THE ROLE OF ULTRASOUND IN THE PRENATAL DIAGNOSIS OF NEURAL TUBE DEFECTS: A CASE SERIES

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ABSTRACT

Neural tube defects (NTDs) are the major targets of prenatal diagnosis, along with down syndrome.¹ Neural tube defects are severe congenital malformations affecting 1 in every 1000 pregnancies and become the second commonest group of birth defects, after congenital heart defects.²,³ The improved resolution of ultrasound has reportedly improved the accuracy of NTD diagnosis from ultrasound over amniocentesis in the patients with elevated maternal serum AFP levels.⁴ Here we present our three interesting cases of NTDs that verify the necessity of ultrasonography as main instruments on NTDs diagnosis making. Conclusively, proper prenatal diagnosis will leads to better outcome; made under repeated evaluations. Prior consultation to other related department and good counseling would be needed to encompass patient on decision-making, and thus, give chance to undergo a primary prevention.

Keywords. Anencephaly, birth defect, myelomeningocele, neural tube defects, prenatal diagnosis, ultrasound.

INTRODUCTION

Congenital malformation (i.e. birth defects) are important causes of infant morbidity and mortality in developed nations.² NTD are severe birth defects of the central nervous system that originate during embryogenesis and result from failure of the morphogenetic process of neural tube closure.⁵ These syndromes encompass a wide range of causes from viral, substance-linked, chromosomal, and other genetic syndromes.⁶ The use of ultrasound in the prenatal diagnosis of fetal genetic syndromes is rapidly evolving.⁶ Neural tube defects are the major targets of prenatal diagnosis, along with down syndrome.¹

NEURAL TUBE DEFECTS

Epidemiology

Neural tube defects (NTDs) are severe congenital malformations
affecting 1 in every 1000 pregnancies and become the second commonest group of birth defects, after congenital heart defects. More than 300,000 cases of NTD are estimated to occur worldwide each year, many of these can be found in low-income countries. A preponderance of female fetuses (up to 3:1) born with anencephaly and (2:1) spina bifida has been observed.

Etiology

Folate is required for the production and maintenance of new cells, for DNA synthesis and RNA synthesis. Folate is needed to carry one-carbon groups for methylation and nucleic acid synthesis. It has been hypothesized that the early human embryo may be particularly vulnerable to folate deficiency due to differences of the functional enzymes in this pathway during embryogenesis combined with high demand for post translational methylations in the cytoskeleton in the neural cells during neural tube closure. Failure of post-translational methylation of the cytoskeleton, required for differentiation has been implicated in NTDs. Importantly, a deficiency of folate itself does not cause neural tube defects. The association seen between reduced neural tube defects and folic acid supplementation is due to gene-environment interaction such as vulnerability caused by C677T Methylene tetrahydrofolate reductase (MTHFR) variant. Supplementing folic acid during pregnancy reduced the prevalence of NTDs by not exposing this otherwise sub-clinical mutation to aggravating conditions.

Neural Tube Closure and types of NTDs

The neural tube closure occurs around day 28 after conception; its closure failure may result in a defect that can range from anencephaly, incompatible with life, to small meningoceles. The type of NTD and the extend of the lesion should be accurately ascertained. ‘Open’ NTDs results from failure of primary neurulation, failure of closure in perspective brain and spinal cords results in anencephaly, myelomeningocele (open spina bifida), and craniorachisis, respectively. The type and severity of these open NTDs vary with the level of the body axis affected. Degeneration of the persistently open neural tube in utero leads to loss of neurological function below the lesion level. ‘Closed NTDs’ are skin-covered disorders of spinal cord structure, ranging from asymptomatic spina bifida occulta to severe spinal cord tethering, and usually traceable to
disruption of secondary neurulation. ‘Herniation’ NTDs are those which meninges, with or without brain or spinal cord tissue, become exteriorized through a pathological opening in the skull or vertebral column (e.g. encephalocele and meningocele).2

Figure 1. Diagrammatic representation of the developmental origin of malformations broadly classified as neural tube in humans.5 (a, b) Disorders of primary neurulation include cranioschisis (a) in which neural tube fails to initiate closure, leaving most of the brain and the entire spine open. If closure initiates successfully, then the cranial and/or spinal neural folds may fail to close (b) generating exencephaly/anencephaly and open spina bifida (myelomeningocele), respectively. (c) Disorders of secondary neurulation comprise failure of the neural tube to separate completely from adjacent tissues, resulting in tapering and diminished mobility. The spinal cord is covered by skin and often associated with fatty tissue accumulation (lipoma) through unknown mechanism. (d) Postneurulation defects can arise when the bony structure of the skeleton fails to develop fully. Herniation of the meninges, with or without brain tissue, through a skull defect (shown here as occipital but sometimes parietal-orfronto-ethmoidal) generates encephalocele, while an analogues defect in the spinal region produces meningocele.5
**Diagnostic Approach**

Studies have shown that a combination of screening strategies using both ultrasound and biochemical characterization are important to achieve high detection rates.\(^{12}\) Previously, the gold standard for the prenatal diagnosis of NTD was increased amniotic fluid and AChE levels.\(^{13}\) When neural tissue is exposed to the amniotic fluid, amniotic fluid AChE increases; when both of these markers are measured, the detection rate of anencephaly and open spina bifida is 100%. False-negative values are extremely rare for amniotic fluid AChE in terms of NTD detection.\(^1\)

Currently, the standard operating procedure for the diagnosis of open and closed NTDs is primary screening for detection of fetal structural abnormalities. Anatomical (high-resolution) ultrasound is used to obtain a detailed image for fetal intracranial and spine assessment.\(^{12}\) It is recommended to use serum markers such as Maternal Serum Alpha Fetoprotein (MSAFP), which leads to a diagnosis rate of 98%.\(^{14}\) Ultrasound screening has now surpassed the original gold standard MSAFP biochemical test because ultrasound screening is reported to have up to 97% sensitivity and 100% specificity in the diagnosis of NTDs in the hands of experienced ultrasonographers. The major pitfall of ultrasonography is the high false-negative rate and the technique is therefore potentially dangerous in the hands of less experienced ultrasonographers.\(^{12}\)

**Prognosis**

Clinical severity of NTDs varies greatly. Open lesions affecting brain (anencephaly, craniorachischisis) are invariably lethal before or at birth. Encephalocele can also be lethal depending on the extent of brain damage during herniation. Open spina bifida is generally compatible with postnatal survival, although the resulting neurological impairment below the level of the lesion can lead to lack of sensation, inability to walk and incontinence.\(^3\)

**Primary Prevention of NTDs**

Folate and vitamin B12 are very important in reducing the occurrences of NTDs.\(^{15}\) Several programs were implemented globally to prevent folic acid preventable-birth defects and other folate deficiency diseases.\(^7\) Folate is a water-soluble B vitamin present in legumes, leafy green vegetables (such as spinach and turnip greens) and some fruits (such as citrus fruits and juices).
Folic acid is the synthetic and most stable form of folate and it is often used in supplements and in fortified foods. The bioavailability of folic acid is approximately 70% higher than folate that is naturally contained in foods, although there are wide variations depending on the methodology used in the measurements.

The impact of folate insufficiency on birth defects in different population varies with each healthcare system. It partly relates to the use and coverage of preventive strategies including education and awareness of the importance of folic acid intake among women of reproductive age. Recent evidence demonstrates that public health policies which include folic acid fortification of staple foods are likely to result in a large-scale prevention of NTDs. These aimed at promoting periconceptional (namely, 2-3 months before and until 3 months after conception) folic acid supplementation through daily multivitamin intake or consumption of folate. The target is to enable all women who are capable of becoming pregnant to take 0.4 mg of folic acid daily rich foods. It would seem reasonable to implement both interventions fully, especially in countries with a high-prevalence of birth defects.

**ROLE OF ULTRASOUND**

**Advancing Technology**

Two-dimensional ultrasonography has long been the modality of choice for diagnosis of fetal anomalies. Increasingly, because of the limitations of two-dimensional ultrasound, three-dimensional and four-dimensional ultrasonography is being used to aid in diagnosing and visualizing suspected fetal anomalies. However, the sensitivity and specificity of the imaging modalities were not significantly different.

Ultrasound as a screening tool for aneuploidy and other anomalies is increasingly being used throughout pregnancy, beginning in first trimester. Advancing technology and new research findings are aiding in the increased accuracy of ultrasound-based diagnosis in combination with other methods of non-invasive and invasive fetal testing.

The improved resolution of ultrasound has reportedly improved the accuracy of NTD diagnosis from ultrasound over amniocentesis in the patients with elevated maternal serum AFP levels. The possibility of an anomaly is low if the ultrasound is normal; reports have proposed the patient, guided by sufficient
information, must decide that subsequent amniocentesis.¹

Timing of Ultrasound

Ultrasound can be used throughout pregnancy to detect fetal abnormalities. It is advised that all pregnant women undergo a fetal anatomic survey in the second trimester. It is important to use a methodical routine in the execution and evaluation of the anatomic survey to assure complete assessment of fetal anatomy.⁶,¹³

First-trimester ultrasound is increasingly being used for nuchal translucency test and also for an early limited anatomic survey. Ultrasound in the first trimester has been shown to be effective in screening for aneuploidy conditions such as trisomy 21.⁶,¹⁷ By ultrasound, it is possible to diagnose cerebral malformations such as holoprosencephaly, ventriculomegaly, anencephaly, etc during 11th – 13th gestational weeks. In a study performed in 2009 by Benoit et al using sonographic measurement of intracranial translucency (IT) during 11th to 13th gestational week to diagnose spina bifida, routine use of midsagittal sonographic view was suggested for early diagnosis of chromosomal defects.¹⁴ In another study, 78% of cases that were eventually diagnosed with anencephaly were actually diagnosed as being so, using sonography at the end of the first trimester. Also by ultrasound, spinal defects and cerebral findings associated with myelomeningocele were detectable in 89% of cases who were ultimately diagnosed with meningomyelocele.¹⁴

The first trimester ultrasound largely focuses on nuchal translucency measurement in the assessment of chromosomal syndrome risk; however the second trimester ultrasound can identify much more specific defects that follow a different pattern for each genetic syndrome. Importantly, some fetal anatomy are more easily visualized later in the second trimester.⁶ Fetal anatomy is assessed systematically through ultrasound after about 18 weeks.

A retrospective study by Conner and Longman (2014) showed that sonographic markers of aneuploidy were present at all gestational ages. And also a prospective study by Schwarzler et al. evaluated that fetuses that underwent an anatomic survey at 20-22 6/7 weeks are less likely to need repeat examination than women who have an ultrasound 18-18 6/7 weeks gestational age.⁶

Ultrasound Findings
The improved resolution of ultrasound has reportedly improved the accuracy of NTD diagnosis from ultrasound over amniocentesis in patients with elevated maternal serum AFP levels. The possibility of an anomaly is low if the ultrasound is normal.\textsuperscript{1, 13} Given the number recorded syndromes, it is important to identify patterns and establish a strategy for identifying abnormalities on ultrasound.\textsuperscript{6} The nuchal translucency measurement in the first trimester, with a cut-off of 3 mm or greater, has been shown to have high sensitivity and specificity for identifying pregnancies at risk for chromosomal anomalies.\textsuperscript{13, 18} In addition, early anatomic surveys have been shown to have good detection rates of most structures when carried out by experienced sonographer.\textsuperscript{6}

Although intracranial signs are critical for open spina bifida diagnosis during ultrasound, they could be absent. Thus, the sagittal images of the spine must be carefully observed for the presence of meningoceles.\textsuperscript{1}
CASE REPORTS

Here we present our three interesting cases of NTDs that verify the necessity of ultrasonography as main instruments on NTDs diagnosis making.

CASE 1

Mrs. NR, 37 years old, was expecting her 4th pregnancy, no history of miscarriage, with unremarkable medical history, and no notable history of genetic disease or delivery of a baby with congenital birth defects among her close relatives or those of her spouse. Her last menstrual period was corresponds to 31 weeks of gestational age, presents to our fetomaternal division and underwent her second ultrasound. Her first ultrasound was performed one week before admission, and evaluated her fetus with anencephaly, so she has been referred to have a confirmed ultrasound.

Abdominal ultrasound showed that the fetus was in a cephalic presentation. Biophysical examinations were performed; physical movement and breathing movement are within normal limit, with a good tone. On our biometry evaluations, the biparietal diameter (BPD) and head circumference (HC) were hard to be determined due to acranii findings. The other biometry markers were within normal limit corresponds to 31 weeks gestational age. The abnormal finding was the amniotic fluid index that increased to the level of 35 and assessed as polyhydramnions. No other concomitant malformations were found.

Termination was recommended with appropriate counseling, and the patient agreed; thus, the cervical ripening is conducted. Misoprostol was administered twice and ripened cervix was achieved, continued with Oxytocin titration, and reach the second stage of labor. The outcome was baby girl, 1500 g, no spontaneous crying, with pulse rate 100 bpm, no neonatal resuscitation was performed, and the baby died within 30 minutes after delivered.
Figure 2 & 3.
Findings of acranii, leads to powerless determination on measuring biparietal diameter and head circumference. The appearance of frogeyes strength the suspicion of anencephaly.

Figure 4 & 5. After birth pictures confirmed the antenatal ultrasound findings of anencephaly.
CASE 2

Mrs. NS, 40 years old, on her first pregnancy without history of miscarriage, with unremarkable medical history, and no notable history of genetic disease or delivery of a baby with congenital birth defects among her close relatives or those of her spouse. Her last menstrual period and date of confinement correspond to 35 weeks of gestational age. Routine antenatal care was performed in the midwife until she has been referred for second trimester screening in our fetomaternal division.

She presents without any complaints, and abdominal ultrasound showed that the fetus in cephalic presentation. The biometry examination showed a good activity and a normal growth of the fetus, equivalents to 35 weeks of gestational age.

The anomalous findings were assessed; thus intracranial signs were observed with appearance of a lemon sign with enlargement of lateral ventricle in the cranium, and in vertebral region, a discontinuity defect with a hypodense cystic mass matched to myelomeningocele. For proper afterbirth management, our division has consulted the fetus condition to birth defect team. The pregnancy was then plan to be terminated abdominally on 38 weeks of gestational age.

Cesarean sections was performed, born baby girl 3400 g, AS 9/10, Grossly, the sac was present measuring up to 81 mm in diameter, and plan to undergo a myelomeningocele repair and VP-Shunt once after NICU slot available for post-operative recovery.

**Figure 6 & 7.** Vertebral region, a discontinuity defect with a hypodense cystic mass matched to myelomeningocele
Figure 8. Appearance of a lemon sign with enlargement of lateral ventricle in the cranium sized 16 mm and 17 mm.

Figure 9. After birth pictures confirmed the antenatal ultrasound findings of myelomeningocele, grossly, the sac was present measuring up to 81 mm in diameter.

CASE 3
Mrs. RA, 43 years old presents to our fetomaternal division due to prior examinations findings of myelomeningocele. No history of miscarriage, with unremarkable medical
history, and no notable history of genetic disease or delivery of a baby with congenital birth defects among her close relatives or those of her spouse. Her last menstrual period and date of confinement correspond to 31 weeks gestation, and the biometry was matched the LMP, with normal growth and activity. Abnormal findings were seen in the spine, a vertebral discontinuity length 16 mm, with a cystic mass sized 58 mm x 46 mm corresponds to myelomeningocele, with the intracranial broadening of third ventricle to 12 mm.

Similarly with the second case, concerning proper afterbirth management, our division has consulted the fetus condition to birth defect team. The pregnancy was then plan to be terminated abdominally on 38 weeks of gestational age on scheduled elective cesarean section. But then the patient came in latent phase of labor; consequently emergency cesarean section been executed.

Cesarean sections was performed, born baby girl 2800 g. AS 8/9, Grossly, the thin sac was present measuring up to 70 mm in diameter, and was found ruptured, thus a primary myelomeningocele repair been performed.
Figure 10, 11, & 12. Vertebral discontinuity length 16 mm, with a cystic mass sized 58 mm x 46 mm corresponds to myelomeningocele.

Figure 13. After birth pictures confirmed the antenatal ultrasound findings of myelomeningocele in the lumbosacral region, the sac was present measuring up to 70 mm in diameter, and was found ruptured.

Figure 14. Appearance of the ruptured thin sac.
DISCUSSION

In 2003, the American College of Obstetricians and Gynecologists recommended that maternal serum AFP be measured in all pregnant women as an NTD test, and most accurate at 16-18 weeks’ gestation. The age, weight, ethnicity, diabetes history, number of fetuses, and gestational weeks also be considered. However, this is only a screening test, limited by its high false-positive rate and low sensitivity, and does not have significant weight in terms of diagnosis; thus genetic counseling and diagnostic examinations must also be conducted.

The fetal spine is sufficiently ossified at approximately 16 weeks of gestation, and is readily observable through ultrasound. At this time, splaying of the posterior ossification centers, a meningocele, or myelomeningocele sac, the presence of placode on the sac surface, or neural elements bridging across the sac are direct evidences of spina bifida. However, observation can be difficult if the mother is obese, the fetus is in the persistent spine posterior position, or if the sac has ruptured. Rather than these direct signs, indirect secondary signs of the fetal skull and brain may be easier to observe in the early stages. It has been reported that 99.6% of NTD fetuses present with at least one intracranial sign. The size of the NTD lesion is reportedly associated with intracranial sign manifestation, however another report has found no association.

The first case of anencephaly, due to poor prognosis, with adequate information, the termination has been chosen by patient to avoid a prolonged anxiety of mother. The patient decided to not becoming pregnant again, and we also give her sufficient information about contraception, and prefer taking intrauterine contraception.

The second and third cases were found comparable, with similar location, and also same broadening ventricle was found. Both have assessed using ultrasonography, with accurate locations and size.

From our case illustrations, the situations clarify the essential of appropriate referral, especially in some developing country, whereas the referral system could need some transits before touching the tertiary hospital. Moreover, the ultrasound first and second trimester screening someway recommended in all pregnancy if possible and feasible, to accomplish better approach and management.

CONCLUSION
NTDs represent arguably the best-understood category of human birth defects. Proper prenatal diagnosis will lead to better outcome; made under repeated evaluations. Prior consultation to other related department and good counseling would be needed to encompass patient on decision-making, and thus, give chance to undergo a primary prevention.

With the screening methods available, the diagnosis of NTD in the first trimester of pregnancy can lead to a decrease in maternal complications associated with pregnancy termination and its cost.
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