Learning objectives

To describe the imaging appearances of fetal neuroblastoma.

To approach differential diagnosis.
Background

Neuroblastoma is the most common malignant tumor found in the neonatal period-arises from precursors of the sympathetic nervous system.

The most common primary site is the retroperitoneum (adrenal gland more often than paraspinal ganglia); less common sites of origin are the posterior mediastinum, pelvis and neck.

The prenatal diagnosis is usually made in the third trimester.

The sonographic appearance may be solid, purely cystic or of mixed echo pattern. The latter is related to necrosis, hemorrhage or spontaneous tumoral involution. Solid masses are more likely to metastasize to the liver. Adrenal hemorrhage often complicates neuroblastoma.

The great majority of these infants have a favorable stage of disease and favorable biologic features (no amplification of N-myc, DNA index > 1).

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.
Findings and procedure details

On ultrasound imaging, fetal adrenal glands have hypoechogenic "cortex" and thin echogenic "medulla" (Fig. 1). Adrenal size increases linearly between 12 and 17 weeks of gestation.

We analyzed retrospectively two cases of fetal neuroblastoma.

**Case 1: a 3-months old female infant**

A fetal magnetic resonance imaging (MRI) revealed a well-defined cystic mass in the retroperitoneum originating from the left adrenal gland.

A series of postnatal ultrasound examinations were performed.

Neuroblastoma markers were negative (serum lactate dehydrogenase, serum non-specific enolase and serum ferritin).

On the fourth postnatal day an abdominal sonogram confirmed the cystic mass (with thin septa) measuring 11x15x16 mm with marginal Doppler signal, located in the left adrenal gland. Hepatic metastases were not seen (Fig 2).

Fetal neuroblastoma involuted in subsequent exams (Fig. 3, Fig. 4 and Fig. 5).

**Case 2: a 5-months old female infant**

A prenatal sonographic examination performed on the third trimester of pregnancy revealed a solid mass in the right posterior mediastinum.

A follow-up sonogram of the female infant 6 days after birth confirmed the 32x23x33 mm mediastinal mass (Fig. 6).

A series of postnatal ultrasound examinations were performed (Fig. 7 - Fig. 12 ).

Serum lactate dehydrogenase, serum ferritin and bone marrow aspirate study were all within normal limits.

Neuron-specific enolase presented moderate serum level.

At 2 months of age a MRI identified liver metastases. Chemotherapy was started.
The follow-up ultrasound performed for the next months showed marked resolution of the nodules in the liver (Fig. 10, Fig. 11 and Fig. 12).

**Differential diagnosis**

**Adrenal hemorrhage** is the most common cause of adrenal mass in the newborn, with an estimated incidence of 1.9/1000 live births. Adrenal hemorrhage has a preference for the right side perhaps due to compression of the gland between the liver and the vertebral column.

The initial sonographic appearance is a hypoechoic cyst that evolves into an area with internal echoes and gradually increasing echogenicity, plus/minus calcifications (Fig. 13, Fig. 14 and Fig. 15).

Distinguishing adrenal hemorrhage from a neuroblastoma is very difficult not only because they have many similar features but also because one of the complications of neuroblastomas is adrenal hemorrhage. Color flow on Doppler sonography will be present in a neuroblastoma but not in a hematoma.

**Wilms' tumor (nephroblastoma)** is the most common abdominal neoplasm in children 1-8 years old. Wilms tumor is a large heterogeneous mass replacing kidney and extending into renal vein and inferior vena cava. May show local invasion or have smooth contour. Calcifications less often seen in Wilms' tumor than in neuroblastoma.

Ultrasonographic findings (similar to CT and MRI): heterogeneous echotexture, large mass, may see local invasion and adenopathy (Fig. 16). Color Doppler is useful to determine tumor thrombus extension versus compression of veins by bulky mass.

The claw sign is useful in determining whether a mass rises from a solid structure (Wilms' tumor) or is located adjacent to it and distorts the outline (neuroblastoma) (Fig. 17).

**Multilocular cystic renal tumor** is a term that encompasses two histologically distinct but grossly indistinguishable lesions: cystic nephroma (CN) and cystic partially differentiated nephroblastoma (CPDN). CN is a segmental, purely cystic mass characterized by multiple septations composed entirely of differentiated tissues. CPDN is also a multiloculated lesion without nodular solid components, but its septa contain embryonal cell.

Imaging cannot distinguish between CN and CPDN. Both tumours are well encapsulated and often large. They are unilateral and involve only one part of the kidney. Often they are located close to the renal pelvis, and herniation of the renal pelvis is a pathognomonic finding on intravenous urography, CT or MRI. They contain multiple non-communicating cysts with thin septa separating the cysts. Cyst fluid can be clear or contain proteinaceous
The differential diagnosis of CN/CPDN includes Wilms' tumor with cystic change, multicystic dysplastic kidney, malignant necrotic and hemorrhagic masses (renal cell carcinoma) and cystic mesoblastic nephroma (Fig. 18).

**Ureteropelvic duplications** is the presence of two separate pelvicaliceal collecting systems in one kidney. Two draining ureters may join above the bladder (partial duplication) or insert into the bladder separately (complete duplication). Most often discovered antenatally or incidentally on imaging studies performed for other reasons.

Associated abnormalities: genital anomalies found in 1/2 of affected females, ureterocele, duplications of bladder, urethra, and genital structures, ureteropelvic junction obstruction is more common in duplicated kidneys (Fig. 19).

**Hepatoblastoma** is a malignant embryonic hepatic tumor composed of epithelial cells, usually present in infancy. The tumor is large, well-defined and heterogeneous (secondary to areas of hemorrhage or necrosis liver mass). Calcifications are present in up to half of the patients. The mass is typically hypervascular on Doppler sonography. Serum alpha-fetoprotein levels are elevated in more than 90% of patients (Fig. 20).

**Embryonal rhabdomyosarcoma (RMS)** is the most common soft tissue sarcoma of the pediatric age group. The head and neck and genitourinary tract are the most frequent location of RMS. RMS of genitourinary system typically affects 2-6 year old children and occurs more often in bladder and pelvic organs than kidneys. RMS of the kidney is extremely rare. There is still a controversy as to whether renal rhabdomyosarcoma is a distinct entity or a variant of nephroblastoma.

Ultrasound is often the first imaging study performed to evaluate urinary symptoms. Solid tumors are typically large and heterogeneous but cystic tumors are multilobulated. Color Doppler is useful in tracing displaced and compressed vessels, vascular invasion is unusual. CT and MRI of abdomino-pelvic are useful in determining the organ of the origin of tumor.

Neurofibromatosis type 1, Li Fraumeni syndrome, Beckwith-Wiedemann and Costello syndromes, and a higher incidence of congenital anomalies (involving the genitourinary and central nervous systems) have been associated with soft-tissue sarcomas. RMS is encountered more frequently in NF1 patients than in the general population (Fig. 21).

Other clinical entities that should be included in the differential diagnosis of fetal neuroblastoma are: subdiaphragmatic extralobar pulmonary sequestration, mesoblastic nephroma, retroperitoneal teratoma, enteric duplication cysts and splenic cysts.
Fig. 1: Normal adrenal glands in neonates.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
Fig. 2: Ultrasound sagital scans showed a cystic mass at the upper pole of left kidney. b) Color-Doppler image showed peripheral vascularity.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
Fig. 3: A repeat sonogram 1 week later showed the same echographic characteristics. Fetal neuroblastoma was slightly decreased in the size (10x14x14 mm).

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
**Fig. 4:** One month later- complete involution of cyst (7,5x12 mm). Medial arm of the left adrenal gland was thick.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
**Fig. 5:** At last follow-up (6-months later) the patient was doing well; the medial arm of the left adrenal gland measured 4.5x11 mm.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
Fig. 6: Ultrasound axial and longitudinal scans showed a vascularized, well-defined solid mass with calcifications located within right posterior mediastinum.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
Fig. 7: Ultrasound scans revealed a slightly increase in the size: 34x39x45 mm.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
Fig. 8: On subsequent scans, the tumor had displaced the inferior vena cava anteriorly

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
Fig. 9: A repeat sonogram showed a gradually increase in size (42x35x50 mm). Minimal right pleural effusion

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
Fig. 10: a) At 3 months of age sonogram scan (after chemotherapy started) showed diffuse metastatic lesions (hypoechoic nodules) in the liver measuring 9 mm. b) Neuroblastoma decreased in the size (32x27x44 mm).

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
**Fig. 11:** a) A follow-up sonogram showed regression of mediastinal tumor (23x15x21 mm). b) The metastatic nodules in the liver decreased.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
Fig. 12: At 5 months of age, the child’s sonogram showed an incomplete regression of mediastinal tumor (13x13x22 mm) with some small calcifications. The metastatic nodules in the liver measured 5/3 mm.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
Fig. 13: 2-weeks old male infant. a) Ultrasound scans revealed a well-defined mass (25x20x15 mm) at the upper pole of the right kidney. The mass had a cystic/solid combination with microcalcifications. b) Color-Doppler signal was absent. Inferior vena cava was not invaded. The right suprarenal was not identified.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
**Fig. 14:** A coronal magnetic resonance image revealed a T2 hyperintense lesion in the right suprarenal location-hematoma.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
Fig. 15: A follow-up sonogram showed a complete resorption of the hematoma.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
**Fig. 16:** A 2-years old infant female. a), b) Ultrasound scans showed a heterogeneous, large mass arising from the right kidney. c) A contrast enhanced Computer Tomography showed a large poor enhancing Wilms’ tumor in the right flank.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
**Fig. 17:** A 2-and-a-half old years infant male. Ultrasound scans showed a heterogeneous echotexture, large mass arising from the left kidney. Note the claw sign (concavity of the renal contour with renal parenchyma cupping the tumor)-blue arrow.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
**Fig. 18:** 6-months old male infant. Renal ultrasound scans showed a large, multiloculated mass at the lower pole of the right kidney. Post surgery, pathological diagnosis was cystic Wilms’ tumor.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
Fig. 19: 1-week old female infant. a) Longitudinal scan of the right kidney - dilatation of the upper collecting system. b) Longitudinal view of the urinary bladder- ureterocele. Urine culture showed urinary tract infection.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
**Fig. 20:** A six years-old female infant. Ultrasound scans showed a large, multinodular mass in the right lobe measuring 110x100x90 mm with heterogeneous echogenicity. The left hepatic vein was normal. The middle hepatic vein was embedded. The right hepatic vein was compressed. The main portal vein and its left branch showed normal flow. The right portal vein was normal in its distal segment and embedded in its proximal segment. The gallbladder was embedded too.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
Fig. 21: A 4-years old male infant with neurofibromatosis type 1. Ultrasound scans showed a large retroperitoneal mass. Histologic diagnosis: embryonal rhabdomyosarcoma.

© References: Department of Radiology, 3rd Pediatric Clinic, Cluj-Napoca.
Conclusion

The ultrasound is essential in the detection and follow-up of fetal neuroblastoma. Fetal MRI is an important adjunct to prenatal sonography.

Fetal neuroblastoma has an excellent prognosis.
References


Houlihan C., Jampolsky M., Shilad A.-Prenatal Diagnosis of Neuroblastoma with Sonography and Magnetic Resonance Imaging, J Ultrasound Med, 2004; 23:547-550


