

CLINICAL-IMAGING CORRELATION AND EARLY DIAGNOSIS IN BRAIN MALFORMATIONS

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Abstract

The malformations of the brain represent a serious pathology in the neonatal period, with major implications for subsequent psychomotor development of children. Thanks to the advanced technology, the diagnosis is established early, even in the prenatal period (fetal ultrasound, or even more recently fetal MRI or early neonatal MRI)-a very important thing for the introduction of the specific therapy and also the anticipation of the short-term and long-term prognosis. The authors are proposing a review of the most frequent brain malformations: encephalocele, myelomeningocele, Arnold-Chiari malformation, holoprocencephaly, the absence of cavum septum pellucidum, septo-optic dysplasia, proliferation and neuronal migration disorders, corpus callosum agenesis, Aicardi syndrome, pencephaly, median line defects, some vascular malformations. Also, the authors want to establish a correlation between the clinical, anamnestic and imaging data for the anticipation of short-term and long-term prognosis in every group that malformations have been identified. Conclusion: Brain malformations represent an important part of neonatal pathology, either due to the emergency situation with life-threatening prognosis or because of the high risk of sequelae which threatens social-integration.

Key words: Brain malformations, diagnostic, prognosis

Introduction

Due to increased morbidity and mortality in the neonatal period and also in infancy and toddlerhood, brain malformation represent a major concern. Short term and long term complication depend primary on the time and severity of the malformation but also on the stage of the cerebral maturity. Those that develop early, during intrauterin development, are usually severe types, with high degree of complexity.

In the pathogenesis of brain malformation, several factors are involved: genetic (chromosomal abnormalities, and genetic mutations), congenital infections (rubella, toxoplasmosis, CMV), radiations, chemical agents, drug consumption, vitamin deficiency or excess, nutritional deficiencies. Brain ischemia may intervene in various stages

of neurological development, leading to different types of brain malformations.

Neural tube defects

Anencephaly – severe damage which involves the absence of the cranial vault, meninges, scalp and cerebral hemisphere. Can be detected intrauterin from 12 weeks gestation. The prevalence is approximately 1 in 2000 births and the risk of recurrence is 4%.

Encephalocele - represent in the bag shaped herniation of the intracranial structures through the frontal or occipital (more frequent) cranial bones defect. Occipital encephalocels – depending on the size of the defect and the herniated structure may be accompanied by microcephaly, visual and auditory disorders. If a stenosis in the aqueduct of Sylvius or Dandy-Walker syndrome is associated, hydrocephaly may occur. Frontal Encephalocele – may have multiple locations (nasal, orbital) or may not be visible – with basal location (sphenoid, nasal cavities, deep in the orbital cavities) with a good prognosis.

Myelomeningocele – it's a neurotube defect which occurs after the closure of caudal neuropore. Often associated with hydrocephaly and Arnold-Chiari II malformation. The vertebral defect – most common in the lumbar and sacral region; it contains dura, leptomeninge and medullary structure. Clinical may associate from motor damage to paresis, absence of skin sensitivity, intestinal motility disorders.

Arnold-Chiari Malformation – consists in the cerebellum hypotrophy, the herniation of the cerebral vermis into the foramen magnum with the posterior displacement of the cerebellum and different degrees of cerebellar dysplasia. Three types of malformation are known, but the most common type is type II associated with myelomeningocele. Classic:

- Type I consist in inferior displacement of the cerebellar tonsils and inferior cerebellum. Without affecting the spinal cord and IV ventricle.
- Type II – inferior displacement (in the superior region of spinal canal) of the inferior cerebellum, tonsils, pons, spinal cord and IV ventricle. This type almost always is associated with myelomeningocele.

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- Type III – the displacement of the spinal cord, IV ventricle and cerebellum into a cerebral and occipital encephalomeningocele. The ultrasound signs are represented by: the inferior displacement of cerebellum, IV ventricle – hard to visualize; cisterna magna obstruction (1). Third ventricle appears dilated with increased intermediate mass. Lateral ventricles (LV) with dilated posterior horns. An anterior and inferior extension of the frontal horn is visualized, with a specific aspect of a “bat wing”* (fig.1a and fig.1b) (2).

Hydrocephaly in Arnold-Chiari malformation is caused by: cerebellum malformation, which leads to the obstruction of IV ventricles, blocking the leakage of cerebrospinal fluid in the posterior fossa; the stenosis of the aqueduct leads to hydrocephaly in 75% of cases (fig.3 and fig.4)

Ventral induction disorders

Holoprosencephaly is the complex and severe brain malformation characterized by the absence of cleavage of the prosencephalon into telencephalon and diencephalon (3). The ventral separation process occurs in the fifth week intrauterine (4). The frequency of the disease is 1 in 10000 living newborns (5, 6, 7) but the incidence is 60 times higher in the aborted embryos.

Depending on the differentiation and severity degree there are known three types of holoprosencephaly (De Mayer classification: alobar, semilobar and lobar). Literature cites different incomplete disease versions.

- Alobar holoprosencephaly (fig.4) – the most severe form characterized by the complete absence of septation, with a unique ventricle on the midline continued by a dorsal bag, fusiform thalamus and undifferentiated brain parenchyma. The cerebellum and the cerebral trunk are present and may have a normal aspect.

- Semilobar holoprosencephaly (fig.5) – consists of a unique ventricle with a fused thalamus. The interhemispheric cleft is present but partially developed, especially in the posterior region. Third ventricle is small or absent, fourth ventricle, cerebellum, cerebral trunk are usually normal. Sometimes a total or partial agenesis of the corpus callosum may be present.

- Lobar holoprosencephaly (fig.6a and 6b) – the least severe form, characterized by the absence of the septum pellucidum, which leads to the development to a unique squared frontal horn with flat roof and a rectangular corners. The bodies of the LV are midline joined but the posterior horns are separated, with normal aspect as well as the thalamus and the posterior interhemispheric groove. The anterior interhemispheric groove is present but shallow and incomplete developed.

Clinically, patients with holoprosencephaly, have facial malformations directly correlated with the severity and the cerebral lesions, from major defects of the midline like cyclopia, the absence of the nasal septum, dehiscence of facial bones, hypotelorism, to micrognathia, fissured palate. The mild form of disease clinically is accompanied by the facial bones hypoplasia and moderated forms of hypotelorism (14%). The least severe forms of disease are

accompanied by dental vicious eruptions and coloboma (36%). Long-term neurological prognosis is correlated with the type of brain malformation. All forms of disease associate muscular tone disorders and dismotility. (8,9,10) Neurological sequelae like mental retardation, epilepsy, spasticity, dystonia, chorioretinitis, as well as endocrine disorders, diabetes insipidus, may be present in a clinical variable intensity.

The absence of cavum septum pellucidum and septo-optic dysplasia

The absence of septum pellucidum is associated with many brain malformations including holoprosencephaly, septo-optic dysplasia, schizencephaly and corpus callosum agenesis (fig.7a and 7b). Severe hydrocephalus and holoprosencephaly are associated with destructive lesions of the septum pellucidum that can be diagnosed by the ultrasound in the early intrauterine period. (11)

Isolated absence of septum pellucidum with an intact corpus callosum is seen in septo optic dysplasia. This condition is characterized by a triad: the absence of septum pellucidum, optic nerve hypotrophy and pituitary gland dysfunction. Clinical is a severe disorder with decreased visual acuity, endocrine dysfunctions – cholestasis and mental retardation (11). Septo-optic dysplasia may be associated with other brain malformations: cortical dysfunctions, corpus callosum agenesis, schizencephaly. (fig. 8a and 8b)

Cell proliferation and neuronal migration disorders

Microcephaly is defined as decreased head circumference with 2 standard deviation (SD) compared to children of the same age and sex. Usually associated with microencephaly, which is followed by mental retardation. May be primary or secondary to some genetic disorders.

Megalencephaly consists in the diffused neuroepithelial proliferation and increase number of cells in the brain. The term is similar with macrocephaly in contrast to macrocephaly which refers only to the increased head circumference more than 2 SD for the same age and sex.

Can be primary, dominant autosomal form, with normal or minimally affected intelligence. Literature cites many genetic syndromes associated with megalencephaly: Sotos syndrome (cerebral gigantism), fragile X syndrome, autism, neurocutaneous syndrome. It also may be found in some metabolic diseases like: Tay-Sachs, Canavan, Alexander disease, which does not debut at birth.

Learning disorders, neuropsychomotor retardation and epilepsy are found in megalencephaly.

Hemimegalencephaly it's a rare brain malformation characterized by the unilateral enlargement of a part of the brain. Only a hemisphere or only the frontal lobes can be affected, with abnormal cells proliferation. Clinically, a non-responsive to treatment epilepsy can be found, hemiparesis, psychomotor retardation. (12) It can be associated with neurocutaneous diseases, hypomelanosis, neurofibromatosis.

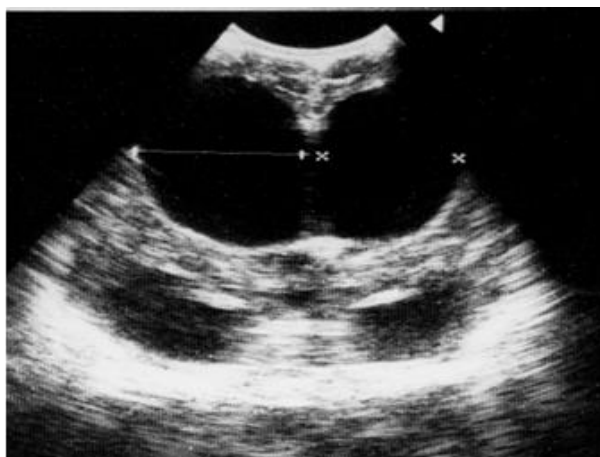


Fig. 1a Progressive hydrocephalus secondary to the myelomeningocele. LV dilatation

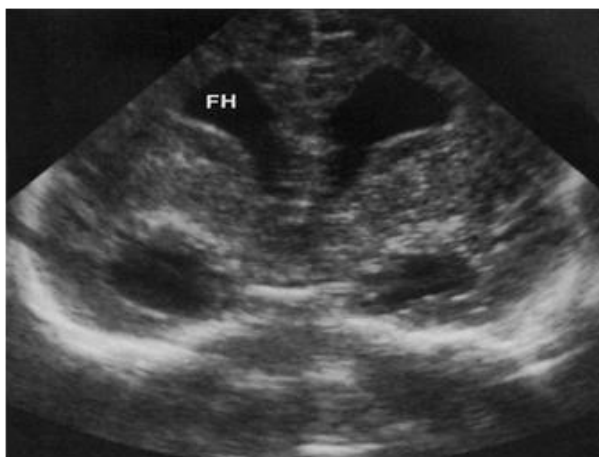


Fig. 1b Medium coronal section. Arnold Chiari type II malformation. Anterior horns dilatation of the LV, distant from the midline.

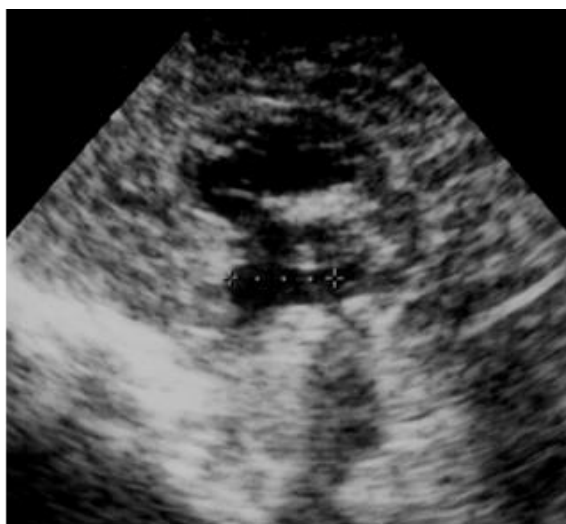


Fig. 2 Medium sagittal section. Third ventricle dilatated with intermedia mass present.

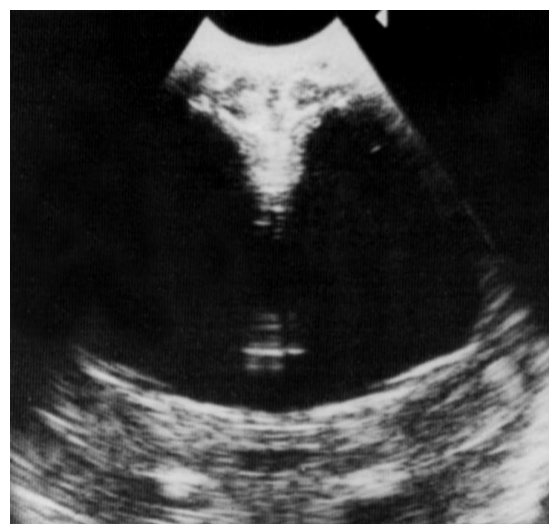


Fig. 3 Progressive severe hydrocephalus. Emphasized dilation of LV especially anterior

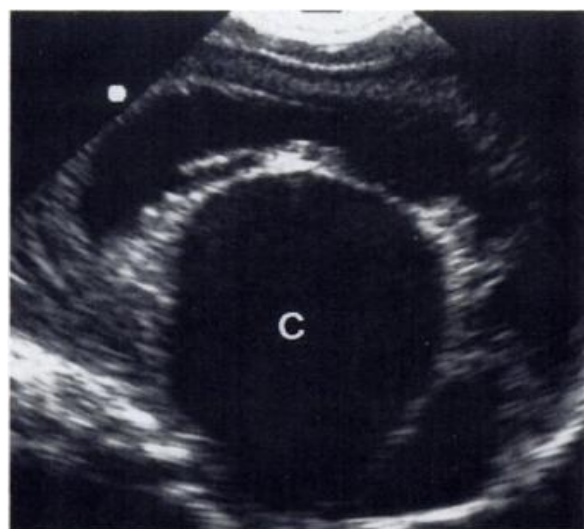


Fig. 4 Alobar holoprosencephaly

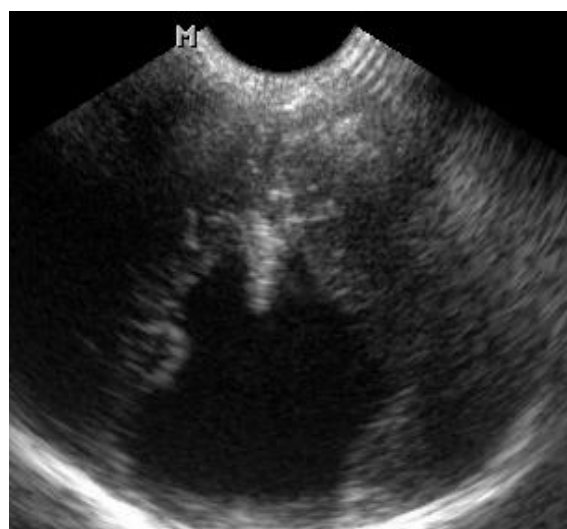


Fig. 5 Semilobar holoprosencephaly

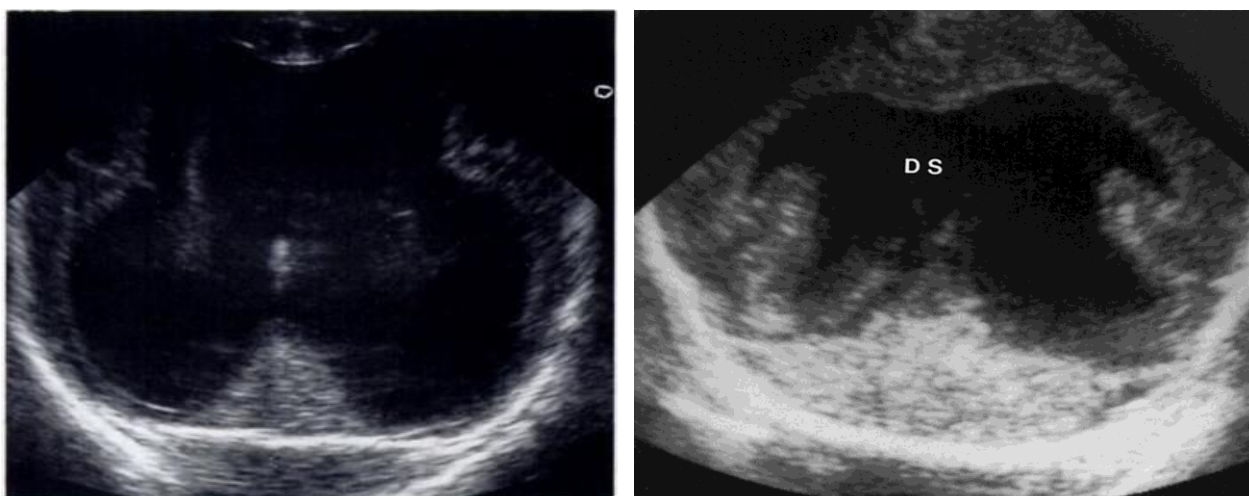


Fig. 6 a and 6b Lobar holoprosencephaly

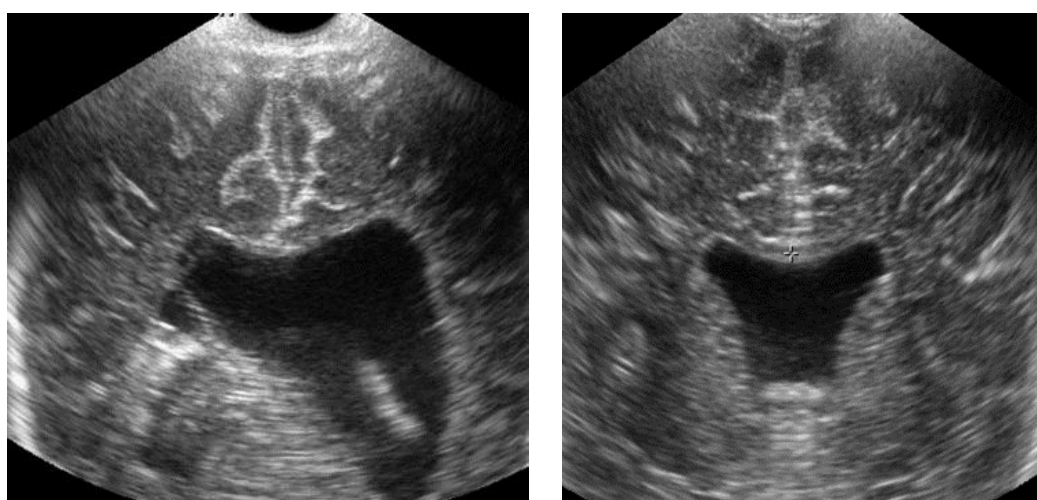


Fig.7a and 7b Absence of cavum septum pellucidum

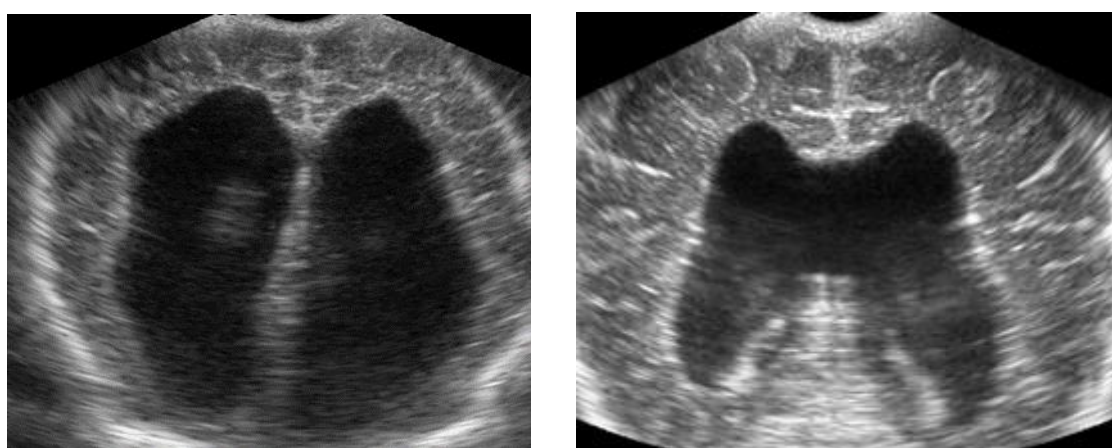


Fig.8a and 8b Septo optic dysplasia

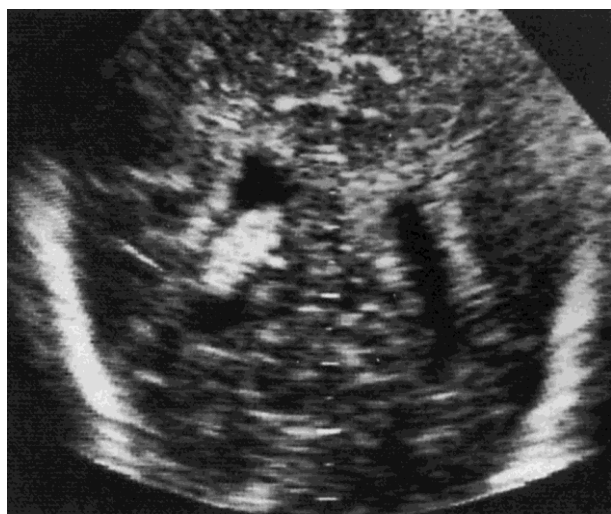


Fig. 9 Lissencephaly-widened Sylvian fissure and subarachnoid space

Neuronal migration disorders

Neuronal migration begins at 40-41 days of gestation until approximately six months of embryonic development, when the neuroblasts from the germinal matrix radially migrates into the cerebellum cortex, cerebellum and spinal cord. At the same time it also take place a tangential migration towards the interior of the cortex. Neuronal migration disorders cause the disorganization of the cortical structure, creating neuronal gaps which leads to the modification of the cerebral cytological architecture. The absence of the neurons in the periventricular areas lead to ventricular heterotopy.

Neuronal migration errors leads to the occurrence of several disorders: lissencephaly, schizencephaly, enterotopy and polymicrogyria. (13)

Lissencephaly and agyria/polygyria

Lisencephaly is defined as deficitary neuronal migration forming the cerebral cortex (fig.9), with few or no gyri ("smooth brain").

Polygyria is defined as a reduction in size of the gyri and grooves usually appears at the same time with lissencephaly. Clinically patients present growth disorders, microcephaly, major neurological retardation and severe form of epilepsy. There are three types of lissencephaly known:

- Type I: characterized by microcephaly and facial dysmorphism (14)
- Type II: characterized by hydrocephalus, retinal dysplasia and muscular dystrophy (12).
- Type III: characterized by microencephaly but without facial dysmorphism.

Gray matter heterotopia

Represents a local anomaly of neuronal migration disorders. The heterogeneous gray matter can be located anywhere along the neuronal migration ray.

Polimicrogyria is characterized by an abnormal thickening of the cortex with a larger number of gyri, fused

to the surface. Histologically is about a four layer cortex and a diagnosis can be established only by biopsy (15,16).

Schizencephaly is characterized by unilateral or bilateral septation of the cerebral hemispheres, with occurrence of irregular cracks of varying sizes that extend from the LV to the cerebral cortex. These cracks have thickened edges made of gray matter in the form of microgyria. The disorder occurs due to the faulty migration of the neuroblasts from the germinal matrix producing local cortical agenesis or hypoplasia. Clinically it can be found: microcephaly, motor retardation, seizures, hyper/hypotonia, epilepsy, developmental disorders. In the severe forms of disease that occurs in the neonatal period preceded by apnea, aspiration syndrome, halting growth (17). Ultrasound viewing reveals wide grooves, filled with liquid, communicating with lateral ventricles. The edges are hyperechoic, because of the thickened brain tissue. Anterior horn of the lateral ventricles are joined due to the absence of the septum pellucidum.

Tuberous sclerosis it's a dominant autosomal transmitted disorder which consists in the presence of tumoral formations in different organs, including the brain, skin, bones, kidneys. Brain tuberousities are formed by subependymal nodules, astrocytoma, giant cells astrocytoma and hematomas.

Affected children clinically describe early onset epilepsy and delayed neuropsychomotor development. The presence of hypopigmented patches and facial angiofibromatosis may lead to clinical suspicious diagnosis but accurate diagnosis is established by cerebral MRI and ultrasound. Subependymal tuberousities are visualized as small heterogeneous formations located in the walls of the LV, sometimes dilated.

In terms of ultrasound, the differential diagnosis is with neurofibromatosis type I, Sturges-Weber disease and neonatal cerebral tumors. (18) Sturges-Weber disease have early onset in the neonatal period and starts with facial hemangiomas. The cerebral abnormality occurs in the lobar region (frontal and occipital). In time, ipsilateral choroid plexus undergoes hypertrophy and around the LV the deep collateral venous branch develops. The necrosis of the adjacent cerebral parenchyma takes place and the intralobular calcifications arise even in the neonatal period. Inside the cortex and the subcortical white matter are found diffused hyperechoic formations hard to distinguish from tuberous nodules.

Complex brain disorders

Corpus callosum agenesis

Is a fibrous structure which connects the two cerebral hemispheres. The development takes place between 6-8 weeks of gestation until 18-20 weeks of gestation.(19) The corpus callosum agenesis can be caused by various factors: infections, congenital metabolic errors, genetic syndromes. In the specialty literature there are known 50 types of congenital syndromes which associate the corpus callosum agenesis (20) and it can be found in chromosomal abnormalities like trisomy 8, 18. The prevalence of the

disease is 0,1-0,7% and increases to 2,3% in patients with various disorders.

The agenesis can be partially, when only the posterior side is missing, and totally when the whole corpus callosum is absent. The ultrasound diagnosis is based on the absence of the corpus callosum and a marked separation of the anterior horns of the lateral ventricles which are pushed sideways by the powerful Probs fascicle (Fig 10 a and 10 b). Posterior horns are more dilated and lead to colpocephaly. This occurs because of the absence of a great number of fibers from the posterior commissure. Other ultrasound signs are: the anterior displacement of the third ventricle between the two lateral ventricles creating a cystic formation, the distortion of the cerebral gyri and grooves with a radial orientation from the bodies of the lateral ventricles. (21, 22)

Aicardi syndrome

Is a malformative complex syndrome defined by the triad: total or partially corpus callosum agenesis, lacunar chorioretinitis and infantile spasms. Other associated signs are: coloboma, polymicrogyria, periventricular heterotopy, choroid plexus cyst, intracranial cysts and brain tumors. The diagnosis is possible through MRI when it's associated with major ocular and brain malformations.

Cystic brain lesions

Hidranencephaly

Is considered to be a severe disorder characterized by the flattening to absence the cerebral hemispheres and replacing them with a bag with thin, membraneous walls filled with cerebrospinal fluid (fig. 11). The external layer of the bag is formed by leptomeninges, and the internal layer is formed by the rest of the cerebral cortex and the white matter. The structure of the median brain and cerebellum are usually intact, and the cerebral trunk can be atrophic. (23)

Hidranencephaly is produced by an intrauterine destruction, when, under the action of the pathogenic factors (ischemia, haemorrhage, infections, vasculopathy) occurs a liquefactive necrosis (20-27 weeks of gestation).

Porencephaly

Consists in the presence of a congenital or inherited focal cavity in the cerebral parenchyma which communicates with the subarachnoid space (external porencephaly) or with the lateral ventricles (internal porencephaly) or the midline (central porencephaly). Porencephalic cyst appears like a small cavity with walls full of liquid, without interior septa. In the specialty literature are present more types of classification: embryonic porencephaly or schizencephaly, early fetal porencephaly (fig.12) and perinatal porencephaly (fig.13a and 13b).

Midline brain malformations

Dandy Walker Malformation

The classic form of disease is characterized by: cerebral vermis complete or incomplete agenesis, cystic dilation of the posterior fossa which communicates with the fourth ventricle and tentorium abnormalities with the enlargement of the posterior fossa.

Posterior brain fundamental anomaly is related to improper forming of the cerebellar vermis and the roof of the fourth ventricle. The starting point can be partially or totally obstruction of the Magendie orifice, which leads to the accumulation of CSF and the dilation of the fourth ventricle. Despite the further opening of the Luschka orifice (usually opened in Dandy Walker malformation), the cystic dilation of the fourth ventricle persists and a deterioration of the leakage of CSF (24). Clinically, infants present hydrocephalus with occipital prominence growth and the emphasized dilation of the fourth ventricle and the enlargement of the posterior fossa. The ultrasound signs of the disease are better visualized in the sagittal sections (20) and are represented by: large homogeneous cyst of the posterior fossa, full of liquid, which actually is the dilated fourth ventricle extending posteriorly; partially or complete absence of the vermis; cerebral hemispheres hypoplasia; abnormally high tentorium (fig.14 and 15)

Dandy Walker version

Consists in moderate hypoplasia of the cerebellar vermis, less developed tentorium and posterior fossa dilation. Neurological impairment of the infants is less intense than the malformation but it also depends by the associated lesions (25). Sometimes marked enlargement of the cisterna magna can be found and in the absence of a cerebral abnormalities the prognosis is good.

Joubert syndrome

Is a complex recessive autosomal disorder, characterized by: cerebellar vermis hypoplasia, thickening and widening of the cerebellar peduncles and the deepening of the interpeduncular fossa. Clinically, the newborn presents marked hypotonia and apnea or tachypnea (26). Psychomotor retardation, ataxia, nystagmus, ocular motor apraxia.

Conclusions

1. Positive diagnosis is relatively easy since the antenatal period using ultrasound, but a certain diagnosis is established by brain MRI.
2. Cranio-cerebral dysraphism although shows a good short-term prognosis immediately after rapid therapeutic intervention, have a high degree of long term sequelae, especially those associated with Arnold Chiari type II malformation.
3. Cell proliferation and neuronal migration disorders are severe due to early damage, neuropathogenic associations, which in the end lead to complex clinical syndromes resistant to treatment, with unfavorable outcome.
4. In ventral induction disorders long term neurological prognosis is correlated with the type of disease, neurological signs are present from the neonatal period and the evolution in the severe forms of disease is unfavorable, leading to death.
5. Generally, brain malformations, represents an important part of the neonatal pathology either due to the vital risk or because of the high risk of sequelae, threatening the social integration.

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