Prenatal Diagnosis of Neuroblastoma

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ABSTRACT

Fetal malignancies are rare complications during pregnancies, but when they appear, they are very challenging for the perinatology team. Because of their low incidence, the information is limited, with data provided from individual case reports or small case series. Although neuroblastoma is the most frequent extracranial solid tumor in childhood, prenatal diagnosis by ultrasound is very rare and almost always discovered during routine third trimester ultrasound. Expectant management is usually indicated prenatally, with serial ultrasound examination. Delivery should be planned in a tertiary center together with pediatric oncologists and surgeons to allow appropriate postnatal management. We present two cases of neuroblastoma diagnosed at 36 and 33 weeks of gestation with multiple aspects of this tumor identified by ultrasound. Both cases needed surgery and had a favorable outcome. The key role of ultrasound in diagnosis and follow-up of neuroblastoma in pregnancy is discussed, together with the management options recommended in literature.

Keywords: Neuroblastoma, Ultrasound, Adrenal gland, Tumor.


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INTRODUCTION

Congenital neuroblastoma is about 30% of all neonatal tumors, being the most common malignant tumor in this age group. The incidence of congenital neuroblastoma had been estimated at about 1 in 10,000-30,000 live births, but in regions where postnatal screening for neuroblastoma during the first 6 months of life was introduced, the incidence was found two to three times higher than expected. Autopsy series also revealed a higher incidence: in situ neuroblastoma was found in 1 of 259 cases. In 1983, Fenart et al first reported ultrasound prenatal diagnosis of fetal neuroblastoma. Since then, there have been numerous case reports and a few case series. Neuroblastomas can have a solid, purely cystic or complex sonographic appearance. The prognosis is generally favorable, but it depends on the early diagnosis. Although surgery alone is curative for most patients, a period of observation may avoid surgery in some infants who may achieve spontaneous regression.

OVERVIEW OF NEUROBLASTOMA

Neuroblastoma is the most common neonatal malignancy, and the adrenal gland is the most common primary site for neuroblastoma. It is a classical embryonic tumor of neuronal lineage that may occur at all sites of sympathetic ganglia from the neck to the presacral region including the adrenal medullae and all stages and degrees of aggressiveness may appear in fetal and congenital cases. Prenatal diagnosis is usually made in the third trimester and the mean gestational age at diagnosis is 36 weeks. Association with other anomalies is unusual. Antenatal features are mainly based on the size, location and tumor secretory activity, with most primaries being small adrenal medullary nodules that are difficult to detect on imaging. Larger lesions may show degenerative features such as cystic changes, hemorrhage and calcification, which can be detected sonographically in utero. Cysts may represent a stage of involution and most of the cystic prenatal neuroblastomas reported have had favorable biologic features. More than 90% of prenatally diagnosed neuroblastomas are adrenal in origin. In contrast, only 35% of all neuroblastomas in infants and young children are adrenal in origin.

A genetic defect was identified, with a loss of a critical region in chromosome 1 (locus p36). Other genetic defects identified are 17q gain or 11q loss. Amplification of the N-myc proto-oncogene is correlated with the aggressiveness of the tumor. Since the gene coding for the S-100b protein is located on chromosome 21, this may inhibit the development of neuroblastoma in Down’s syndrome.

Neuroblastoma produces catecholamines, which decrease peripheral vascular resistance and plasmatic volume, induce centralization of fetal circulation. Also, pulmonary hypertension and fetal cardiomyopathy can occur. The biochemical activity can be evaluated by dosing vanillylmandelic acid (VMA) and homovanillic acid (HVM). These are markers for the evolution of neuroblastoma. The tumors originating from dorsal ganglia do not have biochemical activity.
Fetal adrenal glands can be visualized on ultrasound from the end of the first trimester and have a discoid shape on a transverse view. They appear as Y- or V-shaped structures at the superior border of the kidney on an axial view. The second trimester ultrasound image is usually normal, with the tumor becoming visible in the third trimester. The normal ultrasound image of adrenal in the third trimester is a large hypoechoic cortex surrounding a small hyperechoic medulla Fig. 1. 60 to 90% of fetal neuroblastomas are located in adrenal glands and the right side appears to be more frequently affected. The tumor displaces the kidney inferiorly and laterally and is usually encapsulated Fig. 2.

The ultrasound appearance can vary from one exam to another. It may look solid, purely cystic, suggesting a renal cyst (50%), or with mixed echoes, which is related to hemorrhage, necrosis or tumor involution.

Metastases appears in 25% of cases and the liver is the most commonly affected. Although ultrasonography may fail to diagnose extension of the disease, scanning with a specific marker for the sympathetic tumoral tissue, metaiodobenzyl guanidine, can improve significantly detection of metastases. MRI exam has proven even more sensitive in detecting hepatic metastases in some patients. A nodule or a cystic mass in the liver or in the retroperitoneal nodes should be followed by evaluation of all neural crest regions and especially the adrenals. A suprarenal mass associated with hepatomegaly is highly suggestive for neuroblastoma. Fetuses with extensive liver metastases are at risk for hydrops. Tumoral cells may also invade the placenta, with metastatic foci in the umbilical vessels. Placenta appears bulky, pale and heavy, while tumor deposits are not macroscopically detectable, being identified only on histological examination. Fetal loss may appear in such cases. Fetal hydrops can be a consequence of hepatomegaly with mechanical obstruction of the umbilical vein or inferior vena cava, altered liver function with hypoalbuminemia, metastatic placental invasion, infiltration of fetal bone marrow with subsequent anemia and heart failure, arrhythmia with heart failure due to excessive catecholamine release or due to hypersecretion of fetal aldosterone.

The key to the diagnosis of neuroblastoma is the change in appearance over time. Usually to a cystic mass of decreasing size. Peripheral calcification may remain and its detection has been associated with improved survival, presumably indicating previous tumor necrosis. In neuroblastoma the color Doppler waveform with very low impedance is typically seen Fig. 3.

Follow-up ultrasound examinations should be performed at 15 days from diagnosis to term in order to monitor the size of the mass and to detect rare metastatic antenatal complications. Despite the good prognosis, these tumors have a large growth potential. The size often doubles in less than 15 days when ultrasound measurements are available.
The ‘International Neuroblastoma Staging System’ (INSS) established in 1986 and revised in 1988 stratifies neuroblastoma according to its anatomical presence at diagnosis.18,19

- **Stage 1**: Localized tumor confined to the area of origin.
- **Stage 2A**: Unilateral tumor with incomplete gross resection; identifiable ipsilateral and contralateral lymph node negative for tumor.
- **Stage 2B**: Unilateral tumor with complete or incomplete gross resection; with ipsilateral lymph node positive for tumor; identifiable contralateral lymph node negative for tumor.
- **Stage 3**: Tumor infiltrating across midline with or without regional lymph node involvement; or unilateral tumor with contralateral lymph node involvement; or midline tumor with bilateral lymph node involvement.
- **Stage 4**: Dissemination of tumor to distant lymph nodes, bone marrow, bone, liver, or other organs except as defined by Stage 4S.
- **Stage 4S**: Age <1 year old with localized primary tumor as defined in stages 1 or 2, with dissemination limited to liver, skin, or bone marrow (less than 10 percent of nucleated bone marrow cells are tumors).

Although international agreement on staging (INSS) has been used, the need for an international consensus on risk assignment has also been recognized in order to compare similar cohorts in results of studies. Beginning in 2005, representatives of the major pediatric oncology cooperative groups have met to review data for 8,800 neuroblastoma patients treated in Europe, Japan, USA, Canada, and Australia between 1990 and 2002. They proposed the International Neuroblastoma Risk Group (INRG) classification system. Retrospective studies revealed the high survival rate of 12 to 18 month old age group, previously categorized as high-risk, and prompted the decision to reclassify 12 to 18 month old children without N-myc (also commonly referred to as MYCN) amplification to intermediate risk category:20

The new INRG risk assignment will classify neuroblastoma at diagnosis based on a new International Neuroblastoma Risk Group Staging System (INRGSS):

- **Stage L1**: Localized disease without image-defined risk factors.
- **Stage L2**: Localized disease with image-defined risk factors.
- **Stage M**: Metastatic disease.
- **Stage MS**: Metastatic disease ‘special’ where MS is equivalent to stage 4S.

The new risk stratification will be based on the new INRGSS staging system, age (dichotomized at 18 months), tumor grade, N-myc amplification, unbalanced 11q aberration, and ploidy into four pre-treatment risk groups: very low, low, intermediate, and high-risk.21,22

Dumbbell neuroblastoma is suspected based on neurological symptoms like bowel and bladder dysfunction, paralysis, pain during neonatal period.23-25 10 to 15% of neuroblastomas invade the intervertebral foramina and spinal canal with or without cord compression. Although the oncological outcome of the tumor is very good, functional sequelae can be severe. These tumors are considered to be unresectable and therefore preoperative chemotherapy is recommended.26,27 According to other investigators, surgical resection was only performed if neurological deterioration occurred during primary chemotherapy.28 As a consequence, laminectomy was avoided or delayed in 75% of cases, with less orthopedic complications. Although ultrasound examination, including 3D may identify spinal infiltration, MRI can make the diagnosis of dumbbell neuroblastoma and detect the invasion through the vertebral foramina in the spinal canal.

MRI is probably becoming an important adjunct to ultrasound, especially in cases in which ultrasound findings are unclear due to oligohydramnios or maternal obesity.29 Because its better demonstration of morphological details, MRI is likely to provide a better differential diagnosis of neuroblastoma from adrenal hemorrhage, subdiaphragmatic sequestration or renal cortical cysts.30,31 In the future, when real-time MRI will become available, will add further improve to diagnosis.32

The cystic form of neuroblastoma should be differentiated from adrenal hemorrhage, which is the most common diagnosis in adrenal masses in the new-born.33 This mainly occurs at birth or in the early neonatal period, less frequently during the third trimester in utero. Preferentially affects the right side, probably due to compression of the right adrenal between the liver and the spine.33 Other differential diagnoses include renal cysts, obstructed upper renal pole duplication and Wilms cystic tumor. All may resemble cystic neuroblastoma. Mesoblastic nephroma appears as a solid heterogeneous mass. Sub-diaphragmatic extralobar pulmonary sequestration is three times less frequently than neuroblastoma and the color Doppler exam can identify the pedicle arising from the thoracic aorta. It appears usually as an echogenic mass on the left side in the second or third trimester.34 Alimentary tract duplications may look like neuroblastoma, but they appear from 16 weeks of gestation. Differential diagnosis should be made also with hepatic, choledochal (Fig. 4), ovarian or enteric cysts, renal vein thrombosis and retroperitoneal teratoma.

In most cases of prenatally diagnosed neuroblastoma, the mother is asymptomatic. However, possible maternal
Cristian Andrei et al

Symptoms include palpitations, flushing, sweating and hypertension or maternal ‘mirror’ syndrome due to feto-placental hydrops. These are a consequence of the passage of the catecholamines into the maternal circulation in the third trimester of pregnancy. Such maternal complications may be indicative of poor outcome in the neonate. In fetuses with stage IV or IV-S placental involvement could facilitate this passage and is an element of poor prognosis. Maternal urinary VMA and HVM were increased in one-third of cases diagnosed prenatally, compared to 85 to 90% in infants with neuroblastoma.

The prognosis of neuroblastoma is highly dependent on the stage of the disease, and when diagnosed prenatally, the majority of cases are at stage I. It seems that there are two subsets of neuroblastoma. In the first subset, the tumor has a favorable prognosis, is identified in utero or early in postnatal life, and has a low staging. The survival rate is higher in prenatally detected cases than the overall group of neuroblastomas, partly because spontaneous regression may occur in up to 40% of these cases, and partly because this subgroup is generally associated with good biological features (triploid without N-myc amplification, 1p deletion, 17q gain or 11q loss), so chemotherapy or surgical excision is curative in the majority of cases. The other subset comprises unfavorable neuroblastomas diagnosed in older children and associated with unfavorable genetic prognostic factors. These cases have a poor clinical outcome, even with aggressive treatment. Cases with overt placental involvement however appear to be associated with an adverse prognosis, with reported cases dying either in utero or shortly after birth.

As a guide for management, expectancy is the golden rule in neuroblastoma diagnosed in the third trimester, because of their characteristics of low stage disease and favorable biologic features. Preterm delivery is rarely indicated. Repeated ultrasound examinations should detect fetal hydrops, adrenal enlargement or metastases. In these cases, delivery is indicated after lung maturation. If adrenal enlargement or hemorrhage appears, the mode of delivery should be reconsidered because dystocia and fetal hemoperitoneum have been reported with vaginal delivery. Although spontaneous tendency towards regression of the tumor, even in metastatic cases, has made conservative management for 4 to 6 weeks an acceptable option in some centers, surgical excision of the tumor in the neonatal period is curative in the majority of cases. For selection of the group with favorable biological parameters (N-myc, DNA index), which would clearly benefit from expectant management, a reasonable option may be needle biopsy for solid tumors. Various chemotherapy regimens (cyclophosphamide alone, carboplatin/etoposide, cyclophosphamide/doxorubicin/vinristine) have been used to treat intermediate and high-risk cases in association with surgery.

CASE REPORTS

Case 1

A 32-year-old primigravid woman with a normal evolution of pregnancy, with no anomalies identified at I and II trimester screening and no maternal associated pathology, was diagnosed during a routine ultrasound examination at 36 weeks of gestation with a fetal intra-abdominal mass located at the upper pole of the right kidney, with a mixt echoic appearance, both solid and cystic (Fig. 5). The mass was pushing downwards the kidney. Fetal biometry and morphology were otherwise normal and the fetal heart rate pattern was reactive. The mother did not present any adrenergic symptomatology or hypertension. After 1 week the ultrasound appearance has changed, with a more dominant solid image, although the image remained with mixed echoes, both solid and cystic (Fig. 6). The vessels surrounding the tumor appeared well defined, in a circle or ring manner. At 38 weeks of gestation, the aspect was evolving, with growth in the tumor dimensions (Fig. 7), so we decided to extract the fetus through cesarean section.

The baby was 3100 gm at birth, Apgar score 9 and had a favorable postnatal evolution. Concentration of catecholamine metabolites, VMA and HVM were elevated in fetal urine and supported the suspicion of neuroblastoma. Postnatal ultrasound examination and MRI did not show any secondary determination. The team of pediatric oncologist and surgeon decided for chemotherapy as first line of treatment followed by surgical excision at three months of age. Histopathology confirmed the diagnosis of neuroblastoma. At the age of 1 year, the evolution was excellent, with no signs of residual or metastatic disease.
Case 2

A 30-year-old woman, gravida 2, para 2, was diagnosed during a routine ultrasound examination at 33 weeks of gestation with a hyperechoic mass in the fetal chest, located at the base of the right lung and measured 19 × 17 × 15 mm (Fig. 8). We did not identify any specific vascularization. After 1 week we reviewed the case and decided to perform an MRI, which showed progression in dimensions of the intrathoracic mass. Also the MRI suggested an extension of the tumor through the vertebral foramina leading to suspicion of a dumbbell neuroblastoma, with no osteolytic lesions (Figs 9 and 10). We performed ultrasound examination focused on the motility of inferior extremities to evaluate the presence of spinal cord compression. At 35 weeks the ultrasound revealed an increase by 10 mm in 1 week. A cesarean section was decided and performed in order to start treatment capable of limiting the functional sequelae. A 2600 gm fetus with Apgar score 9 was extracted and admitted into intensive care unit. The initial neurological exam revealed no bowel or bladder dysfunction, but showed hyperreflexia and reduced tonicity of the lower limbs. Ultrasound examination of the spine identified a compressive thoracic intraspinal component measuring about 25 mm. The urinary levels of vanillylmandelic acid (VMA) and homovanillic acid (HVM) were only slightly elevated. The pediatric oncologist instituted chemotherapy from the first postnatal day combined with high doses of methylprednisolone. After two weeks, hyperreflexia was still present and MRI showed an increase in the size of the intraspinal component to 30 mm. The combination of chemotherapy was changed and after 6 weeks the MRI showed a marked regression in the size of the intrathoracic mass and intraspinal component. The urinary levels of VMA and HVM were normal. At 3 months postnatally was performed surgical resection of the intrathoracic mass and the histological exam confirmed the diagnosis. At 1 year, the follow-up revealed no residual tumoral mass and no neurological sequelae.
REFERENCES


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