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Congenital Neuroblastoma

Neuroblastoma (NB) is the most frequent occurring malignant tumor in the newborn and early infancy. Almost one-fourth of congenital malignant tumors are neuroblastoma. NB is an embryonal malignancy composed of immature cells of the nervous system (sympathogonia) derived from primordial neural crest cells which gives rise to the sympathetic ganglia and the adrenal medulla. More than 90% of NB develop in children aged under five years, with the peak of the disease during the first year of life. In general, infants younger that one year have favorable outcomes, with spontaneous regression of the tumor, whereas children older than 18 months require extensive chemotherapy and treatment. Congenital NB is defined as a NB found within the first month of age. Approximately 20% of cases are diagnosed antenatally, while 16% are diagnosed in the first month of life. Approximately 75% of NB tumors are localized to the adrenal gland, with more than half in the right adrenal gland. Fetal ultrasound has increased the antenatal detection of neuroblastoma. NB can be identified as early as 23 weeks of gestation by US. Though most are seen as solid masses, an unique variant that occurs in the perinatal period is called cystic NB (40% of congenital NB), which is characterized by one or more macroscopic or microscopic cysts within the tumor. This unique variant is benign and can regress spontaneously like other NB that develop in infancy. In addition, this variant has a decreased incidence of metastasis and lower tumor marker levels. Congenital NB usually have normal MYCN copies and even abnormal copy numbers do not have a substantial effect on prognosis in the setting of a localized tumor. A noninvasive diagnostic workup with ultrasound, urine catecholamine level and MIBG scintigraphy can lead to an accurate diagnosis of perinatal NB. NB are heterogenous solid lesions, mostly echogenic, calcification is common, either coarse as focal echogenic areas with usually no distal acoustic shadowing, or fine resulting in diffusely increased echogenicity of the tumor. On CT, NB present as large, heterogenous, lobulated soft-tissue masses that show heterogenous or little enhancement. Coarse, finely stippled, or curvilinear calcifications are seen in 85% of abdominal and 50% of thoracic NB on CT. Low attenuation areas seen within the tumor represent pseudo-necrosis or hemorrhage. Encasement a/o or compression of major abdominal vessels can also be seen. The most common clinical presentation of a neonate born with a NB is a palpable abdominal mass The abdominal mass may occur due to metastasis to liver (hepatomegaly). Masses in the neck, chest and head can also occur. Skin lesions described as blueberry muffin spots are suggestive of disseminated disease. Almost 60% of infants with NB have metastatic disease at presentation. Metastases occur via bloodstream and lymphatics with common sites including liver, skeleton, bone marrow and skin. Compression of the renal artery by the

tumor can activate the renin-angiotensin-aldosterone axis and lead to hypertension in the baby. Hypertension and tachycardia can also result from cathecolamines release from the NB. Maternal hypertension and other symptoms have been reported in some cases of fetal congenital neuroblastoma secondary to catecholamines secretion by the tumor. NB is the most common malignancy to involve the placenta. Microscopically the congenital malignant tumors cells are usually confined to the villous capillaries of the fetal circulation occupying the intervillous space of the maternal vascular system. Microscopically, NB is composed mainly of small, rounded blue cells with small rounded or oval nuclei surrounded by a rim of cytoplasm. The presence of delicate nerve fibers is pathognomonic diagnostic sign. NB Stage 4S (the `S' stands for special) is defined as metastatic NB presenting in infants aged less than 12 months, with metastasis limited to skin, liver, and bone marrow (<10% of bone marrow involvement). It is also classified as Stage MS if it occurs in the perinatal period. Patients with localized disease, Stage 4S or Stage MS disease without life-threatening symptoms or adverse genetic features (MYCN amplification or segmental chromosomal abnormalities) carry low risk with most going through spontaneous regression, hence they usually require no treatment. Approximately 90% of perinatal NB have a good prognosis, because the majority of tumors are stage 1 or 2 by the International NB Staging system. Spontaneous regression usually occurs if there are no MYCN amplifications, no loss of chromosome 1p, and near triploid number of chromosomes. Adverse outcomes are highly associated with more than 10 MYCN oncogene copies. Perinatal NB with stage 1, solid with less than 3 cm size, or cystic tumor less than 5 cm can be observed without biopsy. Stage MS or 4S with massive liver enlargement and resultant respiratory and cardiovascular symptoms may require intervention with low dose chemotherapy or radiotherapy. 10% of infants will have stage 4 or stage 4S disease with MYCN amplification and an associated poor prognosis. With only surgery, a younger infant (< 6 months) with localized disease and favorable biology has even better outcome.

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Ureterocele

Ureterocele are cystic dilatations of the intravesical submucosal ureter. With an incidence of one in 4000 live births, they occur more often in Caucasians and 4-6 times more frequent in females. Ureteroceles are classified as simple (intravesical, orthotopic) or ectopic (extravesical) according to the location of the ureteral orifice, with simple being in the

bladder trigone, and ectopic ureterocele in the bladder neck or posterior urethra. Also, ureteroceles are classified as single system ureterocele when there is a normal kidney with only one ureter, or duplex system ureterocele when associated with complete ureteral and renal duplication. The kidney that drains to the ureterocele is frequently hydronephrotic and dysplastic since some degree of obstruction can occur. The bladder can also be obstructed when the ureterocele protrudes into the urethra. Vesicoureteral reflux is frequently associated with an ureterocele. Associated anatomic and pathophysiologic features of ureteroceles in duplex systems include intravesical ureteral obstruction, dysplasia, or obstructive nephropathy of the ureterocele-associated moiety (40-70%), and vesicoureteral reflux (VUR) to the ipsilateral inferior moiety (50%) or contralateral kidney (25%). Presentation of ureterocele can be symptomatic with an infectious process, or asymptomatic with hydronephrosis findings. Recurrent urinary tract infection is the most common presentation at birth. If left untreated, children can develop stone, pyonephrosis, urosepsis, spontaneous rupture of the ureterocele, and even chronic renal failure. Most cases are diagnosed prenatally. The diagnosis of an ureterocele can be performed prenatally in 75% of cases. On prenatal ultrasound the ureterocele presents as a cyst inside the bladder and can be suspected if the fetus shows the presence of two separated noncommunicating renal pelvis and a dilated ureter. The thin wall anechogenic image inside the bladder is known as the "Foley sign". Sometimes the ureterocele can occlude or even protrude through the urethra and a clinical picture of megacystis, bilateral hydronephrosis and oligohydramnios can occur. Prenatal diagnosis of ureterocele improves postnatal outcome, specifically less urinary tract infection and less need for reoperation. Prenatal therapy including ultrasound guided percutaneous drainage, laser treatment or fetoscopy with in utero incision of the ureterocele can be offered in cases of impending renal damage. All prenatally ureteroceles should be referred to pediatric urologist to program postnatal therapy, institute adequate prophylaxis and prevent renal damage. Most ureterocele are associated with complete ureteral and renal duplication systems. The goals of management of ureteroceles include decompression of obstruction, avoiding vesicoureteral reflux, preventing urinary tract infections, promotion of continence, preservation of renal function, and minimizing the number and invasiveness of surgical procedures. Ideal candidate for a conservative management approach to ureterocele include asymptomatic, good, or absent function in ureterocele moiety, absence of grade 3 or 4 VUR, absence of inferior moiety obstruction by scintigraphy, and absence of bladder outlet obstruction. Management of ureterocele might include observation, endoscopic, upper pole nephrectomy, lower tract reconstruction and total nephroureterectomy. Transurethral endoscopic decompression (deroofing, wide excision, single puncture, double puncture) treatment is a widely used treatment. Endoscopic puncture is simple, minimally invasive and can be performed outpatient. Children with a single intravesical ureterocele benefit the most from endoscopic incision. Some have shown that a generous vertical incision along the entire extent of the ureterocele with a period of double J stenting is successful in draining obstructed cases. The use of double J stent appears to reduce the rates of re-stenosis, Successful decompression without reflux can be achieved in 70-80% of such cases. This is not the case of ectopic ureteroceles. Most believe that endoscopic puncture of an ectopic ureterocele is indicated mainly for uncontrollable sepsis and azotemia with bladder outlet obstruction with or without ureterocele prolapse. Reoperation

rate after endoscopic decompression is higher in children with ectopic double-system, ectopic vs intravesical and those associated with preoperative VUR than orthotopic single system ureterocele. The main reason for reoperation is ipsilateral reflux. Almost 50% of double system ectopic ureterocele resolve with endoscopic incision, with 40% needing ureteral reimplantation due to symptomatic VUR. VUR after transurethral incision can be safely followed nonoperatively as long as it is asymptomatic, and it may even resolve spontaneously. Bedside puncture of an introital prolapsing ectopic ureterocele obstructing the urethra and bladder neck in females has been reported without anesthesia or sedation. In the case of ectopic ureterocele with a subsphincteric outlet, urinary incontinence can only be restored by a ureteral reimplantation or heminephrectomy. Other alternative in management includes ureteroureterostomy when the upper moiety has significant functionality, pyelopyelostomy, ureteropyelostomy and superior moiety heminephrectomy. Treatment should be individualized depending on renal function, obstruction, drainage of the contralateral ureter, bladder outlet obstruction and associated VUR and UTI.

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Polycystic Kidney Disease

Polycystic kidney disease (PKD) has two genetic variants: autosomal dominant polycystic kidney disease (ADPKD), and autosomal recessive polycystic kidney disease (ARPKD). ADPKD is the most common inherited human renal disease (1:1000), 85% of cases are caused by mutations in the PKD1 on chromosome 16, and 15% are caused by mutations in the PKD2 on chromosome 4. Males and females are equally affected. In general, renal disease is more severe in males, but more than 80% of patients with ADPKD and severe polycystic liver disease are females. ADPKD accounts for 5% of ESRD development in adults. ADPKD is generally a late onset (5th through 7th decade of life) systemic disease characterized by bilateral progressive enlargement of focal fluid filled cysts occurring in the distal region of the nephron and collecting ducts with variable extrarenal manifestation. Extrarenal manifestation of ADPKD include cystic lesions in the liver, pancreas, spleen and seminal vesicles, vascular anomalies such as

intracranial aneurysms, aortic root dilatation, thoracic aorta dissection, mitral valve prolapse, abdominal and inguinal hernias, along with early onset hypertension. The kidney cysts in ADPKD form in utero. Majority of ADPKD are diagnosed in adulthood, though the disease can present in children of all ages from fetus to adolescents. Clinical manifestations include left ventricular hypertrophy, hypertension, proteinuria, hematuria, nephrolithiasis, flank pain and impaired renal function. The clinical spectrum of ADPKD can go from a severe neonatal condition to asymptomatic development of renal cysts. ADPKD can also be a component of the inherited disease tuberous sclerosis. ARPKD is much rarer (1:10000), primarily affecting two organs, kidney, and liver, belongs to a group of congenital hepatorenal fibrocystic syndromes and is a cause of significant renal and liver-related morbidity and mortality in children during the1st and 2nd decade of life. ARPKD is commonly diagnose in utero or at birth and occurs as a result of mutations in a single gene called the polycystic kidney and hepatic disease 1 (PKHD1). Affected fetus develop oligohydramnios, pulmonary hypoplasia (Potter's syndrome), and massively enlarged echogenic kidneys with death occurring in 20-40% of affected babies due to respiratory insufficiency (pulmonary hypoplasia). Almost 50% of children develops end-stage renal disease during the first decade of life. Disease liver due to cysts also occurs with an estimate of 40% having severe dual organ disease. Overall renal survival rate is only 42% by adulthood. Morbidity is caused by hypertension, progressive renal failure, progressive periportal congenital hepatic fibrosis, esophageal/gastric varices, enlarged hemorrhoids, splenomegaly, hypersplenism and GI bleeding. Intrahepatic bile duct dilatation (Caroli's syndrome) occurs in 30% of ARPKD children. Management of portal hypertension might entail endoscopic band ligation and porto-systemic shunting, sometimes needing dual liver/kidney transplant. All inherited cystic kidney disease are due to mutations in the cilia or basal body/centrosome complex. Both genetic variants of PKD are known as ciliopathies due to abnormal cilia structure and function. The primary cilia is thought to function as mechanosensor that translate mechanical signals such as fluid flow into chemical signals within epithelial and endothelial cells. Both ADPKD and ARPKD are characterized by cystic dilatations of the renal collecting tubules. ARPKD cyst are smaller in size, all the collecting tubules are involved and manifests as fusiform dilatation radiating from cortex to medulla. Cysts compress tissue and reduces renal function, while compression of blood vessels by the cysts leads to hyperreninemic hypertension. Renal cysts present in dysplastic kidneys is called multicystic dysplastic kidneys. Ultrasound is the most common imaging modality used to diagnose ADPKD. Total kidney volume is the standard biomarker for evaluating disease progression with CT or MRI. Genetic diagnostic testing is not necessary for clinical practice. There are currently no disease-specific therapy available from PKD. Current therapy for both ADPKD and ARPKD children and adults that have reach renal failure is limited to dialysis and transplantation. There is promising pharmacological agents to prevent ADPKD progression which are beyond the scope of this review. Treatment is directed at managing or preventing complications of the disease such as hypertension (ACE inhibitors), left ventricular hypertrophy, mitral valve prolapse, urolithiasis, pain management and urinary tract infections. Approximately 50% of patients with ADPKD will progress to end-stage renal disease.

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