Cephaloceles

Mariasavina Severino* and Andrea Rossi
Neuroradiology Unit, Istituto Giannina Gaslini, Genoa, Italy

Abstract

Neural tube defects affect an average of 1 per 1000 established pregnancies worldwide, ranging from 0.2 to 10 per 1000 in specific geographical locations. Cranial neural tube defects encompass a wide spectrum of malformations with variable clinical severity. Here, we address the imaging findings of cephaloceles and related disorders, including the clinical, epidemiologic, pathologic and genetic features that help to understand these conditions and contribute meaningfully to their diagnosis and management.

Background

Neural tube defects affect an average of 1 per 1,000 established pregnancies worldwide (Mitchell 2005), ranging from 0.2 to 10 per 1,000 in specific geographical locations, and are the second commonest group of birth defects after congenital heart defects. They have multifactorial etiology, with genes and environmental factors interacting to determine the individual risk of malformation (Copp et al. 2013). Cranial neural tube defects encompass a wide spectrum of malformations with variable clinical severity. At the severe end of the spectrum, open defects such as anencephaly/exencephaly and craniorachischisis are lethal before or at birth, while close defects (i.e., encephalocele) may be lethal depending on the extent of brain damage during herniation. Cranial neural tube defects are usually diagnosed by ultrasonography from the first trimester of pregnancy. Increased serum AFP is additionally found in open defects.

Anencephaly, Exencephaly, and Craniorachischisis

Anencephaly and exencephaly represent 40 % of all neural tube defects diagnosed in the first trimester of pregnancy (Ghi et al. 2006). Female fetuses with anencephaly or exencephaly are disproportionately represented both in humans and mice, with a male/female sex ratio often approaching 1:3 (Ghi et al. 2006). Most cases of anencephaly/exencephaly are within the spectrum of neural tube defects. However, they may be the result of secondary disruption due to amniotic band sequence (Naidich et al. 1992; Rohrbach et al. 2007).

Anencephaly is characterized by the absence or underdevelopment of the cranial vault (acrania) and absence of most or all of the brain tissue (Naidich et al. 1992; Fig. 1). The anterior and middle cranial fossae are poorly defined and convex upward, while the posterior fossa is usually funnel shaped. The anterior lobe of the pituitary gland is usually present in the sella but may be small while the posterior lobe may be absent. Shallow orbits are associated with protruding eyes. The optic nerves blindly end in the orbits. The cerebellar hemispheres may be absent and the spine is always abnormal.

Exencephaly is defined as acrania or cranium bifidum with protrusion of the central nervous system through the defect. The abnormally developed brain tissue is exposed to the amnios in utero and to the environment after birth (Naidich et al. 1992). This rare defect is believed to be an early form of anencephaly, evolving to frank anencephaly by progressive degeneration and destruction of the protruding neural tissue (Copp et al. 2013). The exencephalic brain is covered by a highly vascular epithelium,

*Email: mariasavinaseverino@ospedale-gaslini.ge.it
usually extending from the nasion to the inion. Typically, it is a disorganized mass of nervous tissue, blood vessels, fibrous tissue, and fluid-filled spaces (Naidich et al. 1992). The skull base and the facial bones are typically preserved.

Fig. 1 Anencephaly. (a) Sagittal T2-weighted image. (b) Sagittal T1-weighted image. (c, d) Coronal T2-weighted images. (e, f) Axial T2-weighted images. There is acrania with dorsal, tissue-lined fluid collection (arrowhead) extending superiorly into the multicystic area cerebrovasculosa, associated with a rudimentary brainstem with absent pontine prominence and cerebellar structures. A small pituitary gland is noted within a hypoplastic sellar region (white arrow). Note the bilateral cochleovestibular malformations (incomplete partition type II) with cystic cochlea and slightly dilated vestibule. Two lateral pseudo-meningoceles (white arrows) are also noted (Case courtesy of Thierry Huisman, Baltimore, USA)
Craniorachischisis results from the failure to initiate neural tube closure leaving the hindbrain and spinal neural tube entirely open. This rare malformation accounts for 3% of neural tube defects, with a higher prevalence in North China and in females (Copp et al. 2013). Craniorachischisis is characterized by anencephaly continuous with complete spina bifida.

Iniencephaly

Iniencephaly is a rare neural tube defect of the craniocervical junction (1:1,000–1:100,000 births) involving the occiput and inion and characterized by three cardinal features: (i) occipital bone defect, (ii) rachischisis of the cervical and thoracic spine, and (iii) fixed retroflexion of the head on the cervical spine (Naidich et al. 1992, 1994a; Fig. 2). Most iniencephalic fetuses are stillborn; however, a limited number of viable newborns have been described in whom surgery allowed the correction of the abnormal position of the head (Erdincler et al. 1998).

The large occipital bone defect and posterior midline schises of the cervical vertebrae are the main features that distinguish iniencephaly from a large occipital encephalocele (Erdincler et al. 1998). The fixed retroflexion of the skull on the cervical spine is due to thick fibrous bands, representing hypoplastic trapezius muscles and a thick ligamentum nuchae (Naidich et al. 1994a). The neck is often absent, and the skin is continuous with the scalp, face, and chest. The abnormal and retroflexed occiput may join the vertebrae of the spine. The overlying skin and dorsal soft tissues may be intact or completely deficient, exposing the neural tissue to the environment (Naidich et al. 1994a). An occipital cephalocele may be associated containing the occipital lobes, cerebellum, and brainstem. Systemic and other CNS malformations may be present.
Cephaloceles

Cephaloceles are characterized by evagination of the brain and/or leptomeninges through a congenital defect of the skull and dura, usually located on the midline. Cephaloceles affect 0.8–3:10,000 viable newborns and represent 8.5 % of all neural tube defects (Mitchell 2005; Ghi et al. 2006). There are significant geographic variations in their location, incidence, and gender predilection. In Western populations, the majority of these lesions involves the occipital bone and occurs in females, whereas anterior cephaloceles involving the frontal, nasal, and orbital bones are more frequent in male patients of Asian descent. These variations suggest that different genetic assets play a causal role.

In cephaloceles, the meninges form the wall of a sac that is filled with CSF and, in some cases, nervous tissue. Depending on the contents of the herniation (Mitchell 2005), cephaloceles are categorized as follows (Fig. 3):

- Meningocele: cerebrospinal fluid (CSF) collection lined by partially epithelized meningeal wall
- Meningoencephalocele or encephalocele: meningeal, variably epithelized sac containing the brain
- Meningoencephalocystocele or encephalocystocele: an encephalocele containing a portion of the ventricles

An additional variant is the atretic cephalocele, a rudimentary form composed of a small fibrolipomatous nodule, usually located in the midline near to the vertex (parietal form) or cephalic to external occipital protuberance (occipital form) (Naidich et al. 1992; Patterson et al. 1998; Gao et al. 2014).

The degree of epithelization of the herniated sac is variable in individual cases. When the arachnoidal lining becomes exposed to the environment, ulceration and infection may ensue. As with other neural tube defects, the skin overlying the abnormality may exhibit birthmarks, such as hairy tufts, hemangiomas, dyschromic patches, and dimples. The neural tissue contained within the sac usually is disorganized and includes zones of necrosis, calcifications, and vascular proliferation (Sarnat 1992). The size of the cephalocele may vary from a small nodule to an enormous sac that may be larger than the head itself. However, size does not predict the severity of the dysgenesis of the portion of the brain remaining within the cranium (Sarnat 1992). Instead, there is a direct relationship between the amount of herniated neural tissue and the degree of microcephaly. This correlates with the eventual degree of mental retardation (Simpson et al. 1984).
Embryology

The development of the central nervous system critically depends on successfully completing neural tube closure. Normal developmental programs required for cranial neural tube closure include neural plate patterning, signaling systems responsible for tissue movement or fusion, and mechanisms responsible for the coordination of cell division, cell differentiation, and cell death (Yamaguchi and Miura 2013). Failure to properly close the neural tube results in significant and lethal open cranial neural tube defects, such as craniorachischisis and exencephaly/anencephaly. On the other hand, the relationship between closed defects such as cephaloceles and neural tube closure defects is debated. Based on the traditional bidirectional, “zipper-like” neural tube closure model, cephaloceles have been related to defects of closure of the anterior neuropore (Menkes and Till 1995). However, intermediate defects, such as occipital or frontal cephaloceles, remained difficult to explain. Conversely, the multisite neural tube closure model suggests that cephaloceles and other neural tube closure defects, such as myelomeningocele, anencephaly, and craniorachischisis, can be explained by failure of fusion of one of the closures or their contiguous neuropore (Van Allen et al. 1993). A striking correlation between the neural tube defects observed in clinical cases and the location of the closure sites and their neuropores is believed to exist by these authors (Van Allen et al. 1993). However, subsequent studies showed that some postulated closure sites do not exist in either mouse or human neurulation (Copp et al. 2003, 2013; O’Rahilly and Muller 2002). What remains is a fairly simple pattern of human neurulation, most akin to the original model. Other authors (Campbell et al. 1986) believe that cephaloceles should be considered post-neurulation defects. The primary event should be traced to failure in the bony covering of the neural tube, and cephaloceles would be caused by events not associated with neurulation, but with distortion and crowding of a rapidly growing brain through the defect. It is still controversial whether cephaloceles result from a primary neural tube nonclosure or from a secondary reopening. The absence of epidermal coverage to the malformation is probably the single most significant indicator of primary failure of neural tube closure. Conversely, it is difficult to determine whether skin-covered cephaloceles result from an incomplete neural tube closure or a secondary reopening. Lateral (i.e., off-midline) cephaloceles most likely result from a secondary neural tube reopening and are usually seen in association with disruptive disorders (Menkes and Till 1995).

The etiology of cranial neural tube defects is heterogeneous. Most cases have a multifactorial cause and are the result of the interaction between genes associated with neural tube closure and environment. Genetic predisposition accounts for most of the risk of neural tube defects, and genes regulating folate–homocysteine metabolism and planar cell polarity have been strongly implicated (Copp et al. 2013). Moreover, chromosomal abnormalities including trisomy 18 and 13 have been reported in neural tube defects. Conversely, a small proportion of neural tube defects are caused by exposure to teratogens such as carbamazepine and valproic acid and maternal diseases such as poorly controlled maternal insulin-dependent diabetes mellitus (Copp et al. 2013). Finally, amniotic band sequence may cause disruption also resulting in anencephaly/exencephaly or cephaloceles of the convexity (Rohrbach et al. 2007).

Clinical Features

The degree of neurological and developmental damage associated with cephaloceles is variable and depends on the amount of herniated neural tissue, the presence of hydrocephalus, and the association with hindbrain lesions or cerebral hemisphere dysplasia which result from the associated disorder of cellular migration and organization (Menkes and Till 1995). Some patients are only mildly impaired. Mental
retardation, spastic diplegia, and cognitive disorders may not become evident until childhood. Patients with meningoceles or atretic cephaloceles have an essentially normal neurological picture, and their prognosis is favorable provided there is neither hydrocephalus nor associated congenital abnormalities. Conversely, children with encephaloceles show a complex clinical picture that depends on variably combined factors such as the size, contents, and location of the herniation, as well as the presence of hydrocephalus, perinatal injury, apneic crises, seizures with consequent hypoventilation, hypoxia, and acidosis (Tortori-Donati et al. 1996).

In general, occipital cephaloceles are associated with an unfavorable prognosis compared to that of skull base cephaloceles. Severe occipital cephaloceles are often associated with distortion of the brainstem and cranial nerves leading to visual disturbances, neurovegetative disorders (apnea, bradycardia, sialorrhea), and cranial nerve deficit (strabismus, nystagmus, dysphagia). Hydrocephalus is often progressive and manifests with increased intracranial pressure, opisthotonus, and hypertonic limbs. Ulceration of the sac may be complicated by local infection or meningoencephalitis. Associated anomalies are especially important, as they often influence the clinical picture more severely than the cephalocele itself. Occipital encephaloceles are often syndromic, most commonly as part of Meckel syndrome (see below). Associated abnormalities account for a variable degree of developmental and psychomotor delay, blindness, superior function compromise (i.e., symbolic functions, language, learning, and memory), motor incoordination, and seizures (Tortori-Donati et al. 1996).

Skull base cephaloceles usually are characterized by severe craniofacial dysmorphisms with cleft lip and palate, coloboma, and microphthalmos. Sphenoidal cephaloceles usually become manifest either with signs of upper airway obstruction or with endocrine and visual dysfunction, due to prolapse of the pituitary gland and optic chiasm into the herniated sac. Visual disturbances may also be due to associated abnormalities, such as holoprosencephaly and septo-optic dysplasia. Anosmia may result from the compromise of the olfactory nerves and bulbs in patients with sincipital cephaloceles.

Ascending infections of the CNS with recurrent meningitides may be caused by occult connections between unsuspected skull base cephaloceles and the nasal and paranasal cavities, rhinopharynx, and inner ear (Tortori-Donati et al. 1996).

**Classification and Neuroradiological Features**

Cephaloceles are usually categorized according to their location into convexity, skull base, and internal cephaloceles (Naidich et al. 1992; Friede 1989). Their neuroradiological evaluation aims to assess: (i) their exact location; (ii) the morphology, size, and content of the sac; (iii) possible associated abnormalities, such as callosal dysgenesis (Rao et al. 1990) and the Chiari II malformation, that portend a poorer prognosis; and (iv) the anatomic relationship with vascular structures, especially the dural sinuses, whose inadvertent damage during surgery may cause profuse bleeding.

MR imaging better defines the extent of herniated cerebral tissue in the encephaloceles. In particular, heavily T2-weighted images (such as DRIVE or FIESTA sequences) are useful for the identification of distorted herniated structures and for the accurate depiction of pituitary gland or optic nerve involvement. Diffusion-weighted sequences are particularly helpful in the detection of cytotoxic edema in the herniated brain tissue (Fig. 4) and to distinguish cephaloceles from dermoid/epidermoid cysts. MR venography clearly identifies the location and course of the major venous structures. Finally, the bony defect can be assessed by three-dimensional (3D) computerized tomography (CT) scan with MPR and volumetric reconstructions for surgical planning.
Cephaloceles of the Convexity

Occipital Cephaloceles

Depending on the relationship of the calvarial defect with anatomic landmarks, such as the external occipital protuberance and the posterior lip of the foramen magnum, occipital cephaloceles are categorized into three subsets: (i) occipitocervical, in which the defect involves the occipital squama, foramen magnum, posterior arch of the atlas, and often the neural arches of the upper cervical vertebrae (Fig. 5); (ii) inferior occipital, in which the defect lies at or below the external occipital protuberance and above the posterior lip of the foramen magnum (Figs. 6, 7, 8, and 9); and (iii) superior occipital, in which the defect lies above the external occipital protuberance (Figs. 10 and 11).

Occipital cephaloceles are obvious at birth and are usually diagnosed antenatally. In newborns, the differential diagnosis includes cephalohematomas, caput succedaneum, and cystic lymphangiomas. Occipital dermoid/epidermoid cysts with dermal sinus tracts and intracranial components are another important differential diagnosis (Fig. 12).

Fig. 4 Diffusion-weighted imaging in encephaloceles. (a) Sagittal T2-weighted image. (b) Sagittal T1-weighted image. (c) Axial diffusion-weighted image (b = 1,000). MR images depict an occipital meningoencephaloceles with hemosiderin deposits indicating spontaneous hemorrhages in the herniated brain tissue (arrows, a). Restricted diffusion consistent with cytotoxic edema is evident in the herniated brain tissue (arrowheads, c) and in the parietal lobes adjacent to the skull defect (arrows, c) (Case courtesy Dr. Chen Hoffmann, Tel Aviv, Israel)
Most of the occipital cephaloceles (80%) are meningoencephaloceles that contain cerebral tissue, cerebellar tissue, or both (Simpson et al. 1984; Lorber and Schofield 1979). However, the content of the sac is not predictable based on the site of the cranial defect (Naidich et al. 1992). The occipital lobes are

![Fig. 5 Occipitocervical meningocele. (a) Sagittal T1-weighted image. (b) Sagittal T2-heavily weighted (DRIVE) image. (c) Coronal T2-weighted image. (d) Axial T2-weighted images. (e, f) Three-dimensional CT scan. Small occipital-cervical meningocele extending inferiorly to C1 (asterisks, a, b, c). Note two small bridges of tissues across the midline at the level of the hypothalamus (interhypothalamic adhesion, thin arrows, b). CT scan clearly depicts the skull defect involving the occipital squama (arrowheads, e, f). The posterior arches of C1 and C2 are not yet ossified]
Fig. 6  Inferior occipital meningocele. (a) Sagittal T1-weighted image. (b) Sagittal T2-weighted image. (c) Coronal T1 IR image. (d) Axial T1-weighted image. Small isolated occipital meningoceles (asterisks, a, d) with large occipital bone defect. Note the CSF pulsation artifacts (black arrowhead, b) indicating increased CSF flow through a smaller dural defect (white arrowheads, a)

Fig. 7  Occipital meningocele. (a) Sagittal T1-weighted image. (b) Three-dimensional CT scan. A complex malformation is associated with an occipital meningocele (asterisk, a). CT scan clearly shows the skull defect (arrows, b)
the single most common portion of brain that is included within the herniation. Dural sinuses and other venous structures may also lie close to or within the sac, generating a risk for hemorrhage and subsequent brain damage during surgery. The overall size of the cephalocele is usually large, exceeding 5 mm in diameter in 72% of cases (Naidich et al. 1992).

Simple meningoceles are usually isolated (Figs. 5 and 6). Conversely, meningoencephaloceles can be associated with other malformations (Figs. 7, 8, and 9), such as holoprosencephaly, callosal dysgenesis, myelomeningocele, Klippel–Feil syndrome, and hydrocephalus. Some of these associations are considered as autonomous entities. The presence of signs of Chiari II malformation (small posterior fossa, tectal beaking, enlarged interthalamic mass) in a child with an occipital cephalocele is designated “Chiari III malformation” (Castillo et al. 1992). These entities are described in detail elsewhere in this chapter.

**Sagittal Interparietal Cephaloceles**

Sagittal interparietal, or vertex, cephaloceles account for about 12–20% of all cephaloceles. They are usually sporadic lesions with no identified causative genes or factors. These cephaloceles are located between the parietal bones in the midline. Abnormalities of the dural sinuses are frequently associated, including persistence of the falcine sinus, bifurcation or fenestration of the superior sagittal sinus, and sinus pericranii (Patterson et al. 1998; Brunelle et al. 2000; Morioka et al. 2009; Hsu and Chaloupka 2012; Figs. 13 and 14). Syndromic forms are usually associated with hydrocephalus and midline malformations, such as callosal dysgenesis and holoprosencephaly.

Atretic cephaloceles are the most frequently encountered variant in this location, extending from the dura to the skin through a small bony defect (0.5–1.5 cm in diameter). They are usually separated from the cerebral parenchyma by the dura although, sometimes, they can have a direct connection (Gao et al. 2014). More rarely, they are connected to or penetrate the superior sagittal sinus. Anomalies of the tentorium are frequently associated. A vertical falcine vein with a CSF tract usually points to a small sub-scalp solid or cystic mass (Morón et al. 2004). A midline fibrous tract may be present connecting the mesencephalic tectum to the overlying dura at the level of the bone defect (Fig. 14). Solid atretic
Fig. 9  (continued)
cephaloceles are composed of neuroglial and fibrous tissues, hyperplasia of meningeal cells, and/or abnormal vessels, while cystic atretic cephaloceles (also called glioceles) contain a CSF-like fluid (Gao et al. 2014). The differential diagnosis in these cases includes also the sinus pericranii and may require further investigations, including color-Doppler ultrasound, CT angiography, or digital subtraction angiography (Fig. 15).

**Lateral Cephaloceles**

Lateral (i.e., off-midline) cephaloceles are very rare (Fig. 16). They are found along the coronal and lambdoid sutures and at the pterion or asterion. Usually, no intracranial malformations are associated (Tubbs et al. 2011). They are believed to result from a secondary reopening of the neural tube. Therefore, they are considered secondary, disruptive disorders (Van Allen et al. 1993).

**Bregmatic Cephaloceles**

Cephaloceles located at the anterior fontanel must be differentiated from dermoids, which are much more common in this location. Diffusion-weighted imaging easily allows the distinction between these entities, showing restricted diffusion in dermoid/epidermoid cysts (Fig. 17). Other lesions typically located at this level are lipomas, hemangiomas (Fig. 18), or venous/lymphatic malformations. CT may be useful to demonstrate the calvarial defect that is associated with cephaloceles.

**Interfrontal Cephaloceles**

They are found between the glabella and the bregma, and the defect lies along the metopic suture. Portions of the frontal lobes may herniate into the sac. Interfrontal encephaloceles have been reported in
association with myelomeningocele and hydrocephalus (Nejat et al. 2013). Patients had severely wide metopic suture and frontal cranium bifidum associated with frontal lobe herniation through the midline defect, resulting in frontal bossing and hypertelorism (Nejat et al. 2013).

**Skull Base Cephaloceles**

Anterior cephaloceles (Fig. 19) usually are found in children with little or no neurological impairment. However, they may be associated with callosal agenesis, interhemispheric cysts, and interhemispheric lipomas. Cortical dysplasia and holoprosencephaly may also be associated, whereas hydrocephalus, albeit possible, is rare. Cephaloceles of the skull base may be accompanied by midline facial defects, such as hypertelorism, cleft lip, and cleft palate (Naidich et al. 1994b). Contrary to occipital cephaloceles, they may be clinically occult and discovered later in life. They may present as soft, compressible, bluish intranasal masses, which transilluminate and increase in size with crying or jugular compression (positive Furstenberg sign). Sincipital encephaloceles present as extranasal masses located over the nose, glabella, medial canthus, or lower forehead.
Sincipital Cephaloceles

Sincipital or frontoethmoidal cephaloceles are categorized according to their relationship with the frontal bone, nasal bones, and ethmoid (Barkovich et al. 1991; Tirumandas et al. 2013; Rojvachiranonda et al. 2003; Connor 2010):

**Nasofrontal or glabellar cephaloceles**: The defect lies between the frontal and nasal bones at level of the “fonticulus nasofrontalis,” a small transient fontanel corresponding externally to the glabella (Barkovich et al. 1991). These lesions may be in the midline or lie slightly off the midline and can be associated with other abnormalities such as callosal dysgenesis, lipomas, holoprosencephaly, and cortical malformations (Fig. 20).

**Nasoethmoidal cephaloceles**: The congenital defect is located between the nasal bones and the cartilage. The cephalocele can develop either on the surface of the nasal pyramid or in the inner canthus of the eye.

**Nasoorbital cephaloceles**: The defect lies at the junction between the frontal, ethmoidal, lacrimal, and maxillary bones. The cephalocele develops either externally on the face or internally in the orbit (Fig. 21).

Fig. 11 Superior occipital atretic cephalocele. (a) Sagittal T1-weighted image. (b) Sagittal T2 heavily weighted (DRIVE) image. (c) Axial T2-weighted image. (d) Phase contrast MRA. Small cystic atretic cephalocele (*asterisks*, a, b, c). A vertical falxine vein (*empty arrows*, a, b, d) and CSF tract point to the subcutaneous cystic mass. Note the mesencephalic tectal beaking (*arrowhead*, b)
These cephaloceles are believed to result from an incomplete regression of a dural outpouching that normally crosses the fonticulus nasofrontalis during fetal life and is subsequently obliterated (Barkovich et al. 1991), resulting in the foramen caecum. The enlargement of this foramen is a hallmark of these lesions and is well demonstrated by CT.

Sincipital cephaloceles must be differentiated from nasal glial heterotopias and dermoids, which share a common embryological mechanism.
Nasal glial heterotopias (Fig. 22) are also called nasal gliomas (Younus and Coode 1986; Penner and Thompson 2003; Hedlund 2006). The term “nasal glioma” is a dreadful, confusing misnomer, as it implies a neoplastic condition with malignant potential, which it is not. Nasal glial heterotopia is a rare developmental abnormality and should be differentiated from glioma, which is a tumor of the brain, and from a primary encephalocele, which is the herniation of the cranial contents through a bone defect in the skull, through which it retains an intact connection with the CNS (Younus and Coode 1986). Nasal gliomas are composed of dysplastic brain tissue located into the nasal fossae or in the subcutaneous tissues of the glabella (Penner and Thompson 2003). They are not connected with the CNS. Embryologically, nasal glial heterotopias are similar to sincipital cephaloceles in that both entities are believed to result from
nervous tissue herniating through the foramen caecum along a dural outpouching. If the proximal portion of the dural stalk regresses, sequestration of distal nervous tissue produces a heterotopia, whereas preservation of the connection at the level of the foramen caecum results in a cephalocele. The differentiation between the two entities is obviously important in view of the inherently different surgical strategy.

Dermoids are dysontogenetic masses that usually are associated with a dermal sinus tract (Fig. 23). The latter arises at an external ostium situated along the midline of the nose and extends deeply for a variable distance, sometimes crossing the foramen caecum to reach the intradural intracranial space (Naidich et al. 1994b; Hedlund 2006). The differentiation of dermoids from nasal glial heterotopia is based on their density on CT, which parallels that of fat, and signal behavior on diffusion-weighted imaging.

Lipomas are the most common benign mesenchymal tumor, arising in any location where fat is normally present. Nasal lipomas are very rare and may be differentiated from a dermoid/epidermoid cyst based on the density on CT or MR signal consistent with that of fat, and absent restricted diffusion on diffusion-weighted imaging (Fig. 24).

**Sphenoidal Cephaloceles**

Sphenoidal cephaloceles usually are not clinically evident at birth and require time to become manifest with either exophthalmos or upper airway obstruction. Therefore, they are generally recognized later in infancy or even in adulthood. Physical examination in these children often reveals a pulsatile rhinopharyngeal mass covered by nasal mucosa that expands with a Valsalva maneuver. Spontaneous fistulas are rare but may be complicated by ascending meningitis. Sphenoidal cephaloceles are further divided into several groups:

**Spheno-orbital cephaloceles**: The defect may involve the superior orbital fissure, the greater sphenoid wing (Elster and Branch 1989), the optic canal, and the walls of the orbit. Exophthalmos may result from chronic mass effect within the rigid orbital cavity (Levy et al. 1989).

**Sphenomaxillary cephaloceles**: The cephalocele herniates through the inferior orbital fissure into the pterygopalatine fossa and usually contains portions of the temporal lobe.

**Nasopharyngeal cephaloceles**: This category includes several forms, depending on the relationship between the bony defect and the ethmoid, sphenoid, and basiocciput. **Trans-ethmoidal cephaloceles** (Fig. 25) cross a defect in the cribiform plate and extend into the ethmoidal cavities, which are deformed and remodeled; sometimes the sac protrudes into the nasal cavity, vestibule, and rhinopharynx. **Sphenoethmoidal** cephaloceles pass between the body of the sphenoid and the ethmoid and occupy the posterior nasal cavity or the rhinopharynx (Rice and Eggers 1989). **Spheno-nasopharyngeal**
Cephaloceles develop through the body of the sphenoid bone and represent the more typical form of sphenoidal cephalocele, classically presenting as a submucosal pharyngeal mass (Fig. 26). When the defect involves the floor of the pituitary fossa, the pituitary gland, hypothalamus, and optic chiasm may herniate into the sac (Boulanger et al. 1989). Basiooccipital-nasopharyngeal cephaloceles are
Fig. 16 Parietal meningocele. (a) Coronal T2-weighted image. (b) Axial T2-weighted image. Large meningocele containing septa in the right parietal region. Widespread cortical malformations, represented by subependymal heterotopia (arrowhead, a) and multiple bilateral polymicrogyric infoldings (arrows, a, b), are recognizable (Case courtesy of Zoltan Patay, Memphis, USA).

Fig. 17 Bregmatic dermoid. (a) Sagittal T1-weighted image. (b) Sagittal T2 heavily weighted (DRIVE) image. (c) Coronal T2-weighted image. (d) Sagittal DWI image (b = 1,000). Bregmatic dermoid cyst (asterisks, b, c) in a patent anterior fontanel showing restricted diffusion on DWI (empty arrow, d).
exceedingly rare and develop through a midline clival defect at the level of the spheno-occipital synchondrosis. The sac may contain a portion of the prepontine cistern, brainstem, and even fourth ventricle (Nager 1987).

Internal Cephaloceles
These very rare cephaloceles are different from both calvarial and skull base cephaloceles in that they are acquired forms resulting from the positional rearrangement of the nervous structures secondary to major trauma or surgery (Sarnat 1992; Copp et al. 2003).

A subset of cephaloceles occurs spontaneously off midline in the lateral sphenoid bone and has been referred to as spontaneous lateral sphenoid cephaloceles (Settecase et al. 2014; Fig. 27). Altered CSF dynamics may play a role in their genesis. They arise from bony defects in the lateral sphenoid, in the absence of predisposing factors such as trauma, surgery, mass, or congenital skull base malformation. Two types of spontaneous lateral sphenoid cephaloceles have been identified. The first type herniates into a pneumatized lateral recess of the sphenoid sinus typically causing CSF leak and/or headache. The second type may be detected incidentally and is isolated to the greater sphenoid wing without extension into the sphenoid sinus, causing seizures, headaches, meningitis, and cranial neuropathy (Settecase et al. 2014).

Fig. 18 Bregmatic hemangioma. (a) Sagittal T1-weighted image. (b) Sagittal contrast-enhanced T1-weighted image. (c) Sagittal DWI image (b = 1,000). (d) Coronal T2-weighted image. (e) Coronal T2-weighted image. (f) Three-dimensional CT scan, MPR coronal image. Soft tissue hemangioma at the level of anterior fontanel (asterisks, d, e) characterized by homogeneous contrast enhancement (arrowhead, b) and facilitated water diffusion on DWI.
Closed internal cephaloceles are also frequent in Hunter syndrome, a rare X-linked recessive disease caused by mutations of the gene encoding for iduronate-2-sulfatase, an enzyme involved in lysosomal GAG catabolism (Manara et al. 2012). In particular, nearly 25% of Hunter patients present with a meningeal or brain parenchymal herniation at the level of the anterior or middle cranial fossa (Fig. 28).
Brain herniations into dural venous sinuses are rare findings with controversial etiology and clinical significance (Karatag et al. 2013; Battal and Castillo 2014; Fig. 29). They are characterized by the herniation of brain parenchyma with surrounding cerebrospinal fluid through the dura into the dural venous sinuses or calvarium without apparent bone defects in the outer table of the skull. Although their exact pathogenesis is unclear, progressive dural and bone thinning secondary to elevated CSF pressure, inflammation, aging, and erosive arachnoid granulations are considered predisposing factors. They are probably incidental findings, although a causal relationship with headache cannot be excluded (Karatag et al. 2013; Battal and Castillo 2014). On MR imaging, the herniated brain and surrounding CSF have the same signal intensity as normal brain parenchyma and subarachnoid spaces. Brain herniation into a dural venous sinus should not be confused with the more common arachnoid granulations, clots, or tumor extensions which have different clinical implications.

**Prenatal diagnosis**

Ultrasound is the noninvasive screening modality of choice for the detection of neural tube defects because of its safety, cost efficiency, and detection sensitivity (Kasprian et al. 2014; Wilson et al. 2014; Neuman et al. 2012; Saleem et al. 2009). Up to 80% of cephaloceles can be detected during the first...
trimester, and almost all cases are identified after the second-trimester scan (Wilson et al. 2014). A detailed neurosonographic examination allows the depiction of the bony skull defect and the size and morphology of the herniated meningeal and brain tissue.

The presence of associated malformations or underlying syndromes is predictive for the cognitive outcome in cephaloceles, justifying a detailed prenatal diagnostic assessment in these patients. Many factors may hamper the ultrasound image quality and accuracy, including gestational age, amniotic fluid volume, position and number of fetuses, and maternal body mass index (BMI). Fetal MRI overcomes these problems and has an important role in the management planning and prenatal counseling of cephaloceles, confirming the results of equivocal ultrasonography findings and identifying additional factors that may affect the outcome.

Fig. 21 Nasoorbital encephalocele. (a, b) Three-dimensional CT scan, volumetric reconstruction with different windowing (soft tissue window, a; bone window, b). (c) Sagittal T2-weighted image. (d) Coronal T2-weighted image. (e) Axial T2-weighted image. (f) Axial T1-weighted image. Patient has a large nasal subcutaneous mass due to herniation of dysplastic malformed nervous tissue, originating from both frontal lobes (asterisks, c, e, f). The bony defect involves the nasal bones, the caudal portion of the frontal bone (arrowhead, b), the anterior portion of the ethmoid (arrowhead, c), and the medial orbital walls (empty arrow, b). The encephalocele extends laterally into the orbits (thin arrows, e, f). Note the abnormal cortical “polymicrogyria-like” pattern in the frontobasal regions (arrows, d) and absent olfactory bulbs and tracts.
anomalies (Wilson et al. 2014; Saleem et al. 2009; Figs. 30, 31, 32, 33, 34, and 35). In particular, fetal MRI may reveal abnormal cortical folding (“polymicrogyria”) patterns (Fig. 34) and subependymal heterotopias (Fig. 33) that are difficult to visualize by ultrasound. Furthermore, posterior cranial fossa malformations are better characterized on fetal MRI, depicting abnormal brainstem configuration, such as a z-shaped or kinked brainstem, or specific signs such as the molar tooth sign, pathognomonic of Joubert syndrome and its related disorders. The association of a high cervical/low occipital encephalocele and posterior cranial fossa crowding (“lemon sign”) with vermician downward displacement is indicative of the so-called Chiari III malformation (Smith et al. 2007). Finally, in cases with amniotic band sequence, fetal MRI is a complementary technique to prenatal ultrasound, providing a comprehensive view of the constricting fibrous strands that may be useful in cases where fetal surgery is contemplated (Fig. 35). Moreover, real-time cine MRI sequences demonstrate restricted motion of the involved extremity (Neuman et al. 2012).

**Fig. 22** Nasal glial heterotopia. (a) Sagittal T1-weighted image. (b) Sagittal T2-weighted image. (c) Gd-enhanced sagittal T1-weighted image. Large mass (asterisks, a, b) involving the subcutaneous tissue of the nasal pyramid (arrowheads, a, b). The lesion is isointense on T1-weighted images (a) and inhomogeneously iso-hyperintense on T2-weighted images (b) and shows inhomogeneous enhancement after gadolinium injection (c).
Syndromes Associated with Cephaloceles

Cephaloceles may be part of malformative complexes, whose pattern of genetic transmission has been established in some cases (Cohen and Lemire 1982; Chen 2008). Cephaloceles may represent either a constant or a possible finding, depending on the nature of the syndrome (Table 1). The association with other congenital CNS anomalies accounts for the often severe psychomotor compromise exhibited by

Fig. 23 Nasal dermoid. (a) Sagittal T2-weighted image. (b) Sagittal heavily T2-weighted (DRIVE) image. (c) Sagittal DWI image. (d) Axial T2-weighted image. (e) Fat-saturated Gd-enhanced axial T1-weighted image. (f) Three-dimensional CT, sagittal MPR image. The frontal intradiploic dermoid (asterisks, a, b) extends intracranially in the extradural compartment (arrowhead, d) and is characterized by restricted diffusion on DWI (empty arrow, c) and absent contrast enhancement. Note a second small intracranial component (arrows, b, c). 3D CT scan demonstrates the intradiploic bone defect involving the inner table at the level of the caudal portion of the frontal bone (arrowhead, f), extending inferiorly into the foramen caecum (thin arrow, a, f)
affected children. Genetic counseling is obviously very important in view of the severe prognosis, which is often associated with these syndromes.

Frontonasal Dysplasia

The term frontonasal dysplasia was coined by Sedano et al. in 1970 to describe a constellation of findings limited to the face and head (Sedano et al. 1970). The disorder is defined as two or more of the following: (i) true ocular hypertelorism, (ii) broadening of the nasal root, (iii) median facial cleft affecting the nose and/or upper lip and palate, (iv) unilateral or bilateral clefting of the alae nasi, (v) lack of formation of the nasal tip, (vi) anterior cranium bifidum occultum, and (vii) a V-shaped or widow’s peak frontal hairline (Sedano and Gorlin 1988). In this malformative spectrum, there is an increased incidence of basal/frontoethmoidal/transsphenoidal encephalocele with pituitary herniation variably associated with intracranial-associated anomalies, such as holoprosencephaly, lipomas of the interhemispheric fissure, and callosal agenesis (Naidich et al. 1988; Figs. 36 and 37). In addition to isolated forms, several subtypes of frontonasal dysplasia have been described based on associated malformations, such as acromelic frontonasal dysplasia, frontofacionasal dysplasia, oculoauriculofrontonasal syndrome, acrofrontofacionasal dysostosis syndromes, and craniofrontonasal syndrome (Wu et al. 2007).

Fig. 24  Nasal lipoma. (a) Sagittal T1-weighted image. (b) Sagittal T2 heavily weighted image. (c) Fat-saturated Gd-enhanced sagittal T1-weighted image. (d) Sagittal DWI image. The nasal mass (asterisks, a, b) is hyperintense on both T1- and T2-weighted images, does not enhance after Gd injection, and saturates on fat-saturated images (arrowhead, c). There is no restricted diffusion within the lesion.
**Fig. 25** Trans-ethmoidal encephalocele. (a) Reconstructed sagittal image from T1-weighted 3D sequence. (b) Coronal T1-weighted image. (c) Coronal T2-weighted image. A large portion of the basal portion of the right frontal lobe herniates through an ethmoidal defect into the nasal cavities (*asterisk, a–c*) (Case courtesy of Zoltan Patay, Memphis, USA)

**Fig. 26** Spheno-nasopharyngeal encephalocystocele. (a) Sagittal T1-weighted image. (b) Coronal T1-weighted image. The anterior third ventricle herniates through the sellar floor in the sphenoidal region (*asterisk, a, b*). The two portions of the pituitary gland (anterior and posterior lobe) are recognizable, although the gland is flattened against the clivus (*arrowheads, a*)
The embryological origin of this syndrome is in the period prior to the 28 mm stage. It is due to deficient remodeling/differentiation of the nasal capsule, which causes the future fronto-nasoethmoidal complex to freeze in the fetal form. It usually is a sporadic disorder, although a few familial cases have been reported (Nevin et al. 1999) and genetic mutations have been identified in a small number of patients (Twigg et al. 2004, 2009; Kayserili et al. 2009, 2012; Uz et al. 2010). There are at least three types of frontonasal dysplasia that are characterized by distinctive clinical features and mutations in aristaless-like homeobox genes (ALX4, ALX3, and ALX1) (Twigg et al. 2009; Kayserili et al. 2009, 2012; Uz et al. 2010). These genes encode transcriptional regulators involved in cell-type differentiation and development of the face and head, especially the nose and surrounding midline facial tissues.

Interestingly, there is pathognomonic nasal configuration in each type of frontonasal dysplasia, and clinicians can predict the ALX-related gene from the phenotype (Uz et al. 2010). Frontonasal dysplasia type 1 (OMIM #136760) is caused by homozygous mutation in ALX3 on chromosome 1p13 resulting in hypertelorism, wide nasal bridge, short nasal ridge, bifid nasal tip, broad columella, widely separated slit-
like nares, long philtrum, and a midline notch in the upper lip and alveolus (frontorhiny) (Twigg et al. 2009). Frontonasal dysplasia type 2 (OMIM #613451) is caused by homozygous mutation in the ALX4 gene on chromosome 11p11. This form is characterized by total alopecia, large skull defects, coronal craniosynostosis, and callosal agenesis. Affected males often have genital abnormalities (Kayserili et al. 2009, 2012). Frontonasal dysplasia type 3 (OMIM #613456) is caused by homozygous mutation in the ALX1 gene on chromosome 12q21.31. Features of frontonasal dysplasia type 3 include anophthalmia or microphthalmos, cleft palate and midline cranial cleft, and low-set backward-rotated ears. This form is typically associated with the most severe facial abnormalities, but the severity of the condition varies widely, even among individuals with the same type (Uz et al. 2010).

Finally, mutations in the gene encoding ephrin-B1 (EFNB1), a ligand to ephrin receptor tyrosine kinases, have been associated with frontonasal dysplasia and a craniosynostosis phenotype named “craniofrontonasal syndrome” (CFNS, OMIM#304110) (Twigg et al. 2004). This X-linked disorder is characterized by a more severe phenotype in heterozygous females than in hemizygous males.

Fig. 29 Brain herniation into a dural venous sinus. (a, b) Coronal T2-weighted images. (c) Axial T2-weighted image. (d) Sagittal T1-weighted image. MR images show a small herniation of temporal lobe parenchyma with surrounding CSF into the left transverse sinus (arrowheads, a–d). The small internal encephalocele is slightly narrowing the left transverse sinus.
Chiari III Malformation
The real incidence of Chiari III malformation and its gender distribution are unknown. It accounts for only 2 of 312 cases of Chiari malformation (0.64%) in our center (Cama et al. 1995). This very rare abnormality is defined by the association of high cervical/low occipital encephalocele with signs of Chiari II malformation, including a small posterior fossa, tectal beaking, and low cervicomedullary junction (Işik et al. 2009; Rani et al. 2013). Other features include hypoplasia of the low and midline aspects of the parietal bones, petrous and clival scalloping, cerebellar hemisphere overgrowth, cerebellar tonsillar herniation, hydrocephalus, dysgenesis of the corpus callosum, posterior cervical vertebral agenesis, and spinal cord syringes (Fig. 38). The encephalocele may contain varying amounts of the brain (either the cerebellum and occipital lobes or cerebellum only), ventricles (fourth and lateral), cisterns, and brainstem (Castillo et al. 1992). Diffusion tensor imaging may allow identification of distorted descending tracts entering the meningoencephaloceles (Zolal et al. 2010).

DK Phocomelia Syndrome
This entity, also known as von Voss–Cherstvoy syndrome, is characterized by phocomelia, occipital encephalocele, and urogenital abnormalities (Cherstvoy et al. 1980; Lubinsky et al. 1994; Bamforth and Lin 1997). Phocomelia usually involves only the upper limbs and is limited to radial anomalies. Other possible CNS findings include callosal agenesis, partial vermian agenesis, and hypoplasia of the olivary
Fig. 31 Nasoorbital encephalocele at 26 gestational weeks (same patient of Fig. 23). (a, b) Sagittal express turbo spin-echo T2-weighted images. (c, d) Axial express turbo spin-echo T2-weighted images. Fetal MR images clearly depict a frontal and nasal bone defect through which neural tissue herniates consistent with a sincipital encephalocele (arrowheads, a–d).

Fig. 32 Occipital cystic atretic cephalocele at 21 gestational weeks. (a) Sagittal express turbo spin-echo T2-weighted image. (b) Axial express turbo spin-echo T2-weighted image. Fetal MR images demonstrate an atretic cystic cephalocele (arrowheads, a, b) associated with a small upward-rotated vermis and enlarged posterior cranial fossa.
Fig. 33 (continued)
nuclei and pyramids (Tortori-Donati et al. 1996). It is usually lethal at birth, although long-term survivors have been reported (Bamforth and Lin 1997). Both sexes are affected, and parental age is not increased. All reported cases were sporadic, except for a patient harboring a mosaicism for a deletion of 13q12 in the fibroblasts but with normal lymphocyte chromosomes (Bamforth and Lin 1997). However, autosomal recessive inheritance has been suggested in at least some instances (Lubinsky et al. 1994).

Fig. 33 Pre- and postnatal MR findings of a complex occipital encephalocele. (a–d) Fetal MRI at 24 gestational weeks. (e–h) Brain MRI at 4 days of life. (a, b) Axial express turbo spin-echo T2-weighted images. (c) Coronal express turbo spin-echo T2-weighted image. (d) Sagittal express turbo spin-echo T2-weighted images. (e, f) Axial T2-weighted images. (g) Coronal T2-weighted image. (h) Sagittal heavily T2-weighted (DRIVE) image. Fetal MR images show herniation of the left lateral ventricle into a large cephalocele through a wide occipital bone defect (asterisks, a, c, d). There is associated severe ventriculomegaly with squared frontal horns and multiple nodules of periventricular heterotopia (arrowheads, b). In addition, the bulbo-medullary junction is tented and angled posteriorly toward the cephalocele (arrowhead, d). Postnatal MR images confirm these findings and reveal aqueductal stenosis (white arrowhead, h). The markedly stretched, distorted posterior aspect of the cervicomedullary junction forms a band of tissue (asterisk, h) extending into a tiny fibroneural stalk that penetrates into the meningocele (thin arrows, h). Note the small hypothalamic adhesion (black arrowhead, h)
Fig. 34 Chiari II malformation and multiple cephaloceles associated with a sacral myelomeningocele at 35 gestational weeks. (a, b) Axial express turbo spin-echo T2-weighted images. (c) Coronal express turbo spin-echo T2-weighted image. (d–f) Sagittal express turbo spin-echo T2-weighted images. Fetal MR images show an occipital encephalocele (white arrowhead, d) with transtentorial herniation of the occipital horn (asterisks, a, c, e) associated with bilateral parasagittal parietal encephaloceles (black arrowheads, b, d). The posterior fossa is small with effacement of the subarachnoid spaces and inferior displacement of the vermis (thin arrow, e). An open spinal dysraphism is evident at the sacral level (empty arrow, f). Note the abnormal cortical gyration pattern of the frontoparietal regions (b)
Ciliopathies

Ciliopathies comprise a group of disorders due to mutations in genes encoding proteins involved in the formation or function of cilia (Vogel et al. 2012; Lee and Gleeson 2011; Barisic et al. 2014; Barker et al. 2014; Logan et al. 2011; Romani et al. 2013, 2014; Shaheen et al. 2014; Poretti et al. 2011). Cilia are highly evolutionarily conserved organelles present in nearly every cell type in vertebrates (Vogel et al. 2012; Lee and Gleeson 2011). The primary cilium plays an important role both during development and in adult life. Ciliary dysfunction can manifest as a constellation of features, including primarily retinal degeneration, renal disease, and cerebral anomalies. Additional manifestations include congenital fibrocystic diseases of the liver and pancreas, diabetes, obesity, and skeletal dysplasias. Over 60 genes have been associated with a large spectrum of ciliopathies, ranging from milder phenotypes, such as isolated retinal dystrophy or nephronophthisis, to the most severe form represented by Meckel–Gruber syndrome (Barisic et al. 2014; Barker et al. 2014). Interestingly, while many genes are associated with a single ciliopathy, mutation in one gene may give rise to different phenotypes. For example, there is substantial overlap in the underlying genetic basis of nephronophthisis, Joubert syndrome, and Meckel–Gruber syndrome (Logan et al. 2011; Romani et al. 2014; Shaheen et al. 2014).

Neural tube defects, including cephaloceles, are frequently encountered in ciliopathies, particularly in Meckel–Gruber and Joubert syndromes. The cilia have a critical role in the development of the central nervous system (Vogel et al. 2012; Lee and Gleeson 2011). In particular, primary cilia are linked to several signaling pathways (i.e., Wnt, Hedgehog, and planar cell polarity pathways) that regulate cell migration, polarization, and differentiation during neurulation and patterning of the neural tube. The disruption of

![Fig. 35 Amniotic band syndrome at 23 gestational weeks. (a) Axial express turbo spin-echo T2-weighted images. (b) Axial T1-weighted image. (c, d) Sagittal express turbo spin-echo T2-weighted images. Fetal MR images reveal a superior occipital cephalocele (arrowheads, a, c) due to a large constricting amniotic band (arrows, a, c, d)](image-url)
<table>
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<tr>
<th>Syndrome</th>
<th>Cephalocele location</th>
<th>Transmission modality</th>
<th>Genes</th>
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<td>Autosomal recessive, X linked</td>
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<td>Sporadic</td>
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<td>DK phocomelia</td>
<td>Occipital</td>
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<td>Meckel–Gruber</td>
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<td>Autosomal recessive</td>
<td>MKS1, TMEM216, TMEM67, CEP290, RPGRIP1L, CC2D2A, NPHP3, TCTN2, B9D1 and B9D2, TMEM231, and CSPP1</td>
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<td>Joubert</td>
<td>Occipital</td>
<td>Autosomal recessive</td>
<td>To date 24 genes including INPP5E, ARL13B, CC2D2A, RPGRIP1L, TMEM67, NPHP1, AHI1, CEP290, CXORF5, and TMEM216</td>
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<td>Walker–Warburg</td>
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<td>Autosomal recessive</td>
<td>POMT1, POMT2, fukutin, and fukutin-related genes</td>
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<td>Knobloch</td>
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<td>COL18A1</td>
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<td>Autosomal dominant Dandy–Walker malformation and occipital cephaloceles (ADDWOC)</td>
<td>Occipital</td>
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<td>Cryptophthalmos</td>
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<td>GDF6, GDF3, MEOX1</td>
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<td>Fetal warfarin</td>
<td>Occipital</td>
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<td>Zechi-Ceide</td>
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<td>Sakoda complex</td>
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<td>Morning glory</td>
<td>Skull base</td>
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these pathways secondary to cilia defects results in neural tube defects both in mice and humans (Vogel et al. 2012; Lee and Gleeson 2011; Barker et al. 2014; Logan et al. 2011).

**Meckel–Gruber Syndrome**

Meckel–Gruber syndrome (OMIM #249000) is a rare lethal autosomal recessive condition affecting 1 in 13,250 to 1 in 140,000 people worldwide. It is more common in certain populations, such as Finnish (1 in 9,000 people) or Belgian (1 in 3,000 people) (Barisic et al. 2014). This condition is characterized by occipital cephalocele, postaxial polydactyly, and dysplastic cystic kidneys (Barisic et al. 2014; Barker et al. 2014). It can be associated with several other conditions, including fibrotic lesions of the liver. The pleiotropic phenotypes for MKS patients may result from the different genes, including MKS1, TMEM216, TMEM67, CEP290, RPGRIP1L, CC2D2A, NPHP3, TCTN2, B9D1 and B9D2, TMEM231, and CSPP1 (Barisic et al. 2014; Barker et al. 2014; Romani et al. 2014; Shaheen et al. 2014). It is estimated that this syndrome corresponds to 5 % of all neural tube defects (Barisic et al. 2014; Barker et al. 2014). Occipital cephaloceles are present in up to 90 % of cases. Other possible CNS abnormalities include microcephaly, holoprosencephaly, cerebral and cerebellar hypoplasia, hypoplasia of pituitary gland, and Dandy–Walker malformation. Eye anomalies (microphthalmos, cataract,
Fig. 37 Frontonasal dysplasia. (a, b) Three-dimensional CT scan, volumetric reconstructions with different windowing (soft tissue window, a; bone window, b). (c) Three-dimensional CT scan, coronal MPR image. (d) Axial and (e) sagittal T2-heavily weighted (DRIVE) images. 3D CT scan shows a large median labiopalatoschisis (arrow, c) and hypertelorism associated with occult cranium bifidum (arrowheads, b). MR images reveal hypoplasia of the left olfactory bulb (arrow, d) and an interhypothalamic adhesion (arrowhead, e).
Fig. 38  Chiari III malformation. (a) Sagittal T2-weighted image. (b) Sagittal T1-weighted image. (c) 3D TOF MRA. (d) Phase contrast MRA. (e, f) Axial T2 heavily weighted images. There is a low occipital encephalocystocele with herniation of posterior fossa contents and occipital lobes. The vermis is inferiorly displaced into the cervical canal (arrows, a, b). The intracranial arteries are markedly distorted (arrowhead, c) and some veins enter into the large cephalocele (arrowhead, d). There is a ventral cleft at the level of the pons (arrowhead, e). The herniated brain tissue is dysplastic and malformed (empty arrows, f)
coloboma), cleft lip and palate, and facial abnormalities (Potter-like face) can also be found (Tortori-Donati et al. 1996).

**Joubert Syndrome**

Joubert syndrome (OMIM #213300) is a clinically and genetically heterogeneous ciliopathy with an estimated prevalence of 1 in 100,000 patients and variable multiorgan involvement. To date, mutations in 24 genes have been found, including INPP5E, ARL13B, CC2D2A, RPGRIP1L, TMEM67, NPHP1, AHI1, CEP290, CXORF5, and TMEM216 (Romani et al. 2013, 2014; Shaheen et al. 2014). Occipital cephaloceles are found in 30% of patients with Joubert syndrome. Clinically, hyperpneic/apneic spells, ataxia, nystagmus, and psychomotor delay represent the classical tetrad. Additional clinical features include retinal degeneration, cystic kidney disease, ocular colobomas, hepatic fibrosis, polydactyly, oral hamartomas, and endocrine abnormalities. Radiologically, the “molar tooth” malformation is a typical feature. Dandy–Walker malformations may be evident in approximately 10% of cases (Poretti et al. 2011).

**Walker–Warburg Syndrome**

Walker–Warburg Syndrome is an autosomal recessive disorder showing characteristic brain and eye malformations (cobblestone complex, cerebellar and brainstem malformations, retinal abnormalities) in patients with congenital muscular dystrophy (Dobyns et al. 1989; Vajssar and Schachter 2006; Kim et al. 2004; Beltran-Valero de Bernabé et al. 2004; van Reeuwijk et al. 2005). Occipital cephaloceles occur in 24% of cases. The overall incidence is unknown but a survey in Northeastern Italy has reported an incidence rate of 1.2 per 100,000 live births (Vajssar and Schachter 2006). Several genes have been implicated in the etiology of this syndrome, including POMT1 and POMT2, fukutin, and fukutin-related genes (Kim et al. 2004; Beltran-Valero de Bernabé et al. 2004; van Reeuwijk et al. 2005).

Walker–Warburg syndrome is the most severe form of congenital muscular dystrophy with most children dying before the age of 3 years. Patients present at birth with generalized hypotonia, muscle weakness, developmental delay, and occasional seizures.

**Knobloch Syndrome**

Knobloch syndrome (OMIM #267750) is an autosomal recessive syndrome characterized by typical eye abnormalities, including high myopia, cataracts, dislocated lens, vitreoretinal degeneration, and retinal detachment, with occipital skull defects, which can range from occipital encephalocoele to occult cutis aplasia (Cohen and Lemire 1982; Knobloch and Layer 1971, 1972; Seaver et al. 1993). It is caused by homozygous or compound heterozygous mutation in the COL18A1 gene on chromosome 21q22.3 (Sertie et al. 2000; Caglayan et al. 2014). There is no correlation between the size or the severity of occipital abnormality and the site of the mutation in COL18A1. Moreover, the variability in the size of occipital skull defects is commonly observed in both intrafamilial and interfamilial cases (Caglayan et al. 2014). Associated brain malformations include cortical malformations such as polymicrogyria.

**Dandy–Walker Malformation**

The Dandy–Walker spectrum of disorders includes autosomal dominant Dandy–Walker malformation and occipital cephaloceles (ADWWOC) characterized by variable cerebellar hypoplasia, meningeal anomalies, and occipital skull defects (Carvalho et al. 2006; Jalali et al. 2008). Patients usually present macrocephaly at birth and have normal neurologic development in most cases. MRI shows hypoplasia and upward rotation of the cerebellar vermis associated with an atretic occipital cephalocele (Barkovich et al. 2009). Mutations in extracellular matrix genes NID1 and LAMC1 have been reported, confirming

**Dyssegmental Dwarfism**

Dyssegmental dwarfism (OMIM #224410), also called the Silverman–Handmaker type of dyssegmental dysplasia, is a lethal autosomal recessive form of neonatal short-limbed dwarfism, characterized by cleft palate and variable limited mobility at the elbow, wrist, hip, knee, and ankle joints (Handmaker et al. 1977). It is caused by homozygous or compound heterozygous functional null mutation of the gene encoding perlecan (HSPG2) on chromosome 1p36 (Arikawa-Hirasawa et al. 2001). In some cases, occipital encephalocele, inguinal hernia, hydronephrosis, hydrocephalus, and patent ductus arteriosus are found.

**Cryptophthalmos**

Cryptophthalmos is a condition that results in failure of eyelid formation. It is divided into three types: the complete, incomplete, and symblepharon variety. The complete variety is the most common; the eyelids do not form and the eyelid skin grows continuously from the forehead to the cheek to cover the underlying globe, which is usually abnormal. Cryptophthalmos is associated with several other congenital anomalies, including abnormal hairline, syndactyly, and an occipital cephalocele in 10% of cases (Tortori-Donati et al. 1996; Goldhammer and Smith 1975).

**Klippel–Feil Syndrome**

The Klippel–Feil deformity is a complex of osseous and visceral anomalies that includes low hairline, platybasia, fused cervical vertebrae with short neck, and deafness. The classical clinical triad consists of short neck, limitation of head and neck movements, and low-set posterior hairline. Bony malformations may entrap and damage the brain and spinal cord. The disorders of the lower vertebral region may become symptomatic in adolescence or adult life. The pathogenesis has been related to anomalous somitic segmentation between gestational weeks 4 and 8 (Tortori-Donati et al. 1996). Associated CNS abnormalities include occipital cephalocele, encephalocoele, Chiari I malformation, syringes, microcephaly, and hydrocephalus (Tortori-Donati et al. 1996; Fig. 39). Several associated abnormalities, such as scoliosis, Sprengel anomaly, posterior bony spin bifida, absence of ribs, conductive hearing loss, mirror movements, unilateral renal ectopia with dilated collecting system, microtia, and preaxial polydactyly, have also been reported. The pattern of bony fusion may involve more than one level, producing the “wasp waist sign” when two adjacent levels are involved (Nguyen and Tyrrel 1993; Cohen and Lemire 1982). Cervical spondylosis, disk herniation, and secondary degenerative changes are more common at levels adjacent to fused vertebrae (Ulmer et al. 1993; Chen 2008). Spontaneous and progressive neurological sequelae and neurological injury may follow minor neck trauma. Most of the cases are sporadic. Genetically, Klippel–Feil syndrome (KFS) has two subtypes with an autosomal dominant trait: KFS1 (OMIM #118100) is caused by mutations in the GDF6 gene (Tassabehji et al. 2008), while KFS3 (OMIM #613702) harbors mutations in the GDF3 gene (Ye et al. 2010). An autosomal recessive subtype, KFS2 (OMIM#214300), also exists, caused by mutation in the MEOX1 gene (Mohamed et al. 2013).

**Roberts Syndrome**

Roberts syndrome (OMIM # 268300) is a rare autosomal recessive disorder characterized by pre- and postnatal growth retardation, limb defects, and craniofacial anomalies. Affected individuals have variable malformations that involve symmetric reduction in the number of digits and length or presence of bones in the arms and legs. Craniofacial malformations include hypertelorism, hypoplastic nasal alae, and a high incidence of cleft lip and palate (Van Den Berg and Francke 1993). Cephaloceles occur occasionally in the
frontal region. The severity of malformations of the facies correlated with the severity of limb reduction. Familial and sporadic cases have been reported. Mutations in the ESCO2 (establishment of cohesion 1 homolog 2) gene located in 8p21.1 have been found in several families. ESCO2 is a member of the cohesion establishing complex and has a role in the effective cohesion between sister chromatids during S phase (Vega et al. 2005). Characteristic cytogenetic findings are “railroad track” appearance of chromatids and premature centromere separation in metaphase spreads.

**Goldenhar Syndrome**

The main features of this condition are unilateral underdevelopment of one ear associated with underdevelopment of the jaw and cheek on the ipsilateral side of the face (hemifacial microsomia), possibly associated with vertebral anomalies and an epibulbar dermoid. The muscles of the affected side of the face are underdeveloped and there often are skin tags or pits in front of the ear or in a line between the ear and the corner of the mouth. Often, there are abnormalities of the middle ear, and the ear canal may be completely absent. Unilateral deafness is extremely common. Cephaloceles (both anterior and posterior), plagiocephaly, and intracranial dermoids are occasionally associated (Tortori-Donati et al. 1996; Aleksic et al. 1983; Gustavson and Chen 1985).

**Amniotic Band Sequence**

Amniotic band sequence, also known as the constriction band syndrome, comprises a broad spectrum of congenital anomalies occurring in association with amniotic bands (Kasprian et al. 2014; Aleksic et al. 1983; Barros et al. 2014; Cignini et al. 2012; Fig. 35). Several pathogenetic theories have been formulated, including early amniotic rupture, vascular disruption sequence, and disruption of Ds gene...
(Robin et al. 2005; Purandare et al. 2009; Moerman et al. 1992). The prevalence of amniotic band sequence varies from 1 in 1,200 to 1 in 15,000 live births. Manifestations range from minor ring defects of digits or extremities to major craniofacial or visceral involvement and fetal death. Prenatal visualization of amniotic bands is difficult, and in some cases they are only noted at autopsy (Lee et al. 2011). Most of the craniofacial defects (encephaloceles and/or facial clefts) occurring in these fetuses are believed to result from a vascular disruption sequence, with or without cephalo-amniotic adhesion (Moerman et al. 1992).

**Fetal Warfarin Syndrome**

In utero exposure to warfarin, a vitamin K antagonist, between gestational weeks 6 and 9 produces a constellation of nasal hypoplasia, punctate epiphyses, optic atrophy, mental retardation, hydrocephalus, and occasionally occipital cephalocele (Tortori-Donati et al. 1996).

**Apert Syndrome**

Apert syndrome (OMIM #101200) is characterized by craniosynostosis, midface hypoplasia, and syndactyly and may be associated with hydrocephalus and nasofrontal cephalocele (Waterson et al. 1985; Wilkie et al. 1995; Cohen and Kreiborg 1994). Apert syndrome is caused by heterozygous mutation in the FGFR2 gene (176943) on chromosome 10q26 (Wilkie et al. 1995). Synostosis constantly involves the coronal sutures bilaterally, but more sutures may be obliterated up to the cloverleaf deformity.

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**Fig. 40** Sakoda complex. (a) Sagittal T1-weighted image. (b) Sagittal heavily T2-weighted (DRIVE) image. (c) Three-dimensional CT scan, sagittal MPR image. There is a sphenos-nasopharyngeal encephalocele associated with partial callosal agenesis (*empty arrows,* a). The third ventricle herniates through the sellar floor in the sphenoidal region (*asterisks,* a, b). The pituitary gland is flattened against the clivus (*arrowheads,* a). 3D CT scan shows a large bone defect between the ethmoid and the sphenoid bones (*empty arrow,* c)
Fig. 41  Morning glory syndrome. (a) Axial T2-weighted image. (b) Sagittal heavily T2-weighted (DRIVE) image. (c) Three-dimensional CT scan, sagittal MPR image. (d) Axial T2-weighted image. (e) Digital subtraction angiography. A small sphenononasopharyngeal encephalocystocele (asterisk, b) is associated with bilateral optic nerve funnel-shaped excavations in keeping with morning glory disc anomaly (arrowheads, a) and moyamoya disease (arrowheads, e). 3D CT scan demonstrates a sphenoid bone defect (empty arrow, c). Note the presence of multiple tiny flow voids in the basal ganglia consistent with moyamoya vessels (arrowheads, d)
Pseudoencephaloceles are also found in Apert syndrome in the frontal region when the metopic suture is not involved (Cohen and Kreiborg 1994).

**Zechi-Ceide Syndrome**
The Zechi-Ceide syndrome is characterized by occipital atretic cephalocele, unusual facies, and large feet (Zechi-Ceide et al. 2007). Additional CNS features are hypoplastic cerebellar vermis and the Dandy–Walker sign. Patients may present mental retardation, cleft lip or palate, narrow auditory canals, oligodontia, large wide feet with a gap between the first and second toes, hypoplastic nails, and short metatarsals and distal phalanges. An autosomal recessive inheritance is suspected for this disorder (Zechi-Ceide et al. 2007).

**Sakoda Complex**
The association of sphenoid meningoencephaloceles, agenesis of the corpus callosum, and median cleft lip and palate was described for the first time by Sakoda et al. in 1979 (Sakoda et al. 1979; Dempsey et al. 2007). The Sakoda complex may be further associated with optic dysplasia, including the morning glory optic anomaly or with bilateral anophthalmia and cortical dysgenesis (Ehara et al. 1998; Fig. 40).

**Morning Glory Syndrome**
The term morning glory syndrome was first coined in 1970 by Kindler, who noted the resemblance of the malformed papilla to the flower (Kindler 1970). Characteristic findings include enlargement of the optic disk opening, funnel-shaped excavation of the peripapillary fundus, chorioretinal pigment disturbance at the edge of the papilla, glial tissue overlying the center of the disk, and retinovascular anomalies. Spoke-like vessels radiate outward from the edge of the anomalous disk. The morning glory disc anomaly is most commonly unilateral, and females are affected twice as often as males. The abnormality has been associated with several other congenital malformations including midline craniofacial defects (Chen et al. 2004), other ocular anomalies, and intracranial vascular anomalies, including the moyamoya disease (Komiyama et al. 2000; Fig. 41).

**References**


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