



Perinatal neuroblastoma

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One-fifth of all neuroblastomas are diagnosed either antenatally or in the first 3 months of life. Over the past two decades, routine prenatal ultrasound has significantly increased the rate of diagnosis of fetal neuroblastoma. More than 90% of these tumors arise in the adrenal gland, suggesting a link between perinatal tumors and the nodular collections of neuroblasts that are part of normal adrenal development. In fact, there is compelling evidence that the cystic variant of perinatal neuroblastoma is caused by a perturbation of the involution program of these neuroblastic nodules. The vast majority of these cases are localized tumors with favorable biological features, which correlates with a 4-year survival of greater than 95%. The high rate of spontaneous regression of these tumors, coupled with the significant risks of resectional surgery in small neonates, has prompted the development of a prospective clinical trial of expectant observation as primary therapy for infants with small, localized tumors. The ultimate goal of such studies is to define an ultra-low-risk group of neuroblastoma patients who do not require invasive procedures or chemotherapy to achieve an excellent outcome.

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Neuroblastoma is the most common solid tumor in children under 1 year of age. Many of these infants are diagnosed in the first few months of life.¹ During the past two decades, more of these tumors have been diagnosed antenatally due to the increasing use of third trimester obstetrical ultrasound. This article will focus on perinatal neuroblastoma, that is, cases of neuroblastoma diagnosed either prenatally or in the first 3 months of life. We will specifically consider those aspects of clinical presentation, treatment, and outcome that distinguish neuroblastoma in young infants from the disease in older children.

As clinical experience has increased, it has become clear that the majority of perinatal cases arise in the adrenal gland during the third trimester of gestation. The typical presentation is a cystic or solid mass detected on fetal ultrasound. These masses normally do not cause symptoms either before or after birth. The clinical course is generally benign:

either the mass is resected in the newborn period or it decreases in size and eventually disappears on serial imaging studies as part of an expectant observation approach. The relatively rare exceptions to this favorable group are patients with very large or widespread tumors. Extensive disease can cause fetal distress or demise, hydrops, or adverse maternal effects during gestation, as well as bad outcomes in the newborn period. This review will examine the biology and pathophysiology of this unique group of tumors with emphasis on the rationale for expectant observation strategies, and the principles of management of fetuses and neonates with more extensive disease.

Embryology of the adrenal gland and "neuroblastoma in situ"

The adrenal medulla develops from neural crest cells in conjunction with formation of the sympathetic nervous system. Initially, cells migrate from the neural crest and form aggregates along the aorta. Through a combination of mi-

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gration and proliferation, these cells form distinct neuroblastic nodules within the adrenal gland. Neuroblastic nodules are consistently observed at the end of the first trimester and reach a peak number of 70 to 100 per gland between the 16th and 20th weeks of gestation. From the late second trimester through the end of gestation, the nodules decrease in number so that relatively few or none are present at birth.^{2,3} The outer cells of the neuroblastic nodules differentiate into pheochromoblasts that will ultimately become chromaffin cells of the adult adrenal medulla. During early postnatal life, there is substantial reorganization of the adrenal gland. The central portion of the gland (fetal cortex) degenerates and the remaining neural tissue condenses around the central veins, eventually maturing into the adult medulla during childhood.⁴

It is likely that perinatal neuroblastomas arise from the cells of the neuroblastic nodules in the fetal adrenal gland. However, it is important to distinguish these clinically apparent masses from the minute collections of neuroblastoma cells that are sometimes seen at autopsy in newborns that die of other causes. When these infants' adrenal glands are analyzed carefully, small clusters of neuroblasts are identified in approximately 1 in 200 specimens. Because these aggregates share many of the morphologic features of neuroblastoma tumors, including the presence of mitotic figures and infiltration of the adult cortex, they have been termed "neuroblastoma in situ."⁵ The distinguishing features are the small size of these nodules (typically less than 3.5 mm in largest dimension), frequent association with intraadrenal cysts, and absence in infants over 3 months of age. Given that the incidence of clinically significant neuroblastoma is between 1/10,000 and 1/30,000 children, it is clear that, even if these smaller nodules are the precursors of macroscopic tumors, 99% of them regress and never become clinically apparent. This entity probably represents abnormal persistence of fetal nodules rather than the precursor of clinically apparent neuroblastoma in fetuses and neonates. Although the average size of these neuroblastic nodules decreases during the third trimester, there is a tendency for the nodules to aggregate so that it is not uncommon to find macroscopic groups of neuroblasts measuring several millimeters in diameter in the adrenal glands of late third trimester fetuses. Any process that delays the degeneration of these nodules in the perinatal period would account for their relatively common observation in neonates.^{2,6}

Aside from the overall size, careful histological analysis may be able to differentiate between persistent fetal neuroblast nodules and true neoplasms. Ikeda and colleagues compared nuclear size between typical fetal neuroblasts and tumor cells from children with neuroblastoma. The mean nuclear size was 4.25 μ in the neuroblasts and 6.2 μ in neonatal neuroblastoma tumor cells, suggesting a true biologic difference between these two entities.³ Given that the vast majority of perinatal neuroblastoma tumors have near-triploid DNA index,⁷ it would be fruitful to study the DNA content of the neuroblastoma in situ cells. A normal DNA

content would imply that this entity is different from perinatal neuroblastoma.

Incidence

Neuroblastoma is by far the most common cancer of infancy with an incidence almost twice that of leukemia, the next most frequent malignancy. The overall incidence is 58/1,000,000 infants per year.⁸ Sixteen percent of infant neuroblastomas are diagnosed in the first month following birth, and 41% present during the first 3 months of life.¹ If one considers that half of all neuroblastomas occur in infants, perinatal neuroblastoma represents one-fifth of all cases of this disease.

Clinical presentation

Imaging

Fetal neuroblastoma is normally diagnosed during the third trimester at an average age of 33 weeks, although there are reports of sonographic diagnosis as early as 23 weeks.^{7,9-13} Approximately 90% are adrenal in location with the remainder either thoracic or cervical.¹³⁻¹⁵ Two-thirds of the adrenal tumors are located on the right side.¹⁶ There are three basic morphologies on ultrasound.¹⁷ Half of the tumors are solid isoechoic masses, with typical diameter between 2 and 4 cm. The remaining cases are either purely cystic hypoechoic masses or complex structures containing both cystic hypoechoic fluid and echogenic solid material.^{18,19} The latter group is typically larger in size, measuring between 3 and 10 cm in their widest dimension. It is common for the solid masses to increase in size on serial antenatal ultrasound exams, whereas the cystic and complex masses may grow or shrink during fetal life.^{13,16,20}

Differential diagnosis

In addition to neuroblastoma, there are several clinical entities that should be included in the differential diagnosis of a suprarenal mass in a fetus. Cystic neuroblastoma must be differentiated from adrenal hemorrhage, which is the most common cause of adrenal mass in the newborn, with an estimated incidence of 1.9/1000 live births.^{16,21} Although most hemorrhages occur at birth or in the early newborn period, there are confirmed reports during the third and even the second trimester.^{21,22} Adrenal hemorrhage has an even greater preference for the right side than neuroblastoma, with 3 or 4 times as many cases on the right than the left, perhaps due to compression of the gland between the liver and the vertebral column.¹⁶ The initial sonographic appearance is a hypoechoic cyst that evolves into an area with internal echoes and gradually increasing echogenicity, plus/

minus calcifications.^{22,23} On the other hand, a right-sided isoechoic or hypoechoic solid mass, detected after the 29th week of gestation, has a greater than 95% chance of being neuroblastoma.^{17,24}

Subdiaphragmatic extralobar pulmonary sequestrations are predominantly left-sided masses with an incidence approximately one-third that of neuroblastoma.²⁴ These anomalies appear during the second trimester as solid, brightly echogenic masses that grow in proportion to the patient. Color flow Doppler examination can sometimes detect the systemic arterial branch projecting from the thoracic aorta.

Several entities included in the differential diagnosis of a cystic mass derive from the kidney, including renal cyst, obstructed upper pole duplication, and cystic Wilms' tumor. On the other hand, mesoblastic nephroma should be considered when presented with a complex mass.^{17,25} Enteric duplication cysts present in the suprarenal location; however, they appear as early as the 16th week, allowing some means of discrimination from cystic neuroblastoma.

Symptoms and signs

Most fetal neuroblastomas are incidental findings on standard obstetrical sonograms; however, there are occasional reports of maternal and/or fetal symptoms and signs that appear to be either direct or indirect consequences of the presence of a neuroblastic tumor. Before the development of medical ultrasound, many clinicians reported an association between congenital neuroblastoma and maternal symptoms of catecholamine excess, such as nervousness, sweating, vomiting, flushing, headache, and/or weakness.^{26,27} Postnatal maternal urinary catecholamines (VMA/HVA) were negative, but these may have been measured too long after the source of catecholamines was removed.²⁷ Since the onset of routine obstetrical ultrasound, it has been possible to measure catecholamine secretion in symptomatic mothers carrying fetuses with suspected neuroblastoma; however, there are no published reports of such studies.

Frank preeclampsia is associated with widely disseminated fetal neuroblastoma, although it is difficult to determine whether this physiologic derangement is caused by catecholamine excess or a "mirror" type syndrome in response to severe fetal distress and/or hydrops.^{10,27,28} Fetal compromise is caused by very large and/or widely metastatic tumors. Metastatic involvement of the placenta is associated with fetal hydrops and maternal preeclampsia, possibly caused by vascular compromise leading to placental insufficiency.^{10,29,30} Direct tumor involvement and occlusion of the umbilical cord has been associated with mid-gestational fetal demise.³¹ Very large tumors may predispose to fetal hydrops either by direct compression of the fetal vasculature or by precipitating high output heart failure through the perfusion demands of the high volume/low resistance tumor vascular bed. Large tumors can also lead to dystocia with fetal or maternal compromise if not detected prenatally.¹⁰

Approximately 25% of infants with prenatal diagnosis of a retroperitoneal mass will have a palpable mass at birth, and 4/5 of this group will ultimately prove to have neuroblastoma. Among patients whose tumors are discovered postnatally, 65% have a palpable mass and the remaining cases are incidental findings on neonatal sonograms obtained for unrelated reasons. Overall, a palpable abdominal mass in the early perinatal period has a greater than 80% probability of being neuroblastoma.³² On occasion, a newborn will present with massive abdominal distension. In such cases, the distension is commonly caused by liver enlargement from hepatic metastases in stage 4 or 4S disease, rather than by the volume of the primary tumor. Such infants may also present with respiratory compromise, skin nodules, or symptoms of anemia secondary to bone marrow involvement. Watery diarrhea caused by a VIP-secreting tumor is a rare presenting symptom in infants with neuroblastoma; however, it is important to keep this diagnosis in mind when treating patients with intractable diarrhea that does not respond to standard therapeutic maneuvers.³³

When elevated, urinary catecholamines are helpful in confirming the diagnosis of neuroblastoma; however, they will be normal in two-thirds of patients with prenatally diagnosed tumors, with a negative predictive power around 70%.^{7,13,32} When all perinatal patients are considered, the sensitivity is 52% with a negative predictive power of 46%.³² ¹²³I methyl iodobenzylguanidine (MIBG) scintigraphy can be useful both for identification of a neuroblastic tumor as well as for detection of metastatic disease. It has a high (>90%) positive predictive value for the presence of a neuroblastoma primary tumor, but its utility is limited by the fact that only 70% of perinatal neuroblastomas are MIBG avid and the negative predictive power is 55%.^{32,34}

Patients with suspected perinatal neuroblastoma should be evaluated for the presence of metastatic disease. Because the liver is the most common site of metastasis, the abdomen should be studied with MRI or CT scanning, which can also be used to look for tumor spread to regional lymph nodes.¹³ Bone marrow aspiration and biopsy are standard means for detecting bone marrow involvement in older children; however, biopsy can be technically difficult in these young infants and alternative methods have been suggested.³⁵ ¹²³I-MIBG and ^{99m}Tc-MDP scintigraphy can be useful in identifying metastatic disease. Although MIBG scanning is more sensitive to the presence of metastatic disease in general, it cannot distinguish between involvement of bone or bone marrow and has a low negative predictive power overall.³² Due to these shortcomings, most patients will require ^{99m}Tc-MDP bone scan to assess cortical bone involvement.³⁶

Clinical staging and biologic prognostic factors

As with tumors in older children, perinatal neuroblastomas are classified according to the International Neuroblastoma

Table 1 INSS stage distribution for perinatal neuroblastoma and all infant cases <1 year of age

| Reference | INSS Stage (%) for Perinatal Cases | | | | |
|---|------------------------------------|----|----|----|----|
| | Stage | | | | |
| | 1 | 2 | 3 | 4 | 4S |
| Acharya et al ¹³ | 67 | 4 | 2 | 5 | 22 |
| Granata et al ⁷ | 76 | 12 | 0 | 0 | 12 |
| Sauvat et al ³² | 87 | 3 | 10 | 0 | 0 |
| INSS Stage (%) for all Infants Cases < 1 Year | | | | | |
| Bernstein et al ³⁹ | 25 | 23 | 12 | 23 | 18 |

Staging System (INSS)³⁷ as well as by sets of biological properties that are associated with favorable or unfavorable prognosis.³⁸ The INSS is a combined clinical/surgical staging system that includes local extension of the tumor, lymph node involvement, extent of resection of the primary tumor, and presence of distant metastatic disease as assessed by diagnostic imaging and bone marrow studies. Localized resectable tumors are either stage 1 or 2, depending on the extent of resection and involvement of ipsilateral lymph nodes. The typical stage 3 tumor is an unresectable midline retroperitoneal mass that involves major vascular structures or a localized tumor with spread to contralateral lymph nodes. Infant neuroblastomas with distant metastases are classified as stage 4S if the primary tumor is consistent with stage 1 or 2, metastatic disease is present only in the liver, skin, and bone marrow, and the marrow involvement is less than 10% of the nucleated cells. All other infants with metastatic disease, ie, those with spread to cortical bone, or with more than minimal bone marrow involvement, are stage 4.

As demonstrated in (Table 1), 90% of patients with perinatal neuroblastoma have stage 1 or 2 tumors. The remaining cases are divided among stage 3, 4S, and 4, although the latter is probably the least common.^{7,13,32} This distribution is clearly different from that of infants as a whole, in which less than half of the tumors are localized and resectable and almost a quarter are stage 4.³⁹ This tendency toward lower stage in the perinatal group probably accounts in part for the improved outcome compared with infants overall.

Most perinatal neuroblastomas have favorable biologic markers. In the three series from the past decade, more than 90% of the tumors have DNA index > 1, which is associated with a better prognosis in infants.^{7,13,32,40} Similarly, less than 5% of perinatal cases have tumors with amplification of the *MYCN* oncogene.^{7,13,32} Furthermore, because *MYCN* amplification does not have as significant an impact on prognosis in patients with localized disease,⁴¹⁻⁴³ it is less important in determining the prognosis in the perinatal neuroblastoma population. Tumor histology, as classified by Shimada and colleagues,⁴⁴ can also be helpful in predicting

outcome; however, greater than 95% of perinatal cases show the undifferentiated, stroma poor, low mitosis-karyorrhexis index histology that is associated with favorable prognosis.^{7,13,32}

Cystic neuroblastoma, that is, any neuroblastoma that contains macroscopic or microscopic cyst(s), is significantly more common in young infants, representing from 23% to 44% of all perinatal neuroblastomas.^{7,13,32} The typical histology is one or more mesothelial cysts, whose walls are composed of fibroblasts, myofibroblasts, collagen, and mucopolysaccharides, surrounded by macroscopic or microscopic collections of neuroblasts.¹⁹ Multiple lines of evidence suggest that cystic neuroblastoma is a particularly benign entity that is likely to stabilize or regress spontaneously. All reported cases of cystic neuroblastoma diagnosed by prenatal ultrasound have been either stage 1 localized tumors or stage 4S disease.^{18,19} The nodular arrangement of neuroblastoma cells adjacent to the cysts is similar to the histology of fetal neuroblastic nodule aggregates and neuroblastoma "in situ."^{2,5} Although there is little evidence that "in situ" neuroblastomas are the precursors of perinatal tumors, the similar histology between the clinically apparent cystic neuroblastomas and the smaller incidental masses suggests that the former group would also have a high rate of spontaneous regression.⁴⁵

Treatment and outcome

A diagnosis of suspected neuroblastoma on antenatal ultrasound should trigger referral to a tertiary center with appropriate expertise in obstetrics, diagnostic imaging, pediatric surgery, neonatology, and oncology. Subsequent sonograms should monitor any changes in the tumor that might aid in the differential diagnosis as well as search for any signs of fetal hydrops. Prenatal care should reflect an awareness of some increased risk for hypertension and/or preeclampsia.¹⁰ Early delivery may be indicated if maternal health is threatened. A late third trimester sonogram is helpful to identify dystocia and need for cesarean section.

Management of an infant with perinatal neuroblastoma is based on INSS stage and consideration of biological prognostic factors. In most cases, neonates with localized primary tumors undergo excisional biopsy, which serves the dual purpose of providing tissue for biological staging, as well as definitive treatment of the mass. Incisional biopsy or partial resection is performed when complete resection of the mass would be associated with a high risk of injury to other vital structures.

The vast majority of these patients will have low stage/low risk disease. Surgical resection alone is adequate primary treatment for these patients and is associated with an event-free survival (EFS) and overall survival (S) of > 91% and > 96%, respectively.^{42,43} Although infants with stage 2 disease have a higher rate of relapse, they can normally be salvaged with moderate intensity chemotherapy and achieve

a good long-term outcome. Infants with stage 3 or 4 disease receive either high or moderate intensity chemotherapy, depending on the presence or absence of *MYCN* amplification. Despite this intensive therapy, infants with stage 4 disease and multiple copies of this oncogene have an overall survival of less than 10%, whereas the survival of the remaining babies approaches that of stage 1 and 2 patients.⁴⁶ Although most neonates with stage 4S disease do not require chemotherapy, those with *MYCN* amplification also require high intensity therapy, and infants with either unfavorable histology or diploid DNA index receive intermediate level treatment. Young infants <3 months with stage 4S disease actually do worse than infants as a whole, with an overall 3-year survival between 71% and 86%, with significant decrements if any negative biological marker is present.⁴⁷⁻⁴⁹

Expectant observation

The excellent outcome of infants with localized, resectable disease, coupled with the observation that some presumed neuroblastomas seen on antenatal imaging have been observed to disappear on subsequent sonograms, has prompted many investigators to consider managing a subset of these patients with expectant observation rather than surgical resection. The rationale for such a strategy is that many small neuroblastoma tumors are likely to regress spontaneously during a period of careful observation, thereby avoiding the need for surgery. Holgersen and colleagues reported a trial of expectant observation on four adrenal masses, two cystic and two solid, originally diagnosed on fetal ultrasound. All four masses resolved spontaneously within 12 weeks after birth. There were no recurrences after 2 to 5 years follow-up.⁴⁵ Size appears to be a reasonable correlate of low stage in infant neuroblastoma; no tumor with an ultrasound-measured volume of less than 32 mL (corresponding to a sphere with a diameter of 3.9 cm) has been reported with INSS stage greater than 1.⁵⁰

The results of population-based screening for neuroblastoma in infants at 6 months of age provide further support for expectant management of perinatal neuroblastomas. Studies performed in both Japan and Canada definitively demonstrated that screening infants for elevated urinary catecholamines increases the total rate of diagnosis of neuroblastoma without decreasing the mortality from advanced-stage disease.^{51,52} The preponderance of masses detected by population-based screening were localized, biologically favorable tumors, leading to the conclusion that stage 1 neuroblastomas in infants are unlikely to progress to the life-threatening advanced-stage disease normally seen in children over 1 year in age.⁵³⁻⁵⁶ In several single-institution trials of expectant observation in patients detected by mass screening, the majority of tumors regressed completely during the observation period, and no patient was up-staged as a result of the nonoperative strategy.⁵⁷⁻⁶⁰ These findings

support the hypothesis that localized neuroblastomas with favorable biological markers, such as small or cystic adrenal masses, can be safely observed with low risk of progression to advanced-stage disease.

The main advantage of expectant observation is that infants whose masses resolve are spared the morbidity of general anesthesia and abdominal surgery. Although no study has specifically investigated the risks of adrenal surgery in young infants, the available literature suggests that there are significant risks associated with resection of adrenal and nonadrenal abdominal neuroblastoma tumors in children under a year of age, with a trend toward higher risk in younger infants.^{61,62} Short-term complications reported with a frequency of 2% or higher include massive hemorrhage (up to 3%), respiratory failure, major vascular injury (4%), intestinal infarction, splenic injury requiring splenectomy, and intussusception. Long-term complications include renal atrophy (up to 10%) and adhesive small bowel obstruction (4%).^{62,63} Infants are also at higher risk of anesthetic complications, with an overall risk of 0.43% and a 0.19% risk of cardiac arrest.⁶⁴ The overall mortality for young infants undergoing adrenal surgery for tumor resection appears to be greater than or equal to 2%. The inherent utility of a therapeutic strategy that avoids major abdominal surgery as the primary therapy is based on decreasing these risks.

Do the benefits of avoiding surgery justify the risks of observing a tumor that is capable of malignant behavior? The potential risks can be divided into potential harm from tumors that continue to grow and/or spread to distant sites and adverse effects of salvage therapy in patients with progressive disease. The 4-year EFS and S rates for all children with stage 1 neuroblastoma in recent studies are in excess of 92% and 96%, respectively,^{42,43} and it is likely that these figures are higher for perinatal cases. Approximately 13% of stage 1 patients under 6 months of age relapse after initial resection.⁴² The salvage rate in this group of patients is in the range of 95% to 97%, although 75% to 90% have traditionally received chemotherapy.^{42,43} Based on these reports, the main disadvantage of an observation strategy is to increase the risk that a stage 1 patient will require salvage chemotherapy for disease progression. If patients on an observation protocol are rapidly referred for surgical resection when there is any reliable evidence of tumor growth, it is unlikely that these children will have a different outcome than the other members of this low risk cohort.

What features indicate a perinatal neuroblastoma for which ongoing observation is no longer safe? Because only a small number of infant neuroblastomas have been studied with expectant observation, there are limited data on the clinical characteristics of biologically unfavorable tumors. The most reliable signs of tumors that are likely to progress to advanced stage are steady growth, increasing urinary catecholamine [vanillylmandelic acid (VMA) and homovanillic acid (HVA)] excretion, and/or inversion of the

urinary VMA/HVA ratio (relative increase in HVA correlates with tumor progression).^{19,53,54,56,65,66} These features can be used to determine which masses should be resected.

The large body of evidence that perinatal neuroblastomas are low risk tumors with a high probability of spontaneous regression prompted the Children's Oncology Group to initiate a prospective, single arm clinical trial of expectant observation for infants with small stage 1 neuroblastomas diagnosed either prenatally or in the first 6 months of life. The central hypothesis of this study is that close biochemical and sonographic observation can safely manage these tumors, with surgical resection reserved for those cases with evidence of continued growth. Parents of all eligible patients are offered the following care: close observation with serial ultrasound imaging and measurement of urinary catecholamine levels. Any increase in tumor volume or catecholamine secretion above a threshold level triggers more frequent surveillance, followed by surgical resection, if growth continues. Parents who prefer that their infant undergo up front surgical resection are asked to allow collection of surgical data and biologic characteristics of the patient and the tumor tissue. It is hoped that this protocol will demonstrate that patients with localized perinatal neuroblastomas as an ultra low risk group who can achieve an excellent outcome without invasive procedures or cytotoxic therapy.

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