The Egyptian Journal of Hospital Medicine (July 2019) Vol. 76 (5), Page 4077-4084

Prenatal Diagnostics for Neurosurgical Pathologies

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ABSTRACT

Background: The advance in the prenatal diagnostics, particularly in imaging tools during the pregnancy (ultrasound and magnetic resonance) allowed the early diagnose of many fetal diseases, including the neurological conditions. This progress brought the neurosurgeons the possibility to propose treatments even before birth.

Objective: The aim is to study the role and effect of prenatal diagnostics for neurosurgical pathologies as regard to early detection and management.

Conclusion: Further progress is necessary to enable fetal neurosurgery in becoming the main technique used in treating fetal neurosurgical diseases. However, we believe that correct prenatal diagnosis and adequate selection of fetuses with myelomeningocele, hydrocephalus, and occipital encephalocele may contribute to the benefits provided by neurosurgical procedures during the fetal period.

Keywords: Prenatal Diagnostics, Neurosurgical Pathologies

INTRODUCTION

The advance in the prenatal diagnostics, particularly in imaging tools during the pregnancy (ultrasound and magnetic resonance) allowed the early diagnose of many fetal diseases, including the neurological conditions. This progress brought the neurosurgeons the possibility to propose treatments even before birth [(1)].

The neurosurgeon can be called on to interpret the meaning of diagnostic studies and must be ready to meet this emerging challenge and benefit from knowledge about which anomalies may require pre- or postnatal intervention, where the birth should take place**I.** and how the baby should be born [(2)].

The prenatal neurosurgical consultation serves three primary purposes. First, it enables prospective parents to learn from a physician knowledgeable about the care and prognosis of infants with a particular condition. Second, it enables the prospective parents and the neurosurgeon to get a head start forging a therapeutic alliance. Finally, prospective parents can participate in decisions about specific interventions such as fetal surgery, the timing and route of delivery, and any surgery that may be required soon after birth [(3)].

Aims of ultrasonography include determination of gestational age and fetal number, evaluation for malformations, testing of fetal well-being, and assistance with invasive diagnostic and therapeutic procedures [(4)].

Amniocentesis, the first available prenatal chromosomal diagnostic testing option, was first described in the 1950s [(1)]. Amniocentesis became increasingly safe and is now used for several purposes, including genetic screening and infectious evaluations. Chorionic villus sampling (CVS) is another diagnostic test and can be performed earlier in gestation[(5)].

Myelomeningocele is the most recognized disease that can be treated during pregnancy with a high rate of success. Additionally, this field can be extended to other conditions such as hydrocephalus and encephaloceles. However, each one of these diseases has nuances in the diagnostic evaluation that should fit the requirements to perform the fetal procedure and overbalance the benefits to the patients [(6)].

AIM OF THE WORK

The aim is to study the role and effect of prenatal diagnostics for neurosurgical pathologies as regard to early detection and management.

Diagnostic Tools

Different types of tests are available during pregnancy, but they can be classified into two main categories [(7)].

A **screening test** shows if a pregnancy is at 'increased risk' of a birth defect. Different screening tests are available in the first or the second trimester of pregnancy. These results indicate the risk that a baby may have a syndrome. A screening test does not give a definite answer, but it does tell us which babies have an increased risk of having a pathology. The results may then help you decide if you want to have a diagnostic test [(8)].

A **diagnostic test** can identify a condition, and is very accurate. Diagnostic **invasive** tests (e.g. chorionic villus sampling and amniocentesis) however, increase the risk of miscarriage. This is why diagnostic tests are not routinely offered to all women. Instead, tests are offered in two stages. All women should be offered a screening test which carries no risk of miscarriage or harm to the baby [(8)].

Ultrasonography:

Ultrasonography is the method most commonly used for fetal imaging because it allows real-time examination of the fetus and avoids radiation exposure. Ultrasonography is exquisitely sensitive to the interfaces between solid tissue and water;

Received:3/5/2019
Accepted:2/6/2019

therefore, the size and shape of the fetal ventricular system are easily seen [9].

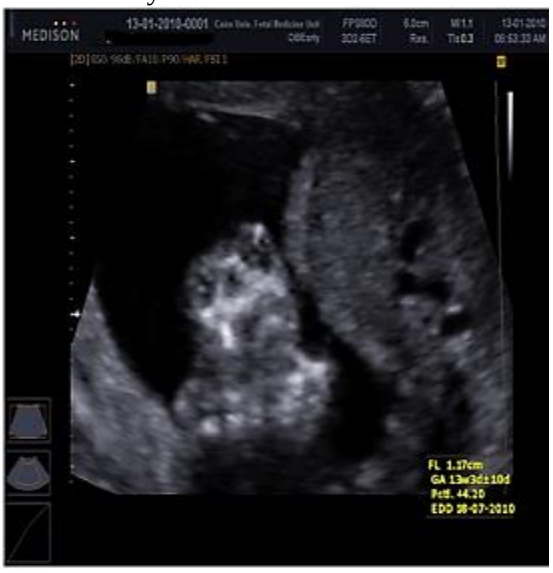

Figure (1): 13 weeks fetus with anencephaly [9].

Magnetic Resonance Imaging

A valuable complement to prenatal sonography, fetal MR imaging is a powerful technique used to evaluate the fetal brain. Fetal MR imaging has higher contrast resolution than prenatal sonography and allows better differentiation of normal from abnormal tissue. Structural abnormalities such as cerebral malformations and destructive lesions can be sonographically occult on prenatal sonography yet detectable by fetal MR imaging [10].

Diagnostic fetal specimen or tissue

Chorionic villus sampling (CVS) has decreased in frequency with the recent increased uptake of cell-free DNA screening. It remains the only diagnostic test available in the first trimester and allows for diagnostic analyses, including fluorescence in situ hybridization (FISH), karyotype, microarray, molecular testing, and gene sequencing. CVS is performed between 10 and 14 weeks' gestation. CVS has been performed before 9 weeks in the past, though this has shown to increase the risk of limb deformities and, therefore, is no longer recommended. It may be performed via either transcervical or transabdominal approach. Via either approach, chorionic villi are collected for genetic evaluation under ultrasound guidance without entering the amniotic sac [6].

CVS allows for earlier prenatal diagnosis, subsequently decreasing time of uncertainty and allowing for earlier (and, therefore, safer) pregnancy termination if desired. A disadvantage of CVS, however, is that approximately 1% to 2% of CVS results may reflect confined placental mosaicism rather than true fetal chromosomal abnormalities. Confined placental mosaicism may increase the risk of having a small-for-gestational-age infant. Pregnancy loss attributed to CVS is approximately 1 in 455 on the most recent estimates [7].

II. Fetal CNS Developmental Anatomy

Brain and spinal cord development begins with neurulation, which is the process of neural tube formation that occurs in the third and fourth weeks of gestation. In the fifth and sixth weeks, prosencephalic development occurs, giving shape to the developing brain**.** Cortical development is divided into stages of cell proliferation, neuronal migration, and postmigrational cortical organization. Myelination and cortical organization are the final steps of brain development and continue well beyond birth [11].

Embryology of Central Nervous system

The central nervous system (CNS) consists of the brain and spinal cord, which develop from the neural tube. The peripheral nervous system (PNS) contains cranial and spinal nerves that consist of neurons that give rise to axons, which grow out of the neural tube, and neurons derived from neural crest cells. Skeletal motor neurons and axons of preganglionic autonomic neurons are derived from the neural tube.Neural crest cells form sensory neurons and postganglionic autonomic neurons. The neuronal cell bodies of these neurons are found in ganglia. Therefore, all ganglia found in the PNS contain either sensory or postganglionic autonomic neurons and are derived from neural crest cells. Chromaffin cells are neural crest cells, which migrate into the adrenal medulla to form postganglionic sympathetic neurons. Neurulation begins in the third week; both CNS and PNS derived from neuroectoderm. The notochord induces the overlying ectoderm to form the neural plate (neuroectoderm). By end of the third week, neural folds grow over midline and fuse to form neural tube [12].

Sonographic Anatomy

The early embryo is best examined transvaginally. The cephalic end is identiiable by about 8 weeks. By 10 or 11 weeks, bones of the vault show mineralization [13].

At this age, the brain mantle is very thin. The ventricles are large and illed with choroid, which provides nourishment for the developing brain. A large, echo-free space behind the hindbrain represents the rhombecephalic cavity**,** which decreases in size as the cerebellum forms and is destined to become the fourth ventricle [14].

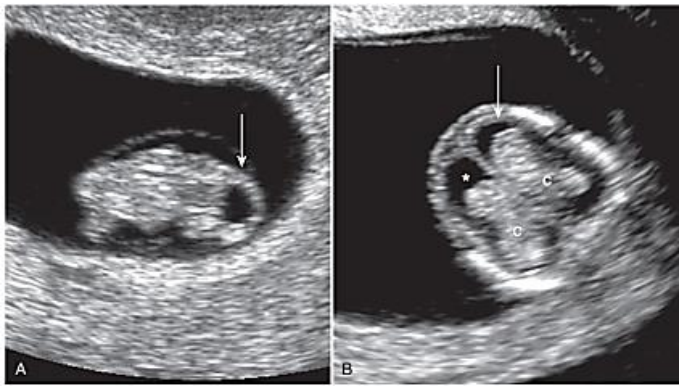

Figure (2): Early normal fetal head images obtained with transvaginal probe. **(A)** At 8 menstrual weeks **(B)** Scan at 12 weeks[14].

III.

Normal Fetal MR Imaging

MR imaging of the fetal cerebrum is characterized initially by the presence of multiple layers that disappear as the brain matures and the sulci form [15].

Knowledge of the timing and appearance of these layers and sulci are very important in the proper interpretation of fetal brain MR imaging studies[15].

The ventricular zone, or germinal matrix, is the innermost layer of the fetal cerebral hemisphere; it forms a smooth, dark band of low T2 and high T1 signal intensity lining the lateral ventricles from early gestation [15].

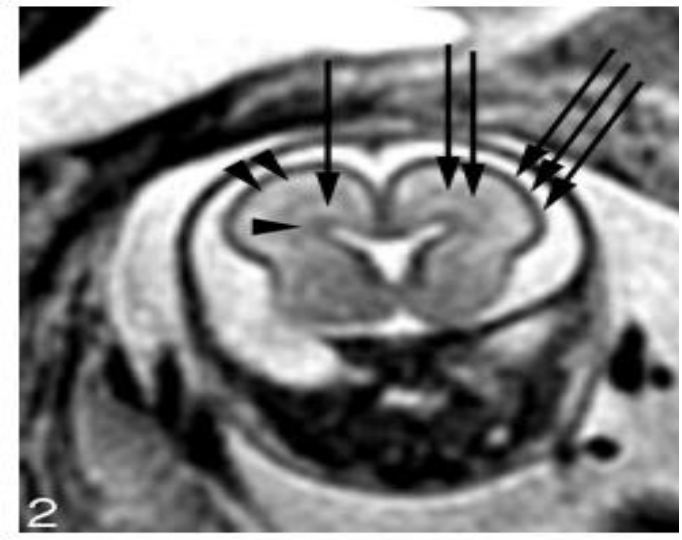

Figure (3): Coronal SS-FSE T2-weighted image at gestational week 23. Germinal matrix (arrowhead) periventricular zone (arrow). Subventricular and intermediate zones (double arrows). Subplate (double arrowheads). Germinal matrix (triple arrows) [15].

The size of the lateral ventricles is best assessed by sonographic measurements of the atria, because both the technique of measurement and the normative values are well established. In particular, the measurement must be made through the posterior aspect of the glomus of the choroid plexus on an axial plane obtained through the thalami, which is easy to obtain with sonography [10].

Fetal MR imaging can be helpful in assessing the shape of the entire ventricular system, and in assessing the walls of the lateral ventricles, which should be smooth throughout gestation. It should also be noted that fetal subarachnoid spaces are prominent, particularly before gestational week 30, relative to a term neonate [10].

Hydrocephalus

Fetal hydrocephalus continues to present a challenge, not only for neurosurgeons but also for obstetricians and the entire community involved in the medical, religious, ethical, and legal aspects related to this condition [16].

In the early twentieth century, fetal hydrocephalus was a cause of maternal mortality due to uterine rupture. Currently, however, with the use of diagnostic tools such as ultrasonography and magnetic resonance imaging (MRI), a pregnant woman has the option to terminate her pregnancy, especially in countries where abortion is legal [1].

Epidemiology

The real incidence of fetal hydrocephalus is probably underestimated because many cases of fetal death early in gestation are often not studied. In fact, it is not even known how often abortions are performed among mothers of hydrocephalic fetuses. It is believed that the incidence rate of such cases varies between 0.2 and 1.5 per 1000 live births. The incidence varies significantly according to different authors and locations [17].

Diagnostic

Obstetric ultrasonography as part of routine prenatal monitoring is the standard method for diagnosing intrauterine ventriculomegaly. Fetal ventriculomegaly or hydrocephalus are complex definitions and are often difficult to differentiate and accurately identify [18].

Advances in ultrasonography caused a revolution in the practice of obstetrics. Especially when used after the 15th week of pregnancy, ultrasound allowed the easy diagnosis of numerous malformations [19].

Clinically, most cases of fetal hydrocephalus are accompanied by polyhydramnios, a fact that may lead the obstetrician into a false diagnosis and suspicion of an error in the gestational age. An ultrasonographic image is then requested for clarification and the hydrocephalus is finally diagnosed [20].

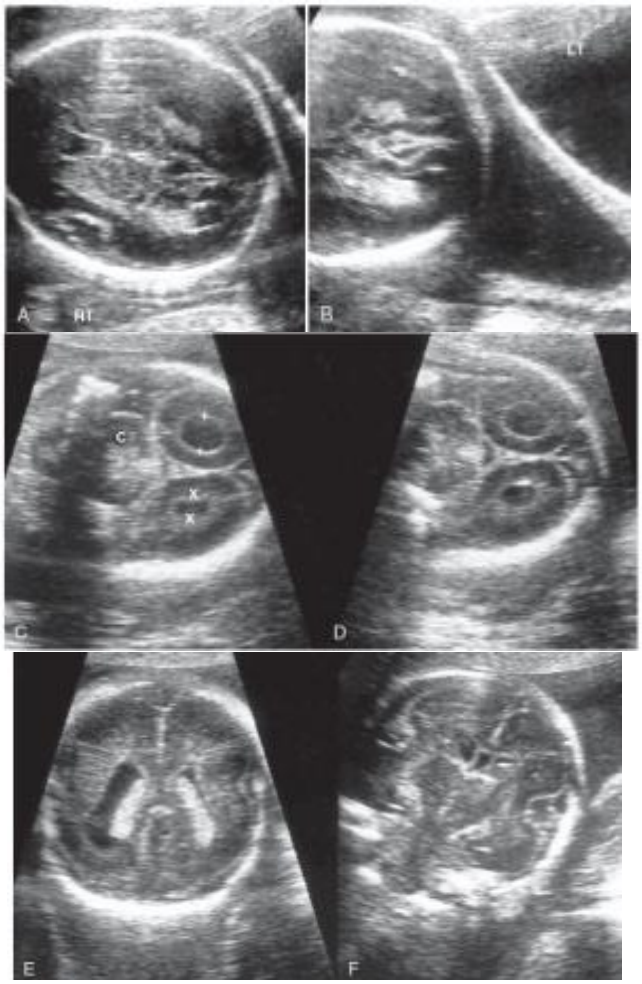

Figure (4): Assessment of ventricles at 23 weeks shows normal, mild asymmetry.

(A) Axial view shows the usually measured lower ventricle (calipers).
(B) By viewing through the posterior squamosal suture, one can visualize the upper ventricle in the oblique axial plane (calipers). Oblique image planes can increase the ventricular measurement; thus it is important to obtain a true axial view that shows both ventricles for measurement if the upper ventricle appears enlarged.
(C) and **(D)** Coronal "owl's eye" view through the lambdoid suture shows asymmetry of the occipital horns (calipers). Mild asymmetry less than 2 to 3 mm is common and normal. c, Cerebellum.
(E) and **(F)** Views taken through the anterior fontanelle analogous to neonatal head ultrasound are an alternate approach to assessing both ventricles. **(E)** shows the occipital horns and **(F)** shows the anterior horns and conirms slight ventricular asymmetry [(20)].

Etiology and Classification

Congenital hydrocephalus is one of the most common congenital anomalies affecting the central nervous system and results from an imbalance of CSF formation and absorption [(17)]**.** This imbalance results in the accumulation of CSF, increased ICP, and dilation of the ventricles [(20)]**.**

In fetal ventricular dilatation, it is very important to differentiate between ventriculomegaly and hydrocephalus. Ventriculomegaly may be the result of atrophy or hypoplasia of the central nervous system or malformation associated with agenesis of the corpus callosum, while in hydrocephalus the ventriculomegaly is hypertensive[(20)].

Technical notes

In order for the intrauterine treatment of hydrocephalus to be successful, the cases should be isolated, progressive, without chromosomal abnormalities and a gestational age less than 30 weeks, with a diagnosis of severe, isolated, acute, progressive, or obstructive hydrocephalus[(12)]**.**

Repeated cephalocentesis was performed under ultrasound guidance with the mother under opioid sedation. The volume of liquor removed varied from 20 to 120 ml. The fetal heart beat was monitored throughout the procedure, and removal of liquor discontinued as soon as any deceleration occurred in the fetal heart rate [(1)]**.**

Cephalocentesis was performed as necessary until pulmonary maturity. Corticosteroid administration to the mother is recommended before the first cephalo- centesis in order to accelerate fetal lung maturity. On average, 4–8 procedures were performed per fetus, with intervals of 4–5 days in between. The indications were mainly for cases of hydrocephalus with hemorrhagic liquor or cerebrospinal fluid with high protein rates, especially when close to fetal lung maturity [(21)]**.**

Ventriculoamniotic shunting was performed percutaneously under ultrasound guidance, and a pigtail catheter (KCH-Rocket Medical PLC, New England) was inserted. One tip of the catheter was left in the fetal lateral ventricle and the other in the amniotic cavity[(21)].

Figure (5): Scheme of ventriculoamniotic shunt placement. (**a**) Ultrasound-guided transabdominal puncture reaching the occipital horn of the lateral ventricle. (**b**) Catheter insertion and intraventricular portion released after partial removal of the trocar. (**c**) Complete removal of the trocar to release the catheter in the amniotic cavity and decrease hydrocephaly. (**d**) Double pigtail catheter. (**e**) Patient at birth exposing the ventriculoamniotic shunt used during the uterine life to treat a fetal hydrocephalus, in detail can be seen that the catheter was still working. **(f)** Example of a fetal hydrocephalus due to aquecdutal stenosis treated by ventriculoaminiotic shunt. The pre and post MRIs show the reduction of the ventricular cavities after procedure[21].

Third ventriculostomy was performed under fetal anesthesia. Always under ultrasound guidance, the umbilical cord was punctured with a thin needle, the umbilical vein catheterized, and a total dose of 5 μg/kg of fentanyl citrate and 0.1 mg/kg pancuronium bromide was administered**.** Five minutes after fetal anesthesia, a small incision was made in the mother's abdominal skin with an 11-blade scalpel. Again, under ultrasound guidance, the fetal skull was punctured with a 2.5-mm-diameter needle on the brim of the bregmatic fontanelle, providing access to the lateral ventricle. As soon as the mandrel was withdrawn, liquor exited under increased pressure. A 2.3-mm-diameter neuroendoscope (Neuroview, flexible scope, 25C, Traatek, USA) was inserted through the needle, as well as a 1 mm working channel connected to a 300 W xenon lighting system**.** Monro's foramen could be identified and the endoscope was inserted into the third ventricle, its floor was opened, and the fetal basilar artery could be visualized. The opening was sufficiently enlarged with a 2-Fr Fogarty catheter, and the endoscope was withdrawn along with the needle. A small occlusive dressing was applied to the mother's abdomen[21]**.**

IV. Neural Tube Defect

Open neural tube defects (ONTDs) are the most frequent malformations of the central nervous system (CNS). Myelomeningocele (MM) is the most severe open neural tube defect that is compatible with life. This closure disorder occurs in the third week of gestation, and biochemical, genetic, and environmental phenomena are involved in its genesis [22]**.**

Comparison of fetal and postnatal surgeries

Some of these changes can be explained during the fetal surgical procedures but cannot be verified in postnatal surgical procedures. These changes include the Bdry brain^ that is verified by the lemon sonographic sign and features intracranial hypotension. Another alteration is the presence of a fibrous ligament in the apex of the placode adhered to the dura mater in the apical portion of the malformation that results in a tethered

cord and pulls the brainstem and cerebellum down and into the rachidian canal resulting in a microcephaly, a small posterior fossa, and poor development of the subarachnoid space of the posterior fossa. With the development of a pregnancy that is associated with intracranial hypotension, the occipital bone, which consists of 8 segments, fuses rapidly, making the posterior fossa inelastic, similar to that in craniosynostosis. In addition, the cerebral aqueduct becomes patent, there is no Chiari type II, and the CSF is circulating; however, globally, there is an accumulation of CSF in the subarachnoid space. This leads to an increase in the head circumference without signs of intracranial hypertension and normal neuropsychomotor development [(23)].

V. Other Fetal Neurosurgical Pathologies

Encephalocele is a congenital neural tube defect characterized by a median cranial bone cleft defect that results in protrusion of the meninges (meningocele) or of the meninges and neural tissue (encephalocele) [(1)].

Encephalocele

It has an estimated prevalence of 0.8–2.0 per 10,000 live births [48–50]. One third of patients die from this condition, with 76% of deaths occurring in the first day of life. Half of the patients who live beyond the first day will experience some degree of neurodevelopmental delay. The strongest risk factors for death are hydrocephalus and microcephaly [(1)].

Tethered spinal cord

Tethered spinal cord syndrome is a clinical entity in which spinal cord function is compromised by inappropriate attachment of and traction upon the cord, which appears to be associated with compromised tissue perfusion. Tethering of the cord is associated with a variety of etiologies, including scar formation from prior surgery (such as myelomeningocele repair) or an anomaly of secondary neurulation resulting in inappropriate conus traction from a filum lipoma or lipomyelomeningocele [(11)].

Diastematomyelia

Diastematomyelia is a rare congenital anomaly that results in a longitudinal split of the spinal cord usually occurring at the level of the upper lumbar vertebrae. The genesis of this anomaly is thought to occur very early in gestation during gastrulation and prior to neural tube closure. The two hemicords are typically separated by a fibrous, cartilaginous, or osseous septum and reside in two separate dural tubes (type I split cord malformation) [(24)].

Type II split cord malformations have both hemicords within a single, non-duplicated, dural tube. Each hemicord usually contains a central canal, one dorsal horn and one ventral horn. The two hemicords typically reunite caudally, though two coni medullarae may be seen in diplomyelia, an embryologically distinct entity. Diastematomyelia is typically associated with vertebral segmental anomalies [(9)].

Vascular anomalies

Brain vascular malformations are rarely diagnosed in fetuses. The most common is the vein of Galen aneurysm. The vein of Galen aneurysm (VGM) is a vascular malformation of the choroid plexuses that drains into the vein of Galen. Because of the high flow the vein dilates and resembles an aneurysm. Other malformations are not usually seen as the draining veins are smaller and therefore not detected by ultrasound [(25)].

Diagnosis: The diagnosis is suspected during the third trimester ultrasound examination when a cyst-like structure is seen in the region of the posterior fossa [(18)].

The Doppler ultrasound and in particular the colour Doppler makes the diagnosis by showing high flow in the structure. The feeding arteries are difficult to analyse but dilated arteries are visible in the region of the malformation [(26)].

Fetal Brain Tumours

Congenital central nervous system tumors diagnosed during pregnancy are rare, and often have a poor prognosis. The most frequent type is the teratoma. Use of ultrasound and magnetic resonance image allows the suspicion of brain tumors during pregnancy. However, the definitive diagnosis is only confirmed after birth by histology [(27)].

Intracranial teratoma

Teratomas are the most frequent type of congenital CNS tumors. They represent approximately 62% of all types of brain tumors diagnosed during pregnancy. The majority of fetal brain teratomas is histologically benign and generally contains both mature components from all three germ layers and immature neuroglial elements. Since the first US description, approximately 100 reports on the prenatal diagnosis of fetal intracranial teratomas were published [(28)].

Choroid plexus papilloma

Choroid plexus papilloma (CPP) is a rare and benign tumor composed of epithelial cells that line the ventricular choroid plexus, and correspond to 0.4%-0.6% of fetal intracranial tumors. The incidence is inversely correlated with age, and 50% of patients in the pediatric age group are diagnosed during the first year of life [(22)].

CPP may develop in the lateral ventricle, third ventricle, and fourth ventricle. It is generally diagnosed during the third trimester and is always associated with unilateral or bilateral ventriculomegaly. CPP has slow growth and noninvasive behavior; however, because of its specific location, CPP can block the drainage of cerebrospinal fluid and cause hydrocephalus [(29)].

Craniopharyngioma

Craniopharyngiomas are benign and represent 2%-5% of all congenital CNS tumors. They develop from remnants of squamous cells originating from Rathke's pouch (ectodermal diverticulum originating from the upper limit of the oropharynx) and are most commonly found in the suprasellar region[(30)].

Although histologically benign, tumor expansion can cause significant destruction of the brain parenchyma and hydrocephalus. An intracranial large echogenic mass (basically indistinguishable from teratomas) is diagnosed by ultrasound [(3)].

MRI can help in determining the remaining brain structures and exact localization of the tumor. The head circumference may be increased because of the size of the tumor, and hydrocephalus may be present because of secondary obstruction of cerebrospinal fluid drainage. Differential diagnoses include: teratomas, astrocytomas, and hamartomas [(3)].

SUMMARY

Thirty years after the first in utero procedure for the treatment of fetal hydrocephalus, and other neurosurgical anomalies, little progress has been made with respect to the neurosurgical techniques for the management of that disease during the gestational period.

Diagnostic techniques have improved vastly and they now have a better ability to evaluate cases of fetal hydrocephalus and associated malformations of the central nervous system.

It is believed that in utero fetal procedures should be performed in cases of acute instances of evolving but nondestructive hydrocephaly without any other associated malformation.

Procedures to prevent hydrocephalus, such as closure of myelomeningoceles in fetuses before the 26th gestational week, should be encouraged.

With the development of diagnostic methods for identifying fetal neurosurgical diseases, it is crucial that neurosurgeons develop minimally invasive surgical techniques that allow fetuses to benefit from the procedures performed early in the intrauterine life.

The main errors made in the treatment of fetal hydrocephalus arise from the difficulty of accurately diagnosing hydrocephalus. It is clear that fetuses with acute obstructive hydrocephalus, which is often caused by a Coxsackie virus infection, benefit from hydrocephalus treatments, while fetuses with chronic destructive ventriculomegaly, such as those seen in Bicker-Adams syndrome or after infection by the Zika virus, will show a catastrophic evolution.

Thus, a multicenter cooperative study is required for the treatment of evolutive fetal obstructive hydrocephalus. Further, the inclusion of an efficient surgical technique is also important.

Cephalocentesis can be performed safely, as it allows not only a better diagnosis but also an isolated measure of intracranial pressure; it can also be used therapeutically when the fetus reaches lung maturity.

They rarely used fetal endoscopic third ventriculostomy due to the difficulty to enter the Kocher's point to access the third ventricle. However, it is possible to initiate the procedure, and in case the third ventriculostomy cannot be performed, a ventriculoamniotic shunt can be placed.

The MOMS results show that it is crucial that several neurosurgery centers are dedicated to this type of treatment during the fetal period. The open surgery technique is the main form of treatment and produces excellent results when compared with those obtained through the traditional technique of closure after birth.

Failure can occur during the treatment of fetal myelomeningocele. In most cases, they found a fibrous ligament that attaches the medulla to the dura mater in the upper part of the dysraphism. This ligament is not always found in postnatal procedures, or it is located in cranial positions, which determine the clinical condition of tethered cords.

Another phenomenon observed in most cases in the postoperative period is the increase in the posterior fossa volume, which is related to the embryogenesis of the occipital bone and increased intracranial pressure after correction of the fistula.

Further progress is necessary to enable fetal neurosurgery in becoming the main technique used in treating fetal neurosurgical diseases. However, we believe that correct prenatal diagnosis and adequate selection of fetuses with myelomeningocele, hydrocephalus, and occipital encephalocele may contribute to the benefits provided by neurosurgical procedures during the fetal period.

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