenital malformations of the brain. One of the common classifications is as follows:

1. Neural tube defects or dysraphic disorders including hindbrain herniations (Osborn et al, 2004), e.g. anencephaly, exencephaly, myelomeningocele with Chiari malformation, and herniations through cranial defects including cephalocele and meningocele
2. Disorders of forebrain induction, e.g. holoprosencephaly, septo-optic dysplasia or callosal dysgenesis
3. Malformations of cortical development, such as polymicrogyria, schizencephaly, grey matter heterotopia, lissencephalies and pachygyria
4. Cerebellar malformations
5. Miscellaneous malformations including lipoma
6. Neurocutaneous syndromes including neurofibromatosis, von Hippel–Lindau syndrome, tuberous sclerosis and Sturge–Weber syndrome.

Clinical and radiological features of some commonly seen malformations of the brain

Arnold Chiari malformations

Chiari I

This is defined as the caudal protrusion of peg-shaped cerebellar tonsils below the foramen magnum, with a normally positioned fourth ventricle but without brainstem herniation (Osborn et al, 2004). Up to 3 mm descent of tonsils below the foramen magnum has been seen in the normal population. However, more than 5 mm is considered abnormal in adults (*Figure 1* and *2*). In children, up to 6 mm is allowed between 5 and 15 years of age.

Numerous causes are postulated including developmental anomalies of the cranio-cervical junction, intrauterine hydrocephalus, acquired skull base abnormalities and intracranial mass lesions. Indeed, some consider this entity as not a malformation at all, but a manifestation of raised intracranial pressure.

In up to 50% of cases, Chiari I malformations may be asymptomatic. Clinical features in infants include impaired oropharyngeal function, apnoea or even sudden death. In children and adults, it may present as headache, neck and back pain, or scoliosis (Osborn et al, 2004). Chiari I spells have been described where the patient may experience headache or syncope following cough or sneeze as a result of an acute increase in intrathecal pressure.

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Chiari II

This is the most common and complex type of Chiari malformation. It is characterized by hindbrain dysgenesis and is associated with myelomeningocele (Osborn et al, 2004). It has been described as a normal cerebellum developing within a small posterior fossa and its hallmarks include caudally displaced fourth ventricle and brainstem, and herniation of cerebellar tonsils and vermis through the foramen magnum (*Figure 3*).

The fourth ventricle becomes flattened, the cervicomedullary junction displays a kink and the tectal plate may assume a beaked appearance. Hydrocephalus is seen in over 90% of patients.

Figure 1. Sagittal T1 weighted magnetic resonance imaging scan showing the protrusion of cerebellar tonsils below the foramen magnum. Note the normal position of the brainstem. This patient had Arnold Chiari type I.

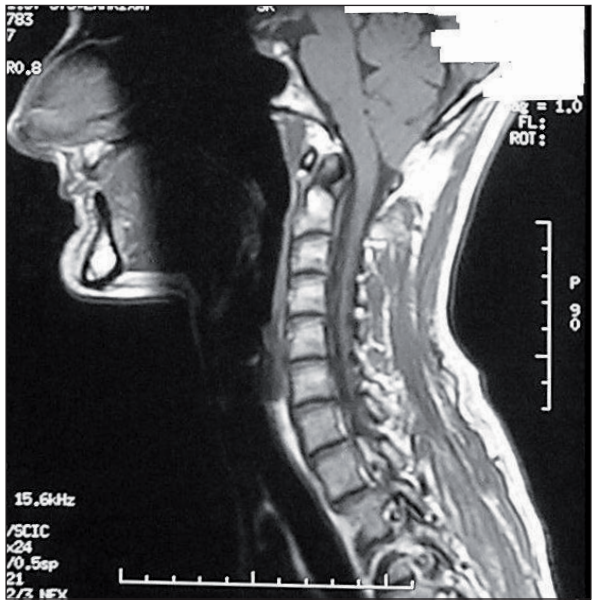
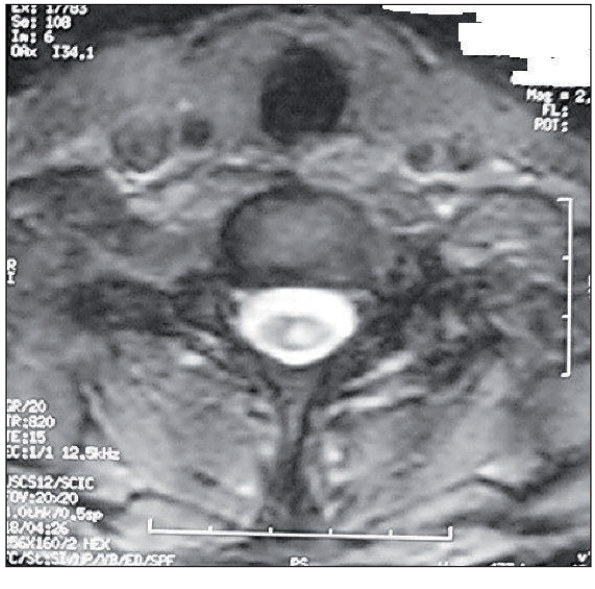


Figure 2. Axial T2 weighted magnetic resonance imaging scan shows syrinx within the cord (same patient as* Figure 1*).



This condition commonly presents in neonates with myelomenigocele. Enlarging head, lower extremity paralysis and sphincter dysfunction may be seen.

Chiari III and IV are rare.

Disorders of forebrain induction

Holoprosencephaly

Holoprosencephaly denotes an incomplete or absent division of the embryonic forebrain (prosencephalon) into distinct cerebral hemispheres (Muenke and Beachy, 2001). This results in a spectrum of congenital structural forebrain anomalies defined by the degree of frontal lobe fusion. Associated malformations of the optic and olfactory system are common. Grossly, there are four types:

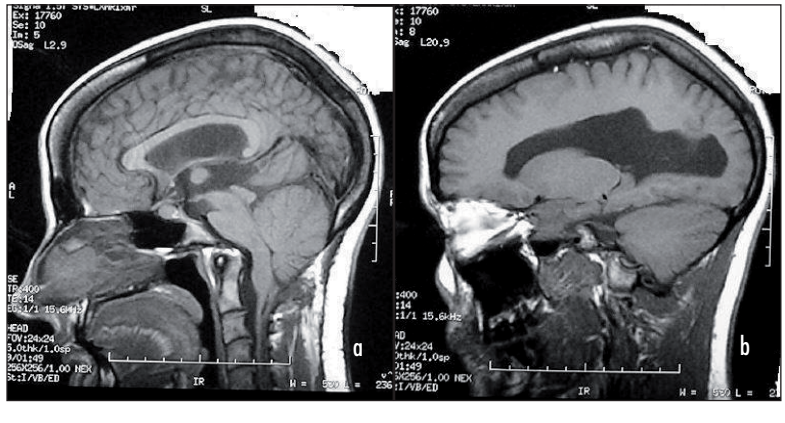
1. Lobar – complete ventricular separation with focal areas of incomplete cortical division
2. Semi lobar – incomplete forebrain division resulting in partial separation of cerebral hemispheres
3. Middle interhemispheric variant
4. Alobar – complete absence of midline forebrain division resulting in a monoventricle and fused cerebral hemispheres.

The lobar type is the least severe and alobar type is the most severe malformation.

On computed tomography (CT) and magnetic resonance imaging (MRI), depending upon the type, findings range from monoventricle, fused frontal lobes, absent anterior midline falx, absent septum pellucidum, to fused diencephalon, basal ganglia and thalami (Sonigo et al, 1998).

Clinical presentation ranges from mild with no facial defects, anosmia or only a single central incisor, cleft lip and palate (moderate) to severe midline facial defects, which usually reflect the severity of the CNS defect. These include cyclopia, ocular hypotelorism with proboscis, single nostril or cleft palate, pituitary or hypothalamic dysfunction, seizures and mental retardation, dystonia and hypotonia. Association with trisomy 13 (or rarely trisomy 18) and maternal diabetes has been reported.

Figure 3. Sagittal T1 weighted magnetic resonance imaging scan shows herniation of both cerebellar tonsils, vermis and brainstem through the foramen magnum. Also note the flattened fourth ventricle and cervicomedullary kinking. These features are typical of Arnold Chiari type II malformation.



Septo-optic dysplasia

This condition is usually sporadic. It is a heterogeneous disorder characterized by hypoplasia of the optic nerves and absent septum pellucidum (Campbell, 2003). Hypopituitary growth hormone deficiency is usual. It may be associated with other anomalies including schizencephaly, callosal dysgenesis, ocular and olfactory anomalies. On MRI, the frontal horns of the lateral ventricles are continuous across the midline because of the absence of the septum pellucidum (Barkovich et al, 1989) (*Figure 4*). MRI may also show hypoplasia of the optic nerve and chiasm if severe but may be normal in milder cases.

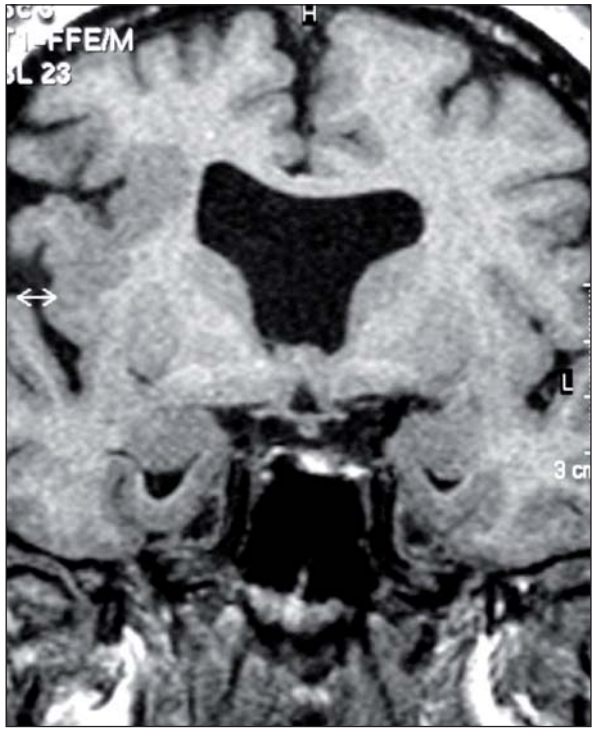
In severe cases, this condition may present in the newborn with hypoglycaemic seizures, apnoea, prolonged jaundice and micropenis (in a boy). Children may present with short stature and other endocrine (particularly pituitary) dysfunction. The amount of visual impairment is variable from normal through to complete blindness. Nystagmus, seizures and mental retardation are the other clinical features of this condition.

Callosal dysgenesis

Agenesis or dysgenesis of the corpus callosum can be complete or partial (Kendall, 1983). When complete, axial CT and MRI will demonstrate widely displaced parallel lateral ventricles with the interhemispheric fissure running in continuity between the lateral ventricles from front to back (*Figures 5* and *6*). The posterior horns of the lateral ventricles may expand into adjacent white matter (Kuker et al, 2003). Other CNS malformations or syndromes are commonly associated with this condition (50–80% of cases) and include neuronal migration anomalies, encephaloceles, Dandy–Walker malformation, Chiari II, interhemispheric lipoma, septo-optic dyplasia and holoprosencephaly (Barkovich and Norman, 1988a).

Signs and symptoms vary widely. Some children are normal and callosal dysgenesis is found on a CT or MRI scan performed for other reasons. Rather than microcephaly, there is more likely to be macrocephaly as a result of hydrocephalus. Common presentation include seizures, developmental delay and hypotonia.

Figure 4. Coronal T1 weighted magnetic resonance imaging scan shows absent septum pellucidum and fusion of the frontal horns of lateral ventricle. Also note the perisylvian polymicrogyria on the right side. The optic chiasm was also noted to be hypoplastic. This patient had septo-optic dysplasia.



Malformations of cortical development

Polymicrogyria and pachygyria

In polymicrogyria, there is abnormality in late neuronal migration and cortical organization. The migrating neurons reach the cortex but their organization is abnormal, resulting in the formation of multiple small gyri (Barkovich et al, 1999). While polymicrogyria is most common around the sylvian fissure, it may affect any part of the

Figure 5. Midline sagittal T1 weighted magnetic resonance image shows complete absence of corpus callosum, indicating callosal agenesis.

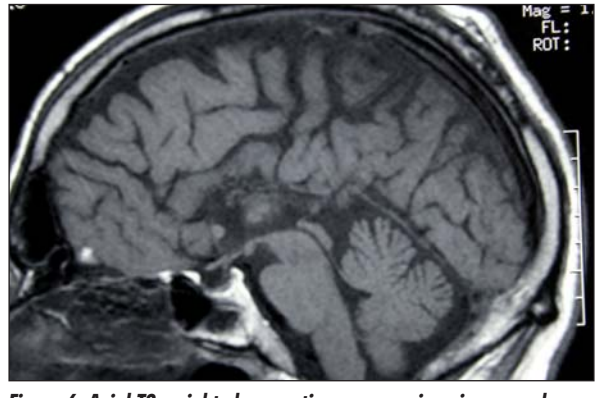
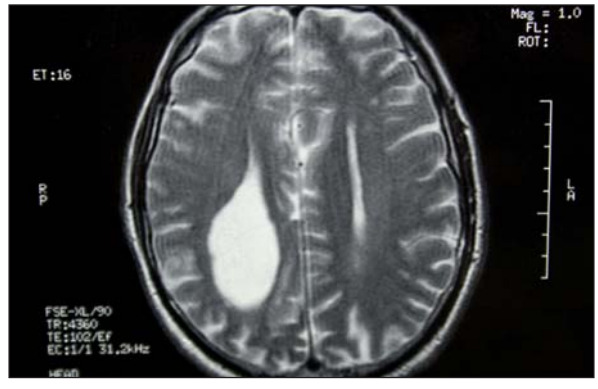


Figure 6. Axial T2 weighted magnetic resonance imaging scan shows widely displaced parallel lateral ventricles with the interhemispheric fissure running in continuity between lateral ventricles from front to back. The posterior horns of lateral ventricles are expanded into adjacent white matter (colpocephaly). These are typical features of corpus callosal agenesis.



cortex. On axial CT and MRI, an irregular bumpy outer and inner cortical surface is typically seen (Kuzniecky and Andermann, 1994) (*Figure 7*). The abnormally organized cells are typically iso-intense to the normal grey matter in all MRI sequences but may occasionally show areas of hyperintensity or rarely calcification (*Figures 8* and *9*).

Pachygyria is another malformation caused by abnormality in late neuronal migration and characterized by sparse, broad, flat gyri. This term is often used interchangeably with incomplete lissencephaly. Often this abnormality is found in the parieto-occipital region. A characteristic figure of eight appearance of the cerebrum, vertical shallow sylvian fissures and smooth brain with thick cortex may be found on MRI.

Clinical symptoms depend upon the amount of brain involved. In polymicrogyria, faciopharyngoglossomasticatory diplegia, development delay, seizures and hemiplegia may be seen. Hypotonia and seizures may occur in pachygyria.

Schizencephaly

Schizencephaly is an uncommon disorder of neuronal migrational characterized by a grey matter-lined cleft, which extends across the entire cerebral hemisphere, from the ependyma of the ventricular surface to the periphery of the brain (Barkovich, 1996) (*Figure 10*). There are two types – closed lip or open lip. In the closed lip type, the opposite walls are apposed with no intervening CSF whereas in the open lip variety, the lips are open with CSF filling the gap.

Imaging reveals bilateral or unilateral full surface clefts, which are lined by grey matter. These are usually located in insula or adjoining the pre or post central gyri (Barkovich and Norman, 1988b). Deformity of the ventricle at the site of the closed lip type points to the cleft. As in most other malformations, clinical features depend upon the amount of brain involved and include seizures, hemiparesis, hydrocephalus and developmental delay.

Grey matter heterotopia

Grey matter heterotopias are common malformations of cortical development. In this condition, the normal migration of nerve cells from the periventricular germinal

Figure 7. Axial computed tomography scan shows irregular, bumpy, thickened outer and inner cortical layer on the right cerebral hemisphere. This is typical of polymicrogyria.

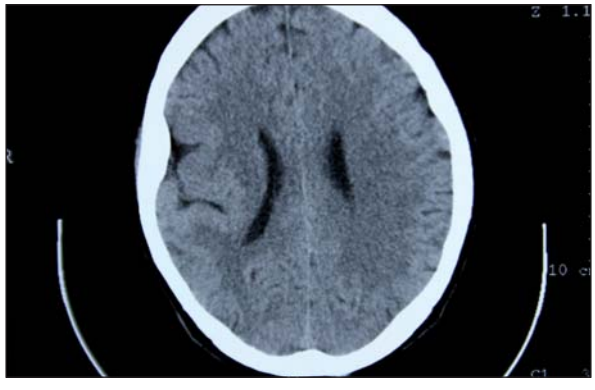


Figure 8. Coronal T1 weighted magnetic resonance imaging scan shows similar appearance as computed tomography scan. Note that the polymicrogyria is in the peri-sylvian region, which is its characteristic location.

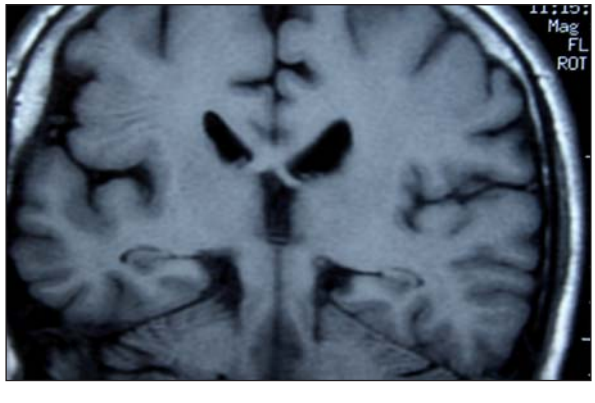


Figure 9. Coronal T1 weighted magnetic resonance imaging scan shows multiple small gyri on the right cerebral hemisphere, which is clearly abnormal (compare to the normal appearance of left side). This is typical of polymicrogyria whereas pachygyria will have broader, flatter and lesser number of gyri.

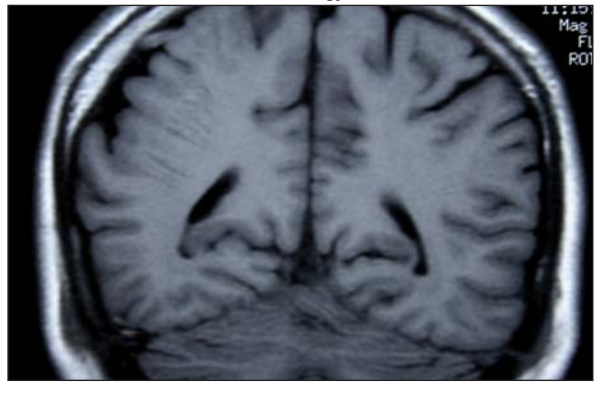
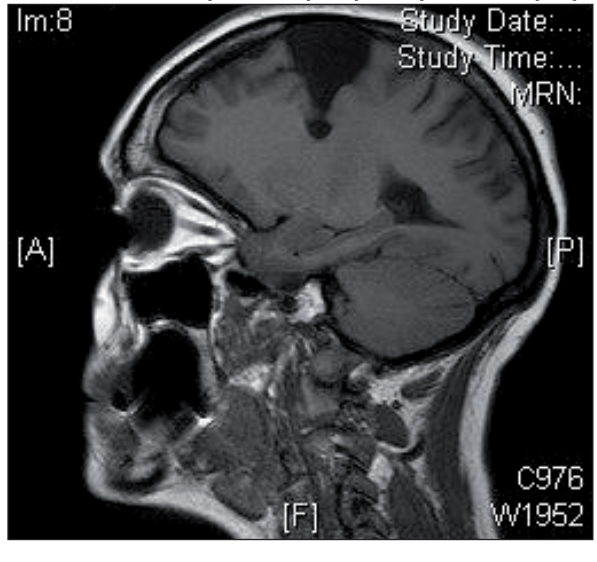


Figure 10. Sagittal T1 weighted magnetic resonance imaging scan shows the grey matter-lined cleft extending from the surface of cerebral hemisphere all the way into the lateral ventricle. It is filled with CSF: a classic example of the open lip variety of schizencephaly.



zone to the cortex is arrested. This results in cells being left in abnormal locations, known as areas of heterotopias (Barkovich and Kuzniecky, 2000). On MRI, they appear as nodular or broad areas of tissue which have the same signal intensity as normal grey matter in all sequences.

They are classified into three types based on their location. In subependymal heterotopia, there are smooth nodules projecting into the lateral ventricle (*Figure 11*). In focal subcortical heterotopia, the grey matter and/or nodules are seen in a subcortical position and may contain vessels and CSF as a result of the infolding of the adjacent cortex. In band heterotopia, the grey matter and/or nodules are seen as a circumferential band deep to grey matter, from which it is separated by a layer of white matter.

Clinical presentation, age of onset and severity depends on the location and amount of abnormally positioned grey matter. Severe cases present in infancy with seizures and developmental delay whereas mild cases can be asymptomatic and discovered incidentally on imaging.

Cerebellar malformations

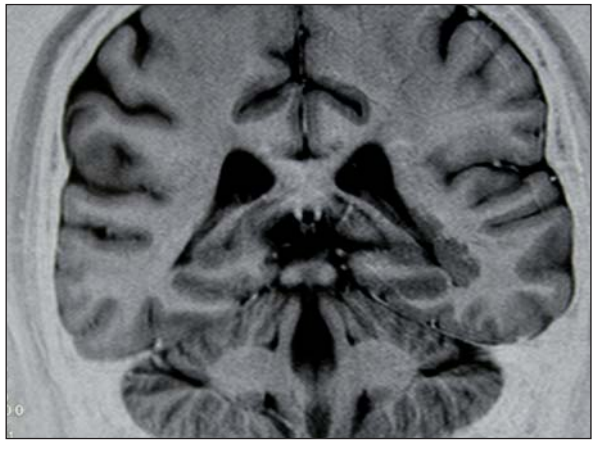
Dandy–Walker malformation

This condition is characterized by agenesis or hypoplasia of the cerebellar vermis, cystic dilatation of the fourth ventricle, and enlargement of the posterior fossa (*Figure 12*). There are variants of this disorder which may be less severe. Hydrocephalus, corpus callosal anomalies, polymicrogyria or heterotopia may be associated.

Patients with Dandy–Walker malformation present with developmental delay, enlarged head circumference, or signs and symptoms of hydrocephalus. Imbalance, spasticity, motor incoordination, developmental delay, seizures and respiratory failure may be present (Hart et al, 1972).

While CT is useful, MRI gives much more information, which is helpful for surgeons. Hypoplasia or absence of the cerebellar vermis, enlarged posterior fossa, cyst formation in the posterior fossa, anterolaterally winged cerebellar hemispheres (winged outward) and absence of falx cerebelli are the main imaging findings (Altman et al, 1992).

Figure 11. Coronal T1 weighted magnetic resonance imaging scan shows grey matter which is abnormally located in the subependymal region. This patient has subependymal grey matter heterotopia.



Miscellaneous malformations

Intracranial lipoma

These are rare lesions, thought to arise from maldevelopment of primitive developing meninges (Truwit and Barkovich, 1990). The majority of these occur at or near the midline, mostly in the peri-callosal region (*Figure 13*). They may also occur in other regions including the quadrigeminal, superior cerebellar, sylvian cisterns and cerebellopontine angle. They are often associated with other CNS anomalies including corpus callosal anomalies, absent septum pellucidum, spina bifida, encephalocele, and myelomeningocele. Abnormal arterial and venous

Figure 12. The cerebellar vermis is hypoplastic or absent and there is also cystic dilatation of the fourth ventricle in the posterior fossa. Appearances are typical of Dandy–Walker malformation.

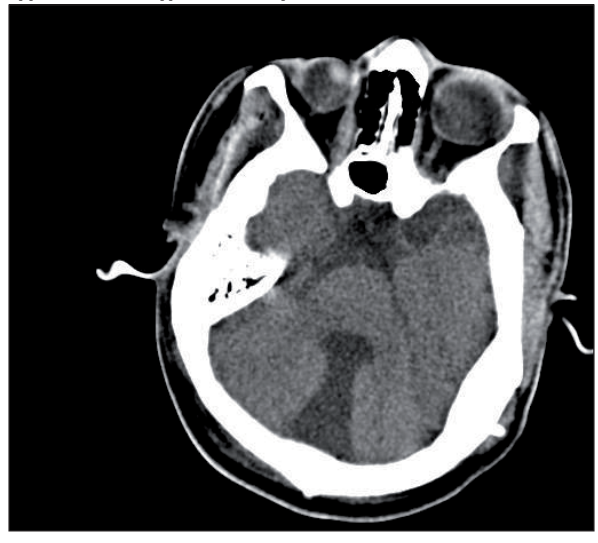
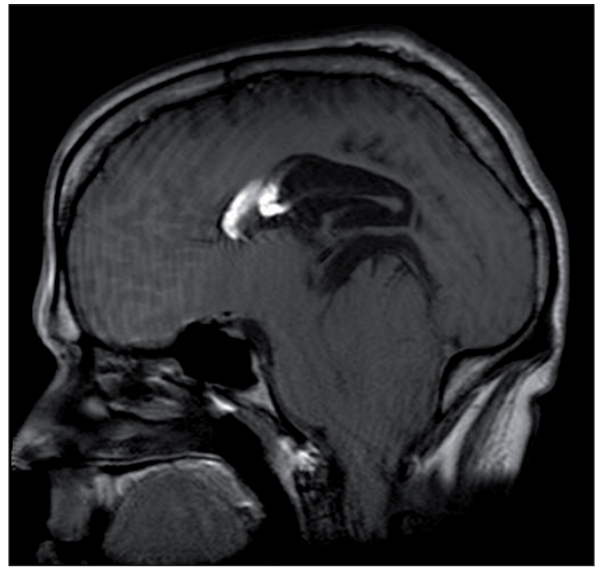


Figure 13. Sagittal T1 weighted magnetic resonance imaging scan shows high signal lesion in the interhemispheric region. This is a typical appearance and position for intracranial lipoma. Also note that this patient has agenesis of corpus callosum and Arnold Chiari malformation, which are commonly associated anomalies with intracranial lipomas.



vasculature may be seen in association with lipoma and cortical dysplasia (Saatci et al, 2000). Intracranial lipoma can occur as an isolated lesion and this may be completely asymptomatic (and spotted as an incidental finding) or may be symptomatic and cause seizures and headaches.

Neurocutaneous syndromes

Neurocutaneous syndromes or phakomatoses are disorders of the CNS which involve the retina as well as the skin. These tissues have a common ectodermal origin.

Neurocutaneous syndromes are congenital or hereditary conditions that have many features in common: hereditary transmission, involvement of organs of ectodermal origin (nervous system, retina and the skin), slow evolution of lesions in childhood and adolescence, and disposition to fatal malignant transformation. The major neurocutaneous syndromes are genetically determined (except for Sturge–Weber syndrome) although sporadic cases can occur. The common neurocutaneous syndromes include neurofibromatosis, tuberous sclerosis complex, Sturge–Weber syndrome and von Hippel–Lindau syndrome.

Neurofibromatosis

Neurofibromatosis is an autosomal dominant disorder, probably of neural crest origin, that affects all three germinal layers (Friedman and Birch, 1997). There are two types: neurofibromatosis type 1 is a result of a defect in chromosome 17 whereas neurofibromatosis type 2 is associated with a defect in chromosome 22.

Neurofibromatosis type 1 is associated with optic nerve glioma, cerebral glioma, spinal gliomas and neurofibromas, plexiform neurofibromas, dural ectasia, and skeletal and vascular dysplasias (Dahnart, 2007) (*Figure 14*). In about 80% of these cases, there are high signal lesions in the cerebellum, brainstem, internal capsule, basal ganglia and white matter. Although there are many postulates, their exact nature is not clear and hence these are called unidentified neurofibromatosis objects.

Neurofibromatosis type 2 is an autosomal dominant condition which has the following manifestations: bilateral acoustic neurofibromas, other cranial nerve schwannomas, intracranial meningiomas, spinal canal meningiomas and schwannomas, and spinal cord ependymomas (Smirniotopoulos and Murphy, 1992; Evans, 1999). Owing to the greater degree of CNS manifestations, neurofibromatosis type 2 was formerly called central neurofibromatosis.

Von Hippel–Lindau syndrome

Von Hippel–Lindau syndrome is an autosomal dominant, inherited, neurocutaneous dysplasia complex. This affects various organ systems including the CNS, retina, liver, kidney, pancreas and spleen. It causes multiple lesions, including cysts, vascular tumours and carcinomas. It is characteristically associated with CNS haemangioblastomas, retinal haemorrhage, clear cell carcinomas, cystadenomas, phaeochromocytomas, pancreatic neoplasms and multi-organ cysts (Maher et al, 1990; Conway et al, 2001).

Sturge–Weber syndrome

Sturge–Weber syndrome is a neurocutaneous disorder with angiomas involving the leptomeninges and skin of the face, typically in the ophthalmic (V1) and maxillary (V2) distributions of the trigeminal nerve (port wine stain) (Roach, 1992). Clinical manifestations include seizures, hemiparesis, hemianopia, headaches, developmental delay and mental retardation, glaucoma and choroidal haemangioma.

CT scan may show calcifications in infants and even neonates (*Figure 15*); other findings include brain atro-

Figure 14. Sagittal T1 weighted magnetic resonance imaging scan shows subcutaneous neurofibroma on the skull vault and occipital region. This patient had neurofibromatosis type 1.

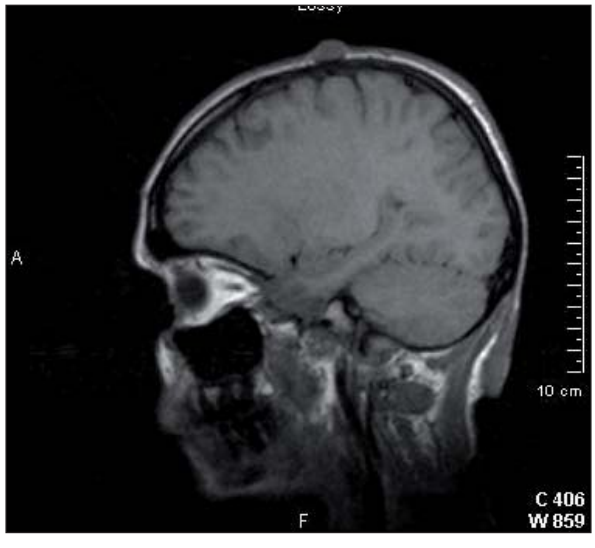
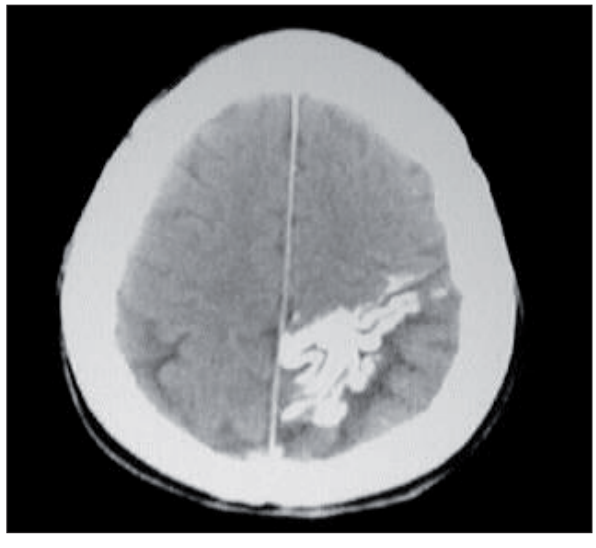


Figure 15. Gyral calcification is seen in this axial computed tomography scan, which is typical of Sturge–Weber syndrome. This patient had a port wine stain on the same side of the face as the gyral calcification.



phy, ipsilateral choroid plexus enlargement and abnormal draining veins. Although MRI does not show calcifications, gadolinium enhancement may show pial angioma; so MRI may permit early diagnosis of Sturge–Weber syndrome, even in the newborn with a facial port wine stain (Thomas-Sohl et al, 2004). Determining the maximum extent of disease may require a combination of structural and functional neuroimaging, since a mismatch may occur among neuroimaging modalities. Each modality may demonstrate abnormalities not detected by the other. This is especially important in identifying the epileptogenic region when considering surgery for refractory seizures.

Tuberous sclerosis

Tuberous sclerosis is a neurocutaneous disorder with a genetic background, affecting cellular differentiation, proliferation and migration early in development, which results in a variety of hamartomatous lesions that may affect virtually every organ system of the body (Harding and Copp, 1997). It is an autosomal dominant condition with two thirds of cases arising from spontaneous mutations. The classic clinical triad is epilepsy, mental retardation and adenoma sebaceum, but less than one third of affected persons fit the classic constellation of symptoms.

The major intracranial manifestations include cortical tuber, subependymal nodule and subependymal giant cell astrocytoma. Other features include facial angiofibromas, periungual fibroma, hypomelanotic macules (also known as ash leaf spots), Shagreen patch, multiple retinal nodular hamartoma, cardiac rhabdomyoma, lymphangioleiomyomatosis and renal angiomyolipoma (Crino et al, 2006).

Conclusions

Fetal malformations contribute to significant mortality and morbidity. Approximately 3% all newborns have major malformations, of which one third involve the CNS. Although some of these disorders have multifactorial aetiology, many remain of unknown aetiology, and most have non-specific clinical presentations. As some of these conditions may present in childhood or in adults, it is important to be aware of commonly encountered malformations of the brain to ensure proper management. BJHM

KEY POINTS

- In Chiari I malformations, only the cerebellar tonsils herniate through the foramen magnum (more than 5 mm).
- Along with the cerebellar tonsils, the brainstem also herniates through the foramen magnum in Chiari II malformations.
- The extent of facial deformity reflects the severity of holoprosencephaly.
- Remember to look for other associated anomalies in corpus callosal dysgenesis and intracranial lipoma.
- Neurofibromatosis type 2 is the diagnosis in patients with bilateral acoustic neuromas until proven otherwise.
- Von Hippel–Lindau syndrome is the most likely diagnosis if patients have two or more CNS haemangioblastomas or one CNS haemangioblastoma with retinal haemorrhage.
- Gyral calcifications and facial port wine stain are characteristic of Sturge–Weber syndrome.

Conflict of interest: none.

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