What do we know about nephroblastomatosis? Imaging in diagnosis and follow-up.

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Learning objectives

To review the genetics, histology, and imaging of nephroblastomatosis in its diverse clinical presentations. To review the relationship between nephroblastomatosis and Wilms tumor. To discuss the current roles of different imaging techniques in the diagnosis and follow-up of nephroblastomatosis. To be aware of how findings in our day-to-day experience can differ from the classically established findings reported in the literature.

Background

Nephroblastomatosis has a low prevalence; thus, few reports discuss it. Beckwith et al. reviewed the nephroblastomatosis complex and proposed a new terminology and classification. They defined the concept of "nephrogenic rest" as a focus of abnormal nephrogenic cells persisting beyond 36 weeks' gestation that can be induced to form a nephroblastoma. Nephrogenic rests are found in 1% of autopsies on newborn babies. These authors classify nephrogenic rests into perilobar or intralobar on the basis of their relation with the renal lobar topography (Fig. 1, Fig. 2). Nephroblastomatosis is defined as the diffuse or multifocal presence of hyperplastic nephrogenic rests and is classified into perilobar, intralobar, combined, and universal.

Beckwith reported a 41% association between Wilms tumor and nephrogenic rests. Intralobar rests (less common) imply a disruption earlier in development and are more likely to transform into a nephroblastoma; the risk of a metachronous contralateral tumor is increased in cases with intralobar rests associated to Wilms tumor. In synchronous bilateral Wilms tumor, the incidence of nephrogenic rests is about 99%, with perilobar rests being twice as common as intralobar rests. These rests can be found in different dynamic stages; some disappear, others regress and sclerose, whereas others have hyperplastic growth, sometimes undergoing malignant transformation.

The pathogenesis of Wilms tumor is complex and multifactorial. Although nephrogenic rests are a predisposing condition for the development of Wilms tumor, not all kidneys with nephrogenic rests develop Wilms tumor. For example, among kidneys removed for Wilms tumor, more than 40% contained nephrogenic rests outside the area of the tumor.

Genetic aspects.

Syndromes that predispose to Wilms tumor.
Current models of Wilms tumor development propose a genetic mutation that predisposes to nephrogenic rests. As stated above, these rests can be intralobar, perilobar, or diffusely distributed.

Intralobar nephrogenic rests (lesions in the renal lobe, in the renal sinus, or in the walls of the calyces) are associated with WAGR syndrome and Denys-Drash syndrome.

Perilobar nephrogenic rests (multiple lesions in the periphery of the renal lobe) is associated with Beckwith-Wiedemann syndrome and hemihypertrophy.

Nevertheless, the association between the type of nephrogenic rest and the predisposing syndrome is not absolute.

**Causes.**

1. Germ-line mutations of the WT1 gene are responsible for about 10% to 15% of Wilms tumors.

   - These mutations of the WT1 gene can give rise to an isolated Wilms tumor (i.e., Wilms tumor without evidence of an underlying syndrome).

   - These mutations of the WT1 gene can also give rise to Wilms tumor in the context of WAGR, Denys-Drash, or Frasier syndromes.

2. Epigenetic and genetic alterations in chromosome 11p15 give rise to Beckwith-Wiedemann syndrome.

3. Other genes predispose to familial Wilms tumor.

   **A. Causes due to defects in WT1 in the context of syndromes.**

   - **WAGR syndrome** (Wilms tumor, Aniridia, Genitourinary anomalies, mental Retardation) is caused by a deletion in chromosome band 11p13, which includes both PAX6 and WT1. The aniridia is due to the elimination of PAX6, which is found 0.6 Mb from WT1. In an individual with isolated aniridia, it is mandatory to rule out the risk of Wilms tumor: if the genetic study shows the integrity of the WT gene, the risk is the same as in the general population.
In WAGR syndrome, Wilms tumor presents earlier and is usually bilateral. These patients have a high incidence of intralobar nephrogenic rests and tumors with a favorable histology.

- Most patients with **Denys-Drash syndrome** have a mutation in exon 8 or 9 of WT1; in individuals with a 46,XY karyotype, this results in gonadal dysgenesis (from ambiguous to apparently female external appearance) and diffuse mesangial sclerosis that leads to renal failure and to Wilms tumor: the risk for Wilms tumor is 90%.

- **Frasier syndrome** is caused by point mutations in intron 9 of WT1; in individuals with a 46,XY karyotype, this results in gonadal dysgenesis, segmental and focal glomerulosclerosis, and gonadoblastoma. Although Frasier syndrome is not typically associated with Wilms tumor, several cases of Wilms tumor in the context of Frasier syndrome have been reported. These reports, together with reports of gonadoblastoma in individuals with Denys-Drash syndrome, have led to the suggestion that these two syndromes might represent different extremes of a phenotypic spectrum.

- **Genitourinary anomalies without renal failure.** Other mutations in WT1 give rise to genitourinary anomalies and Wilms tumor.

**B. Causes due to defects in 11p15 in the context of syndromes.**

- **Beckwith-Wiedemann and hemihypertrophy.** In the context of Beckwith-Wiedemann syndrome, the risk of developing Wilms tumor is approximately 5%. Paternal uniparental disomy of 11p15 or increased methylation in IC1 is associated with increased risk for Wilms tumor and hepatoblastoma.

In over 80% of individuals with Beckwith-Wiedemann syndrome, molecular genetic testing detects one of the following five alterations:
- Loss of IC2 methylation in the maternal chromosome.
- Increased IC1methylation in the maternal chromosome.
- Mutation of the maternal allele CDKN1C.
- Paternal uniparental disomy of 11p15.5.
- Duplication, inversion, or displacement involving the p15.5 band of chromosome 11.

**C. Other syndromes associated with Wilms tumor.**

- Autosomal dominant disorders:
  - Li-Fraumeni syndrome.
• Sotos syndrome.
• Hyperparathyroidism-jaw tumor syndrome (gen CDC73).
• Neurofibromatosis type 1.

- Autosomal recessive disorders:

• Fanconi anemia.
• Bloom syndrome.

- Linked to the X chromosome;

• Simpson-Golabi-Behmel syndrome.

- Perlman syndrome.

- Trisomy 18.

Images for this section:
Fig. 1: Intralobar nephrogenic rests. Photomicrograph (original magnification, x100; H-E stain) shows immature epithelial tubules (arrows) and normal glomeruli (curved arrows) with interspersed immature epithelial tubules of intralobar nephrogenic rests.

Fig. 2: Perilobar nephrogenic rests. Photomicrograph (original magnification, x75; H-E stain) shows clusters of purple-staining cells, representing blastema of perilobar nephrogenic rests, arranged in nests at the periphery of the renal cortex (arrows)
Imaging findings OR Procedure details

Classically, the nephrogenic rests remain occult until they are discovered incidentally on imaging tests (MRI, CT, or US)\textsuperscript{3,5,9,10} or are found in conjunction with Wilms tumor during surgery. Diffuse nephroblastomatosis sometimes manifests as unilateral or bilateral palpable masses that are generally discovered at physical examination in the first year of life.

The US appearance of nephroblastomatosis varies from diffuse enlargement of both kidneys with areas of subtle changes in echogenicity and echostructure that alter the differentiation of the cortex from the medulla, in some cases with a small mass effect, that are occasionally difficult to see to hypo-, iso-, or hyper-echoic masses surrounding both kidneys, as typically occurs in perilobar nephroblastomatosis.

On CT and on voiding urography, the abnormal tissue enhances slightly and homogeneously (in comparison to the intense enhancement of the normal renal parenchyma). **Diffuse nephroblastomatosis can be impossible to distinguish from autosomal recessive polycystic kidney disease, leukemia, or lymphoma.**

On MRI\textsuperscript{10}, these lesions are typically hypointense compared to the renal cortex in T1-weighted sequences and iso- or slightly hyper-intense in T2-weighted sequences, with mild enhancement after contrast administration; small superficial plaques of nephroblastomatosis can be imperceptible and difficult to differentiate from renal lymphoma.

Note that the table 1 shows the commonly accepted classification and the appearance of nephrogenic rests on different imaging techniques.

However, even so, in our experience we have seen that children with WAGR (in whom intralobar rests are more common) can have perilobar rests. Moreover, these perilobar rests can also be associated to renal alterations like calyceal diverticula that can be the first sign of concomitant alterations in the renal parenchyma; these alterations might not be seen at first on US studies, for example. The patient developed a Wilms tumor when he was 18 months old.

**In this case, neither the perilobar nephrogenic rests nor the presence of calyceal diverticula had been reported in the context of WAGR syndrome.**
These findings underline the fact that the association between the type of nephrogenic rest and the predisposing syndrome is not absolute and the need for detailed examination of all the regions, regardless of the syndrome the patient has.

A common approach to the radiological management of nephroblastomatosis is **US follow-up every 3 to 4 months until the age of 7 years** (no cases of malignant transformation have been reported after this age)\(^4\); **if an increase in the size or number of lesions is seen, MRI and/or CT examination should be considered.**

**MRI** is the most sensitive technique for foci of nephroblastomatosis; thus, in patients with syndromes that involve a very high risk, such as WAGR or Denys-Drash syndromes, MRI examination should be considered from the start.

**The treatment of nephroblastomatosis is controversial.** The risk of transformation to a Wilms tumor is somewhat greater in nephroblastomatosis due to the greater number of cells with a risk of malignant transformation. As a general rule, treatment should be tailored to the individual patient, and periodic imaging tests are very useful for planning an appropriate treatment strategy and avoiding the unnecessary resection of benign rests.

Likewise, the use of neoadjuvant chemotherapy\(^6\) is controversial because:

1) The chemotherapy is aimed at a benign process that usually regresses spontaneously (about 70%); 2) the final outcome is uncertain because chemotherapy does not totally prevent neoplastic growth; 3) chemotherapy can potentially damage healthy cells, because it might be more active against healthy cells than against the nodules in nephroblastomatosis; 4) the effects may be only temporary because the lesions can become smaller but not disappear "remaining dormant".

**Images for this section:**
Fig. 3: Diffuse nephroblastomatosis. Child with flank mass and hemihypertrophy. Nephroblastomatosis foci (yellow arrows). The surface of the kidney may reveal lobations.
Fig. 4: Child with WAGR syndrome. Calyceal diverticula (yellow arrows). Kidneys with NB often have concomitant cystic and dysplastic malformations of the renal cortex, adding to the difficulty of diagnosis by IVU or US.
Fig. 5: MRI. T2-weighted sequences. Calyceal diverticula (yellow arrow).
Fig. 6: MRI. Enhanced T1-weighted sequences. The foci of NB (nephroblastomatosis) were well shown on Gd-DTPA enhanced T1 weighted spin echo sequence, as non-
enhancing lesions (yellow arrow), whereas the lesions were not detectable in native T1 and T2 weighted MR scans.
Fig. 7: MRI. Gd-DTPA enhanced T1 weighted sequence (delayed phase). Perilobar non-enhancing lesions (yellow arrows) in child with WAGR syndrome.
**Fig. 8:** MRI. Gd-DTPA enhanced T1 weighted sequence (excretory phase). Calyceal diverticula (green arrow).
**Fig. 9:** Abdominal radiography. Right flank mass displacing abdominal structures. This child did not make all controls (comes a year later).

**Fig. 10:** Child with WAGR syndrome. The patient developed a Wilms tumor when he was 18 months old. At US, the mass has heterogeneous echogenicity, which represents hemorrhage and necrosis.
Fig. 11: CT demonstrates the heterogeneous mass, as well as areas of hemorrhage and necrosis. Intravenous administration of contrast material is mandatory to detect nodal or hepatic metastases, tumor extension into the renal vein or inferior vena cava, contralateral synchronous tumor, and associated nephrogenic rests. Imaging findings of Wilms tumor vary depending on the amount of necrosis, hemorrhage, calcification, fat, and cystlike formation present; however, a well-defined solid mass with a pseudocapsule usually is seen.
Fig. 12: MRI. Gd-DTPA enhanced T1 weighted sequence (delayed phase). Bilateral perilobar non-enhancing lesions (yellow and red arrows) in child with WAGR syndrome.
Fig. 13: Enhanced CT. The perilobar foci of nephroblastomatosis (see Fig. 12) have become a bilateral Wilms tumor in child with WAGR syndrome. In synchronous bilateral Wilms tumor, the incidence of nephrogenic rests is about 99%, with perilobar rests being twice as common as intralobar rests.

<table>
<thead>
<tr>
<th>Type*</th>
<th>Plain/IVU</th>
<th>US**</th>
<th>CT***</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial</td>
<td>N</td>
<td>N/small peripheral masses,</td>
<td>Non-enhancing peripheral lesions</td>
<td>Multiplanar excellent</td>
</tr>
<tr>
<td>Multifocal</td>
<td></td>
<td>usually hypoechoic</td>
<td></td>
<td>Contrast resolution</td>
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<tr>
<td>(Perilobar)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>Size increases,</td>
<td>Size increases</td>
<td>Size increases</td>
<td>Multiplanar view of the same</td>
</tr>
<tr>
<td>Diffuse</td>
<td>Increase parenchymal thickness</td>
<td>peripheral hypoechoic rim</td>
<td>Peripheral non-enhancing confluent</td>
<td>(post-gadolinium)</td>
</tr>
<tr>
<td>(Perilobar)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Deep</td>
<td>N/underlying calyx may show mass effect</td>
<td>N/small, deep irregular mass</td>
<td>Non-enhancing irregular mass deep within parenchyma</td>
<td>Multiplanar view of the same</td>
</tr>
<tr>
<td>(Intralobar)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Generalised</td>
<td>Large kidneys stretching and splaying of calyces</td>
<td>Usually hypoechoic size increases (bilaterally)</td>
<td>Size increases (bilaterally) very little of collecting system seen or non-functional</td>
<td>Multiplanar view</td>
</tr>
<tr>
<td>(Pulmonary)</td>
<td></td>
<td></td>
<td></td>
<td>Quantification of normal residual</td>
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Conclusion

It is important to know the repercussions of nephroblastomatosis as a precursor of Wilms tumor and to be aware of the roles that different imaging techniques (US, CT, and MRI) play in the diagnosis of these conditions.

Importantly, not all foci of nephroblastomatosis will give rise to a Wilms tumor. Nevertheless, we believe that all patients with increased risk of developing a Wilms tumor (like those with WAGR or Denys-Drash syndromes) should undergo an initial MRI examination to detect nephroblastomatosis, bearing in mind that the association between the type of nephrogenic rest and the predisposing syndrome is not absolute. In patients with a lower risk, like those with Beckwith-Wiedemann syndrome, US follow-up is sufficient.

Personal Information

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References


