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Sonographic Diagnosis of Schizencephaly

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Abstract

Schizencephaly is a congenital brain malformation in which clefts develop in the cerebral hemispheres. This aberration may be described as open lip (type I) or closed lip (type II) and may be further expressed as unilateral or bilateral. Using historical and current research, this article provides embryogenesis, pathogenesis, and possible etiologies of schizencephaly. Furthermore, the postnatal sonographic appearance is discussed, along with associated anomalies and possible outcomes for this exceedingly rare but disruptive brain malformation.

Keywords

schizencephaly, cerebral clefts, open-lip, closed-lip, polymicrogyria

Embryogenesis

Endeavoring to understand the elaborate embryogenesis of the brain can be overwhelming. However, it is essential for the sonographer to have a fundamental knowledge of embryogenesis to appreciate how even minimal departure from normal development can result in congenital brain malformations. In addition, because many brain malformations appear sonographically similar, familiarity with embryogenesis can guide the sonographer during a sonographic examination and can therefore beneficially affect patient care.

Brain development begins at approximately 14 days after fertilization. At this time, the neural plate is located along the dorsal aspect of the embryo. On day 21 postfertilization, the neural tube forms as the neural plate folds and fuses at its midpoint.[1] During the early weeks of embryonic life, the brain undergoes rapid differentiation, with the neural tube eventually forming the immature brain and spinal cord by 6 menstrual weeks. The brain subsequently begins to partition into the three primary vesicles: the prosencephalon (forebrain), the mesencephalon (midbrain), and rhombencephalon (hindbrain). These structures continue to expand and will form all major mechanisms of the brain. The prosencephalon develops into the cerebrum, thalamus, and lateral ventricles. The mesencephalon eventually becomes the midbrain and cerebral aqueduct, whereas the rhombencephalon becomes the cerebellum, fourth ventricle, and part of the brainstem.

The four main categories of congenital brain malformations, based on the time of occurrence, have been described as (1) disorders of dorsal induction; (2) disorders of ventral induction; (3) disorders of histogenesis, proliferation, and differentiation; and (4) disorders of neuronal migration.[1] The latter, neuronal migration, is the group of congenital brain malformations to which schizencephaly has often been classified.[1–4] However, it is important to note that Lopes and colleagues[5] not only place schizencephaly as a late neuronal migration disorder but also classify it as a disorder of cortical organization.

The progression of neuronal migration occurs until 25 gestational weeks, with the majority taking place between 8 and 16 weeks.[4] The origin of neuroblasts is within the germinal matrix along the periventricular region. The anomalous migration of neuroblasts, the predecessors for neurons, from the germinal matrix can produce an assortment of structural and dysfunctional brain disorders. Proper migration of neuroblasts from the periventricular region of the cortex to their predestined locations is obviously vital, as their position can affect the formation of gyri, sulci, and major commisures, or junctions, within the brain.

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Other neuronal migration defects include agenesis of the corpus callosum and lissencephaly.

Discussion

Schizencephaly is a structural abnormality of the brain characterized by congenital clefts within the cerebral mantle. The word part *schiz* (*schizo*) is of Greek origin, meaning "split" or "cleft." Therefore, schizencephaly strictly refers to the development of clefts within the brain. These clefts typically extend through the full thickness of the brain. That is to say, the cleft extends from the lateral ventricle to the subarachnoid space.

Schizencephaly clefts are further lined by gray matter. Unfortunately, the gray matter lining the cleft is abnormal and typically reveals evidence of polymicrogyria or pachygyria.[6] Gyri, plural for *gyrus*, are the ridges or folds of brain tissue. Polymicrogyria is characterized by an excessive number of small and prominent convolutions spaced out by shallow and enlarged sulci, giving the cortical surface a lumpy characteristic. Pachygyria describes the abnormal flattening of the gyri, subsequently resulting in a smooth surface.

Schizencephaly was first described over 60 years ago by Yakolev and Wadsworth. A neuropathologic analysis was performed on five autopsied patients who had exhibited severe mental and neurological deficits. Yakolev and Wadsworth found three distinctive features among these individuals: symmetric location of the clefts, extension to the ventricle, and cerebral clefts lined by gray matter.[7] These distinctive features led Yakolev and Wadsworth to define schizencephaly as a true congenital brain malformation rather than an acquired condition.

Schizencephaly can be further described by location and type (Table 1). It may be unilateral or bilateral and can occur in any hemispheric region, although the most common location is the area of the Sylvian fissures. The Sylvian fissures are located bilaterally within the cerebral cortex and are prominent landmarks that separate the frontal and temporal lobes of the brain. Unilateral clefts occur slightly more frequently than bilateral ones, with approximately 60% of cases diagnosed by magnetic resonance imaging (MRI) being unilateral.[7] Bilateral schizencephaly clefts are most often located symmetrically but may differ in size.[5]

Schizencephaly can be subsequently classified as closed lip (type I) or open lip (type II). When the cleft walls are in contact with each other, the schizencephaly is termed *closed lip*. *Open lip* is when the walls of the cleft are separated. Open-lip clefts are much more discernible with sonography, as they are filled with cerebrospinal fluid and can be noted extending from the lateral ventricle to the subarachnoid space. Closed-lip and open-lip clefts occur at an equal rate in unilateral cases, whereas open-lip clefts are more common in bilateral schizencephaly.[7] It is important to note that patients may have coexisting type I and type II schizencephaly.

Table 1. Summary of the Differnt Types of Schizencephaly

Type of Schizencephaly	Description	Definition	Location
Type I	Closed lip	Fused cleft(s)	Unilateral or bilateral
Type II	Open lip	Separated cleft(s)	Unilateral or bilateral

Pathogenesis

Researchers have not determined the precise pathogenesis of schizencephaly. The etiology may be the result of either genetic factors or acquired causes. Whether schizencephaly is an inherited disorder is not clear. Recent literature reveals that there may be a genetic mutation of the *EMX2* (empty spiracle 2) gene in some families with schizencephaly.[2,7,8] This association is currently being investigated. The theory originally hypothesized by Yakovlev and Wadsworth, that a failure of normal migration of primitive neuroblasts results in the development of cerebral cleft, appears to be an accepted rationalization of the origins of schizencephaly by some.[9,10] Granata et al.[7] noted that there is some support to the hypothesis that schizencephaly and polymicrogyria share common pathogenic pathways, both being the result of malformations stemming from impaired neuronal migration and cortical organization during late cortical ontogenesis. However, it is still disputed whether schizencephaly is a true developmental defect or possibly the result of lesions affecting an already developed brain.[2,7]

Another theory proposes that fetal exposure to certain viruses during crucial times of neural development may lead to schizencephaly. This theory was supported by data obtained through experimentation performed on animals. Researchers introduced the Kilham strain of the mumps virus during the time of fetal neuronal migration in hamsters. This exposure produced cerebral hemorrhage, cortical micro-sulci, and the formation of a cleft through the entire thickness of the cerebral mantle.[7] Also, fetal exposure to cytomegalovirus infections has been linked to the development of clefts within the brain.[2]

Studies have also been performed to establish that cleft development is associated with a vascular disturbance, such as an ischemic episode occurring during the seventh week of gestation.[9–11] In a number of cases, venous anomalies are present and associated with dysplastic gray matter, as

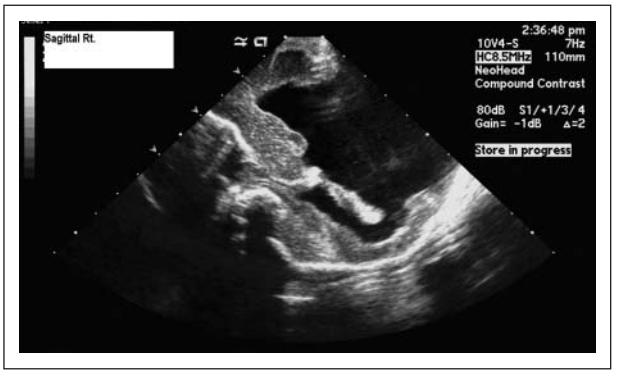

Figure 1. Sagittal sonogram of the neonatal brain image of schizencephaly.

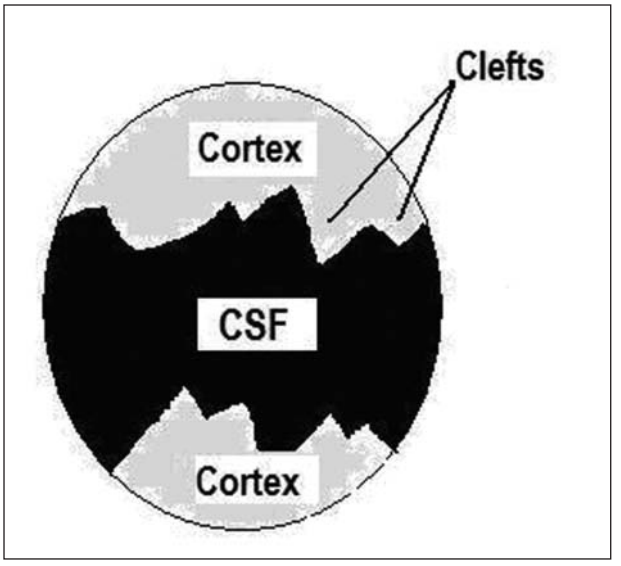

Figure 2. Diagram of schizencephaly identifying the cerebral cortex (Cortex), clefts (Clefts), and cerebrospinal fluid (CSF).

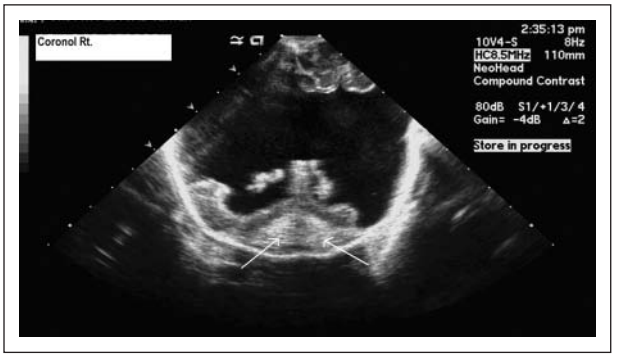

Figure 3. Coronal sonogram of the neonatal brain image of schizencephaly at the level of the cerebellum (arrows).

seen with schizencephaly.[3] Further tests have shown that the right middle cerebral artery demonstrated persistent occlusion. These findings suggest that a vascular lesion, such as occlusion of the middle cerebral artery, may result in the development of clefts within the brain tissue.[8]

Sonographic Appearance and Associated Anomalies

Sonography provides a noninvasive imaging instrument that can aid in the diagnosis of schizencephaly. Neurosonographic images are obtained through the fontanelles, most commonly the anterior fontanelle, in both sagittal and coronal scan planes. The postnatal sonographic appearance of schizencephaly has been well documented. The diagnosis of schizencephaly can be straightforward in some cases, although coexisting abnormalities add complexity.

The optimal sonographic scan plane for detection of clefts appears to be coronal, as dilation of the ventricular system noted in the sagittal scan plane may be merely confused with uncomplicated ventriculomegaly (Figure 1). Open-lip schizencephaly appears as anechoic, fluid-filled spaces in the brain (clefts) that are found most often in the area of the Sylvian fissures. The clefts extend from the lateral ventricle medially to the subarachnoid space laterally.[6] The edges of the clefts are typically echogenic due to the presence of cortical tissue and yield underlying hypoechoic gray matter (Figures 2–4).[1,6]

Multiple associated intracranial malformations can exist in the presence of schizencephaly, including ventriculomegaly, agenesis of the cavum septum pellucidum and corpus callosum, and optic nerve hypoplasia.[1,2] The cavum septum pellucidum is absent in between 50% and 90% of the cases, with the corpus callosum often small or absent as well.[3,9,12] The brainstem and cerebellum are usually spared.[6] Closed-lip schizencephaly may be difficult to identify with sonography and may require MRI or computed tomography (CT) for diagnosis. Cortical infolding, with secondary irregular thickening due to packing of microgyri, can be delineated better with MRI.[2,12]

Differential Diagnoses

The sonographic findings of schizencephaly may be similar to other intracranial abnormalities, including porencephaly, lobar holoprosencephaly, and intracranial cysts. It may be extremely difficult to distinguish schizencephaly from a large porencephalic cyst, especially one in the area of the Sylvian fissure. One vital different sonographic feature between schizencephaly and porencephaly is that porencephaly is typically unilateral, has an uneven edge, and may contain hemorrhagic components.[9] History of previous intracranial hemorrhage is a critical indicator for the manifestation of porencephaly. In lobar holoprosencephaly, the

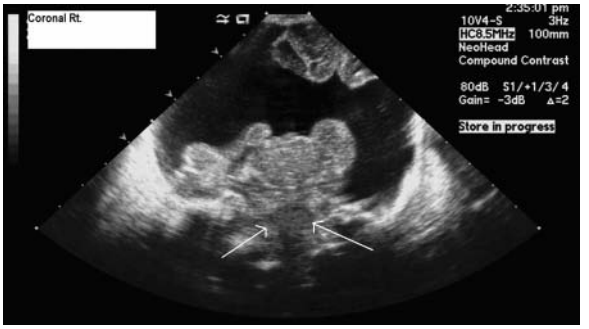

Figure 4. Coronal sonogram of the neonatal brain image of schizencephaly at the level of the brainstem (arrows).

cavum septum pellucidum is absent and the frontal horns are fused, similar to most cases of schizencephaly. However, the presence of cortical clefts differentiates schizencephaly from lobar holoprosencephaly. Intracranial cysts may occur in the area of the Sylvian fissure, but they will not communicate with the lateral ventricles.[9]

Prognosis and Treatment

The information and data concerning schizencephaly are particularly complicated. As mentioned earlier, the research has not yet established a concrete etiology. This may be secondary to the rarity of this disorder and the fact that many individuals with schizencephaly have other structural defects. The prognosis and final outcome is unpredictable for the patient diagnosed with schizencephaly. Bilateral open-lip schizencephaly tends to be more devastating functionally and is often associated with other devastating structural anomalies, whereas those with unilateral closed-lip schizencephaly have milder clinical expression, although they often suffer from seizures.[5,9]

Central to the clinical findings with schizencephaly is the manifestation of epilepsy and the presence of motor impairment.[7] Approximately 81% of all patients with schizencephaly develop epileptic seizures, with those suffering from bilateral malformations presenting earlier in life, typically before age 3 years.[5,11] Although it is certain that most schizencephaly patients suffer from epilepsy, several authors suggest that there is no correlation between epileptic severity and the extent of cortical involvement among the different types of schizencephaly.[5,7] In fact, one study noted that out of nine patients (six with unilateral schizencephaly and three with bilateral schizencephaly), the six who had unilateral schizencephaly suffered more seizures compared with the three with bilateral schizencephaly. Those affected by bilateral lesions had other brain malformations and therefore suffered more severe cognitive and motor deficits.[13]

Patients with bilateral open-lip schizencephaly typically have microcephaly and spastic quadriparesis.[11] They may also suffer from significant psychomotor developmental delays, mental retardation, cognitive impairment, and blindness.[2,5,12,13] Although epileptic seizures may not always correlate with cortical architectural divergence, cognitive and motor manifestations have been established to correlate with the extent of cortical involvement, an observation that may be confirmed by the presence of clefts in the frontoparietal lobes of the brain.[5,7] Some patients with unilateral closed-lip schizencephaly, although suffering from seizures, may actually have normal intelligence.[10,12] In some patients with unilateral involvement, the contralateral hemisphere can take over the function of the affected side.[2]

In summary, patients with unilateral closed-lip schizencephaly, although suffering from epilepsy, can display normal mental abilities, whereas those with bilateral or even unilateral open-lip schizencephaly not only tend to suffer from seizures but also are prone to additional functional and developmental challenges.[7,9] Early imaging detection of structural brain malformations associated with epilepsy, such as schizencephaly, is vital for the prognosis of the individual, as a distinct connection between imaging and clinical features has been established. Motor and cognitive deficits have been consistently correlated with not just the presence of an open-lip cleft but its size.[7]

Treatment for schizencephaly usually consists of physical therapy and the administration of antiepileptic medications. Seizures, when associated with bilateral disease, may not respond well to medications.[11] Many patients also have concomitant hydrocephalus and therefore require the placement of a ventriculperitoneal shunt. Termination of pregnancy can be offered if the diagnosis of schizencephaly is made before viability.[9]

Summary

Schizencephaly is a rare brain malformation that may be identified during a sonographic examination of the infant brain. To substantiate schizencephaly, the sonographer should demonstrate evidence of clefts, most likely in the area of the Sylvian fissures. These clefts will be noted in communication with the enlarged lateral ventricle medially and the subarachnoid space laterally. One should also anticipate various associated brain malformations with sonography in the presence of schizencephaly, such as an absent cavum septum pellucidum or agenesis of the corpus callosum.

Neonatal sonography provides an exceptional preliminary imaging modality for the identification of schizencephaly.

Its noninvasive technique offers minimal disruption to patient environment while at the same time contributing to the establishment of a concrete diagnosis. Sonographers should have a fundamental understanding of the sonographic appearance of congenital brain malformations such as schizencephaly, with the ultimate aim of providing optimal images to aid in the diagnosis of this potentially devastating abnormality.

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Article: Sonographic Diagnosis of Schizencephaly
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Category: Neurosonography (NE)
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Objectives: After studying the article titled "Sonographic Diagnosis of Schizencephaly," you will be able to:

1. Describe the embryogenesis of schizencephaly.
2. Discuss the sonographic characteristics of schizencephaly.
3. Compare the differential diagnosis.

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1. Which of the following is not a distinctive feature of the original description of schizencephaly?
   a. Localized to the Sylvian fissures
   b. Symmetric location of the clefts
   c. Extension into the ventricles
   d. Cerebral clefts lined by gray matter

2. Brain development begins at approximately how many days after fertilization?
   a. 7
   b. 14
   c. 21
   d. 28

3. The prosencephalon is also called which of the following?
   a. Forebrain
   b. Midbrain
   c. Hindbrain
   d. Brainstem

4. In which of the following categories of congenital brain malformations is schizencephaly classified?
   a. Dorsal induction
   b. Ventral induction
   c. Histogenesis
   d. Neuronal migration

5. Which of the following is not a pathogenesis associated with schizencephaly?
   a. Exposure to viruses
   b. Genetic factors
   c. Maternal diabetes
   d. Vascular disturbance

6. What is the optimal scan plane for detecting clefts?
   a. Caudal
   b. Sagittal
   c. Coronal
   d. Lateral

7. When does the majority of neuronal migration occur?
   a. 8 to 16 weeks
   b. 17 to 24 weeks
   c. 25 to 33 weeks
   d. 34 to 40 weeks

8. Which of the following is not associated with intracranial malformations that exist with schizencephaly?
   a. Ventriculomegaly
   b. Agenesis of the cavum septum pellucidum
   c. Abnormalities of the cerebellum
   d. Optic nerve hypoplasia

9. The cleft in schizencephaly occurs where?
   a. From the hindbrain to the midbrain
   b. From the brainstem to the cerebellum
   c. From the lateral to the subarachnoid space
   d. From the folds to the gray matter

10. Which of the following is described by the abnormal flattening of the gyri resulting in a smooth surface?
    a. Pachygyria
    b. Prosgyria
    c. Polymicrogyria
    d. Rhombengyria