**Neuroblastoma versus Wilm’s Tumor by Prof. BaHakim:**

**Introduction in brief about abdominal masses in children**

* Although most of abdominal masses in infants and children are benign, the finding of an abdominal mass should be taken very seriously.
* A complete history, meticulous physical exam, consultation with a pediatric oncologist and specific radiological studies like ultra sound, CT scan and/or MRI should be carried out.
* Some hints helpful for diagnosis will be there such as the age of the child and location of the tumor, and some abnormal physical findings might be their in association with the tumor (like those abnormal findings found in 20% of children with Wilm’s tumor)
* Here are examples of hints:

1. Most of abdominal masses in a neonate are benign and most are related to urinary treat or G.I. treat like: Hydronephrosis, fecal (materials, full bladder due to obstruction multicystic kidney, polycystic kidneys, mesoblastic nephroma, renal vein thrombosis, pyloric stenosis, intestinal duplication.

* Here are examples of malignant abdominal masses in relation to age:
  + In neonate and infants up to one year of age: Neuroblastoma, Wilm’s, hepatoblastoma, sarcoma, etc.
  + In infants and young children (1 - 3 years): Neuroblastoma, Wilm’s, hepatobl, rhabdomyosarcoma.
  + Children 3 - 11 years: Neuroblastoma, Wilm’s, lymphoma.
* Here are signs and symptoms and abnormal physical findings and associations which are important in differentiating Wilm’s tumor Neuroblastoma:

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| **Neuroblastoma (adrenal medulla)** | **Wilm’s tumor (renal tissue)** |
| Patient is irritable and chronically sick (skin on bones). Irritable due to metastasis to bones which is not visible but very painful and mimicking bone fracture. | The patient looks happy, healthy and not irritable (The disease does not metastasize to the bone), and no loss of weight. |
| Some may have fever and intermittent watery diarrhea because of vasoactive intestinal peptide (VIP) production. VIP induces secretory diarrhea, which might contribute weight loss. | No diarrhea because there is no VIP production. |
| On physical examination: the mass is irregular, nodular and easily palpable (superficial palpation is enough for its detection). In 75% of the cases the mass crosses the midline meaning that both ipsilateral and contralateral lymph nodes are involved, which makes it stage 3. | Regular, smooth upon palpation. The mass never crosses the midline, unless in neglected cases (like stage 4).  Frequent or vigorous palpation might lead to mass rupture leading to its dissemination (because the mass is very fragile). |
| No congenital skeletal deformities, but maybe associated with neurofibromatosis (café au lait spots), and hirschsprung disease. | It is associated with congenital abnormalities (20%): skeletal deformities, undescended testis, hypospadius or hemi hypertrophy of extremities or of body or of the face hypospadius. |
| Anemia is due to the invasion of blasts to the bone marrow or due to chronic disease. | Chronic microscopic hematuria (25%), which does not lead to anemia (in adults RCC causes gross hematuria leading to anemia). On the other hand, many of them have polycythemia due to the secretion of erythropoietin by the tumor. |
| Episodic secretion of norepinephrine leads to episodic transient increase in blood pressure. | 25% of the cases will have continuous elevation of blood pressure. |
| Almost always unilateral in a few of cases. | Bilateral in some. |
| History of mother’s phenytoin ingestion is interesting. | Familial there is often a family history of renal disease. |
| Both are associated with familial and genetic mutations. | |

Note the following facts:

1. Malignant abdominal Masses which present in the majority of cases during infancy and before 3 - 4 years of age include: Wilm’s tumor, neuroblastoma (which is the most common intraabdominal maligncot tumor during the first year of life), also khabdomyosaecoma, and other tumors.
2. Babies are born with Neuroblastoma Or Wilm’s and both these tumors might not be palpable during the first few- to- 6 months of life. Then later in time the mothers will discover the tumor and will bring the baby to the pediatrician.
3. Most of these babies had already come to pediatricians in OPD and in ER for the usual minor illnesses or for checkups or for vaccines while the mass was in the abdominal. This might bring a serious question about why the tumor was not detected? By deep palpation of abdomen?

* Neuroblastoma is very aggressive and is often discovered at an advanced stage and needs chemotherapy, radiotherapy and multiple surgeries. It has a poor prognosis, because more than 70% of the cases present with metastasis 80% might die, 20% might survive but with severe side effects of chemotherapy and radiotherapy.
* Wilm’s has good prognosis because majority have differentiated histology and majority don’t present with metastasis and the disease starts as malformation kidney tissue.
* Investigation (in order of importance):

1. CT scan with contrast: it can show Neuroblastoma and Wilm’s. In neuroblastoma the kidney will be healthy but only displaced with no anatomical distortion (the calcyeal system and the kidney’s structure is normal).
2. Histology is diagnostic in both Neuroblastoma and Wilm’s, but it’s only prognostic in Wilm’s. Very few cases of Wilm’s are anaplastic, but majority have favorable histology
3. 24 hours urine collection: will show high VA and VMA in 90 % of Neuroblastoma patients.
4. Bone scans to check for bone metastasis.
5. MIBG (iodine) I131 is excellent investigation because it’s taken by tumor cells any where in the body even if it was very small metastasis.
6. In case of Neuroblastoma, it is indicated to do bilateral Bone Marrow biopsy to discover neuroblasts, which are arranged rosettes.

* Respiratory distress can be a complication of both Neuroblastoma and Wilm’s. In Wilm’s, it’s due to lung metastasis (sclerotic parenchymal invasion- called Cannon ball- that is usually resistant to chemotherapy and might require surgical removal and is a bad prognostic factor (stage 4). While in Neuroblastoma, the resp. distress is due to the huge mass compressing the diaphragm.
  + If there was any respiratory symptom it’s more suggestive of Wilm’s, and you need to do CXR and chest CT scan to check for parenchymal mets, whereas in NB it does not invade the parenchyma.
* Both metastasize to the liver.
* Wilm’s does not metastasize to the bone marrow.
* Neuroblastoma rarely goes to the brain.
  + 2% of Wilm’s have brain metastasis.
  + If the child has ataxia, nystagmus, and abdominal mass, it’s most likely that the mass is Neuroblastoma and in this case there is a good prognosis because it is not the tumor that spread to the brain but the IgG formed against the tumor and crossed the BBB, which mean patient has a better immunity. The IgG indicates that the child is using his immunity against neuroblastoma.
* Rosette cells are found in neuroblastoma, medulloblastoma and retinoblastoma if they invade the BM.

**Bleeding disorders**

* It can be caused by

1. Platelets decrease in number or by platelet dysfunction that results in petechiae.
2. Coagulation protein deficiency, which usually results in ecchymosis. It can also be caused by vasculopathy, vasculitis that are very rare in children.

* In cases of bleeding, start with taking history about the child bleeds, and ask about family history (history of prolonged bleeding in parents and in siblings and uncles, history of heavy menstruation); if the bleeding is spontaneous or not; and assess the severity including the early age of onset (how early the child bled e.g. after circumcision).
* Note the following facts:

1. Regarding the extrinsic pathway and in the absence of liver disease and vitamin K deficiency and DIC, then the reason for bleeding in child might be due to factor 7 deficiency. The deficiency will be detected by abnormal (prolonged) PT only. The PTT will be normal.
2. Regarding the intrinsic pathway defects: we think of factor 8 (more common) and 9 deficiency (11, 12 can also be affected but these two are very rare and aren’t worrisome). These will be reflected as an increase in APTT while other parameters are normal (PT is normal).

* The coagulation profile is considered prolonged if there is more than 4 seconds difference between the control and test, also note that PTT is the test to detect VW disease.
* Hemophilia is an X-linked disease, seen in males, while females are carriers. Hemophilia (intrinsic pathway disorder, factor VIII antigen (molecule) is normal but with defective function) is the most problematic in pediatric age group (increase in APTT).
* If a mother has 2 children with hemophilia or one child and one brother with hemophilia, then the mother might be obligate carrier but she needs to be tested by genes.
* You need to do genetic analysis to know if the mother is a carrier or not because 25% of mutations are spontaneous.
* The severity depends on the functioning amount. That is the percentage of the factor that functions in coagulation. For example, if only 1% of the factor functions then the disease is severe, and 1-5% is moderate disease, and more than 5% will have mild disease.
* In the common pathway disorders, factor I (fibrinogen), II (prothrombin), V and X will be affected causing an increase in both PT and APTT.
* If a patient came bleeding and had a normal PT (factor VII is normal); normal APTT (factor VIII and IX are normal); platelet count and function are normal; then think about factor XIII deficiency. Factor XIII function isn’t measured by PT or PTT, it’s the only one that isn’t measured by coagulation profile. It is tested by a clot-dissolving test (adding urea or acetoacetic acid (weak acids), if the clot dissolves, then there is factor XIII deficiency). After the clot-dissolving test that is suggestive for factor XIII deficiency, ask for factor XIII assay (measure of function).
* Case: a 4-5 year old child that have never bled before came with ecchymosis on both tibias (only site of ecchymosis). There is no need to do any further investigation because it’s localized to the tibia (traumatic).
* In anti-phospholipid syndrome (lupus anticoagulant): the coagulation profile shows a normal PT, and significantly prolonged APTT. Because most phospholipids acts on the intrinsic factors and Von Willebrand factor with a recent history of viral infection, then the child’s IgG might cross-react against phospholipid (coated by IgG). After any surgery, watch the child for thrombosis and prevent it by early mobilization and hydration. If the IgG cross-react with RBC causing hemolytic anemia it will result in ITP.
* Some children are referred by surgeon to hemotology clinic because of prolonged PTT. The child may need to undergo tonsillectomy but the surgery is cancelled or postponed because of pre-op screening tests showing prolonged PTT. But the history shows no past history of bleeding and family history shows no history of bleeding either. The hematologist will ask the lab to look for antiphospholipid antibody (IgG) by using mixing study. In the lab, the blood of the patient will be mixed with all the coagulation profile including Factors 8, 9, 11, 12, etc.
* If the PTT is done but still prolonged. This means that the patient doesn’t have any factor deficiency because all those factors were added to the blood of the patient but they didn’t correct the PTT. Then the blood will be tested for antibody like IgG while intrinsic pathway. The IgG is against phospholipid molecules, which are found in the platelet and also found in some factors.
* Conditions: the child can undergo surgery and will not have complications of bleeding