In the name of god

.Neuroblastoma

Introduction:

accounts for 97 percent of all neuroblastic tumors

-are heterogeneous, **varying** in terms of **location**, **histopathologic appearance**, and **biologic characteristics** .

-they have a **broad** spectrum of **clinical** behavior, which can range from **spontaneous regression**, to maturation to a **benign ganglioneuroma**, or aggressive disease with **metastatic dissemination** leading to **death** .

- **Clinical diversity correlates** closely with numerous clinical and biological factors (including **patient age, tumor stage and histology, and genetic and chromosomal abnormalities**), although its molecular basis remains largely unknown.
- For example, **most infants** with disseminated disease **have a favorable outcome** following treatment **with chemotherapy and surgery**, although the **majority** of **children** older than one year of age with advanced-stage disease **die** from progressive disease despite intensive multimodality therapy.

Clinical presenation:

- Neuroblastomas **can arise anywhere** throughout the s**ympathetic nervous system.**
- The **adrenal gland** is the **most common** primary site (40 percent) , followed by abdominal (25 percent), thoracic (15 percent), cervical (5 percent), and pelvic sympathetic ganglia (5 percent).
- **Less commonly**, tumors arise within the **central or autonomic** nervous systems .
- Neuroblastoma metastasizes to lymph nodes, bone marrow, cortical bone, dura, orbits, liver, and skin, and less frequently, to pulmonary and intracranial sites**.**

Presenting symptoms:

- The presenting symptoms reflect the location of the primary tumor and the extent of metastatic disease, if present.
- Patients with localized disease can be asymptomatic, whereas children with advanced disease appear ill at presentation, usually with systemic symptoms.
- Signs and symptoms of neuroblastoma may include:

- Abdominal mass (retroperitoneal or hepatic)
- Abdominal pain or constipation
- Proptosis
- Periorbital ecchymoses ("raccoon eyes", from periorbital ecchymosis caused by orbital metastases)
- Horner syndrome (miosis, ptosis, anhidrosis)
- Localized back pain, weakness (from spinal cord compression)
- Scoliosis, bladder dysfunction
- Palpable nontender subcutaneous nodules
- Otherwise unexplained secretory diarrhea (from paraneoplastic production of vasoactive intestinal polypeptide [VIP])
- Systemic symptoms (fever, weight loss)
- Bone pain
- Anemia
- Heterochromia iridis (different colors of the iris or portions of the iris)
- Hypertension
- Unilateral nasal obstruction

- Abdominal tumors :

- two-thirds of primary neuroblastomas arise in the abdomen; (two-thirds are from the adrenal glands).
- can present with abdominal pain or fullness, abdominal mass, or rarely intestinal obstruction.
- the child may have symptoms related to compression of the bowel or bladder (eg, constipation, reduced bladder capacity, enuresis).
- Large abdominal tumors also can compress venous or lymphatic drainage, leading to scrotal and lower extremity edema.
- A sudden and dramatic increase in tumor size with abdominal distention and discomfort can result from spontaneous hemorrhage into the tumor.

•Paravertebral tumors:

- primary tumors (usually in the retroperitoneum or mediastinum) are able to invade the spinal canal (dumbbell tumor) .
- The subsequent epidural spinal cord compression,(oncologic emergency), can cause **pain**, **motor or sensory deficits, or loss of bowel and/or bladder control**.
- The subtle and gradual onset of such neurologic symptoms in young children can make diagnosis difficult.

- Involvement of the **cervical paravertebral** sympathetic chain and **inferior cervical** (stellate) ganglion can result in the **Horner syndrome** (ipsilateral ptosis, miosis, and anhidrosis).
- **Heterochromia iridis** (different colors of the iris or portions of the iris) is common among infants who have congenital Horner syndromed was the presenting sign in nine (2 percent).

- **Infants** with an isolated, congenital Horner syndrome should undergo careful **examination for cervical and abdominal masses**, and a measurement of **urinary catecholamine metabolites**, vanillylmandelic acid (VMA) and homovanillic acid (HVA).
- **Radiologic evaluation** of the **head, neck, and chest** is warranted for those who have acquired Horner syndrome, or whose Horner syndrome is associated with other signs (eg, increasing heterochromia, cervical mass, other cranial nerve palsies).

- Catecholamine secretion:
  - Neuroblastoma tumor cells are characterized by catecholamine synthesis, which results in the accumulation and excretion of the intermediates homovanillic acid (HVA), VMA, and dopamine. **Secretion of these catecholamines may give rise to symptoms.** In addition, HVA and VMA **can be measured in the urine** and are useful for **diagnosis** and in **monitoring** disease activity.

- Paraneoplastic syndromes: Several unique paraneoplastic syndromes can be associated with both localized and disseminated neuroblastomas.

•Opsoclonus myoclonus:

- Opsoclonus-myoclonus-ataxia (OMA) is a paraneoplastic syndrome that occurs in 1 to 3 percent of children with neuroblastoma. Almost 50 percent of children with OMA have an **underlying neuroblastoma**; **neurologic symptoms precede** tumor **diagnosis** in about half of these. The disorder is believed to have an **autoimmune pathogenesis**.
- The characteristic **symptoms** of OMA are **rapid**, **dancing eye movements**, **rhythmic jerking (myoclonus) involving limbs or trunk, and/or ataxia.**
- All children with OMA must be evaluated for neuroblastoma. If the initial evaluation is unrevealing it should be repeated in several months.

- Secretion of vasoactive intestinal peptide (VIP) :

is a paraneoplastic syndrome that is **rarely** associated with neuroblastoma.

-can cause **abdominal distension** and **intractable secretory diarrhea** with associated **hypokalemia** ; these symptoms usually resolve after removal of the tumor .

- diagnosis: presence of an unexplained high-volume secretory diarrhea and a serum VIP concentration in excess of 75 pg/mL.
- A single elevated VIP level should be confirmed by additional testing.

- # Metastatic disease :

- Neuroblastoma metastasizes by both **lymphatic** and **hematogenous** routes.
- Regional lymph node involvement (in 35 percent of children who have apparently localized disease) .
- Involvement of lymph nodes outside the cavity or region of origin (ie, abdomen, thorax, pelvis) is considered to represent **disseminated disease**.
- **Hematogenous** spread extends **most often** to **bone**, **bone marrow, skin, and liver.**
- Metastatic involvement of the **liver** is **common** in **infants**.
- Neuroblastomas also may spread to **lung** and **brain parenchyma**, but this **usually** occurs **as a manifestation** of **relapsing or end-stage disease** .

- Metastatic spread to the bones and bone marrow **can cause pain** (especially with ambulation), **blood count abnormalities**, and **fever**. In young children, who cannot complain of pain, bone pain may manifest as a **limp** or **unexplained irritability**.
- Tumor infiltration of the periorbital bones, typically unilateral, can cause the characteristic periorbital ecchymosis ("**raccoon eyes**"), **ptosis**, and **proptosis**.
- Metastatic spread to the **skin** manifests as **papules** or subcutaneous **nodules** that can be distributed **over the entire body**. These lesions are typically described as **firm, bluish-red, and nontender** .
- Children with skin nodules that are **biopsy-proven** to be neuroblastoma should undergo a full tumor evaluation by an oncologist.

- Prenatal diagnosis:
- Obstetrical sonography. (third-trimester)
- Prenatally detected adrenal masses typically are found during ultrasonographic examinations performed after 32 weeks gestation, with the earliest observed at 18 weeks.
- One hundred children per year in North America are diagnosed with neuroblastoma either prenatally or at younger than three months of age.
- **Urine catecholamines** also may be helpful in **distinguishing** a neuroblastoma from other **potential masses** including **adrenal hemorrhage and vascular malformations**, although a negative result does not exclude the diagnosis.

• DIFFERENTIAL DIAGNOSIS :

- includes a variety of neoplastic and nonneoplastic conditions, and varies according to tumor location. Distinguishing these conditions from neuroblastoma may be particularly difficult in patients whose tumors do not produce catecholamines or who do not have an obvious primary tumor.
- When the tumor arises in a **suprarenal** location, **Wilms' tumor** and **hepatoblastoma** should be considered.
- In **thoracic and retroperitoneal** locations, **lymphoma**, **germ cell tumors**, and **infection** should be considered.

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- Metastatic involvement of the **bone marrow** must be distinguished from **lymphoma**, **small cell osteosarcoma**, **mesenchymal chondrosarcoma**, the **Ewing sarcoma** family of tumors, **primitive neuroectodermal tumors** (PNETs), undifferentiated soft-tissue sarcomas such as **rhabdomyosarcoma**, and **leukemia**, particularly **megakaryoblastic leukemia**.
- If the **spinal canal** is involved, the differential diagnosis should extend to other neurodevelopmental tumors such as **desmoid tumors**, **epidermoid tumors**, and **teratomas**, as well as **astrocytomas**.

- Opsoclonus-myoclonus syndrome may occur in association with other conditions besides neuroblastoma :

- **Tumors**: Hepatoblastoma
- **Infections**: Poliovirus, parainfluenza virus, coxsackie virus B3 and B2, Epstein-Barr virus, St. Louis encephalitis virus, salmonella, Lyme disease, rickettsia, syphilis, psittacosis, and HIV
- **Ingestions**: Lithium , phenytoin , amitriptyline , diazepam , cocaine
- **Toxic exposures**: Toluene, thallium, organophosphates, chlordecone, strychnine
- **Metabolic derangements**: biotin-responsive multiple carboxylase deficiency, hyperosmolar nonketotic coma

- The differential diagnosis of skin nodules :
- dermoid and other cysts
- subcutaneous fat necrosis
- benign tumors (eg, infantile myofibromatosis, congenital self-healing reticulohistiocytosis)
- other malignant tumors (eg, infantile fibrosarcoma, rhabdomyosarcoma, and congenital leukemia).
- Biopsy may be required for definitive diagnosis.

- The causes of secretory diarrhea are:

- Factitious diarrhea (laxative abuse)
- Rectal villous adenoma
- Neuroendocrine tumors :
  - vasoactive intestinal peptideoma
  - Carcinoid syndrome
  - Gastrinoma (Zollinger-Ellison syndrome)
- Lymphocytic or collagenous colitis
- Self-limited cryptogenic diarrhea
- Congenital diarrhea
- Bile salt enteropathy

DIAGNOSTIC AND STAGING EVALUATION:

All patients with suspected neuroblastoma should undergo a **complete history** and **physical examination**.

Most patients will undergo **laboratory** evaluations including **routine blood counts**, serum **chemistries**, and **tests of liver and kidney function**. Evaluation of **urine or serum catecholamine metabolite** levels, VMA and HVA, should be obtained to assist in **diagnosis** and **monitoring** of disease response

ferritin and **lactate dehydrogenase** (LDH) concentrations may be helpful; they **may be elevated** initially and can be expected to return to normal during adequate treatment.

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Diagnostic criteria : diagnosis of neuroblastoma requires one of the following:

- An unequivocal histologic diagnosis from tumor **tissue** by light microscopy, with or without immunohistochemistry, electron microscopy, or increased urine (or serum) **catecholamines** or their metabolites.

- Evidence of metastases to bone marrow on an aspirate or trephine **biopsy** with concomitant elevation of **urinary or serum catecholamines** or their metabolites

• Staging workup

Stage	Definition
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive)
2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically
2B	Localized tumor with or without complete gross excision; with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
3	Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined for stage 4S)
4S	Localized primary tumor (as defined for stage 1, 2A or 2B), with dissemination limited to skin, liver, and/or bone marrow (limited to infants <1 year of age)

• Radiologic evaluation :

- Ultrasonography (US) is often the initial radiologic study in the evaluation of a child with an abdominal mass, the most common presentation of neuroblastoma. it should be followed by either CT or MRI.
- CT or MRI of the primary tumor may reveal a **heterogeneous mass**, possibly containing **calcifications** . When the mass is adjacent to the spine, an MRI is particularly helpful for evaluation of spinal canal invasion.
- A radionuclide bone scan is a sensitive tool for evaluating metastatic spread to cortical bone.
- Plain radiographs are not as sensitive as bone scans because of the degree of cortical bone destruction needed to visualize a lesion on plain film.
- In addition, in infants younger than one year of age, bone scans may be difficult to interpret because immobilization is difficult, and improper knee positioning (on account of slight knee flexion and external rotation of the leg) may cause superimposition of the epiphysis and metaphysis, obscuring the usual tracer concentration gradients. Thus, plain radiographs (eg, a skeletal survey) may be necessary in young infants.

•Urine catecholamines :

- HVA and VMA can be measured in the urine, and are useful in both diagnosis and monitoring disease activity.

Biopsy:

- Histologic confirmation is required for definitive diagnosis. Tissue is usually obtained by incisional biopsy of the primary tumor or bone marrow biopsy/aspirate in patients who are suspected to have metastatic disease in the marrow.
- For tumors that appear to be localized and resectable without substantial morbidity, the initial diagnostic procedure may include a complete or near-complete resection of the primary tumor and sampling of non-adherent ipsilateral and contralateral lymph nodes.
- The initial procedure should not include resection of vital structures (eg, kidney, spleen) or major motor or sensory nerves (the section of which would lead to permanent disability).

- Bone marrow disease is evaluated by aspiration and biopsy of the bone marrow, usually at the posterior iliac crests.

- **PROGNOSTIC FACTORS:**

- **Tumor stage** : The extent of metastatic spread at presentation is the most important factor in determining outcome for patients with neuroblastoma. Although regional spread to lymph nodes attached or adjacent to the primary tumor does not significantly affect outcome, distant metastatic disease (eg, bone marrow involvement) confers a much worse prognosis.
- **Stage 4S disease:** Stage 4S neuroblastoma is a special category that is reserved for infants below one year of age. These infants have resectable primary tumors (Stage 1 or 2) and metastases that are limited to the liver, skin, and bone marrow; infants with metastases to cortical bone are excluded from this category.

- **Age at diagnosis：** The age at presentation is an important prognostic factor in children with neuroblastoma . The significantly better outcome of disseminated disease in children under the age of one compared to other age groups is reflected in the special 4S category of disease stage, which applies only to infants.
- The younger the age at diagnosis, the better the survival rate. An age of 18 months appears to be appropriate for risk group stratification.

- **Newborns :**

- Neonates (younger than four to six weeks) who have stage 4S neuroblastoma are an exception to the general rule that younger age is associated with better outcome.
- neuroblastoma in the liver can grow rapidly, resulting in pulmonary compromise and renal failure in approximately 30 percent of cases .
- Such infants must be monitored closely even after treatment initiation.
- In contrast, newborns who have limited adrenal disease (typically diagnosed by prenatal ultrasound) have a favorable prognosis and frequently do not need treatment.

- **Pathologic risk classification :**
- Histology, in addition to age, is important prognostically. In 1984, Shimada et al derived a pathologic risk classification scheme that relates the histopathologic features of the tumor, other biologic variables, and patient age to clinical behavior . Tumors are classified as favorable or unfavorable based upon the degree of neuroblast differentiation, Schwannian stroma content, the frequency of cell division (the mitosis-karyorrhexis index [MKI]), and age at diagnosis.
- The International Neuroblastoma Pathology Classification (INPC) system, a modification of the Shimada system, was established in 1999 and its prognostic value subsequently confirmed. In one validation study, five-year event-free survival (EFS) was more than three times greater among children with favorable compared to unfavorable disease (90 versus 27 percent) .

-According to this system, favorable tumors include those that are:

- Poorly differentiated or differentiating neuroblastoma, with **low or intermediate** mitosis-karyorrhexis index (MKI), patient age ≤1.5 years
- Differentiating neuroblastoma and low MKI tumors in patients 1.5 to 5.0 years of age
- Ganglioneuroblastoma, intermixed, regardless of age
- Ganglioneuroma, regardless of age

-Unfavorable tumors include those that are:

- Undifferentiated or high MKI tumors in patients of any age
- Poorly differentiated and/or **intermediate MKI** tumors in patients 1.5 to 5.0 years of age
- Any grade of differentiation and any MKI class in patients ≥5 years of age
- Nodular ganglioneuroblastoma, regardless of age

- **Cytogenetics and molecular genetics :**

- certain molecular and cytogenetic characteristics correlate with prognosis, including MYCN (N-myc) amplification, DNA content (ploidy), and gain or loss of whole or partial chromosomes.

•TREATMENT:

- The **modern treatment** of neuroblastoma is determined **based on risk categories**. Patients are classified into **low**, **intermediate**, and **high risk categories** based on the following characteristics at the time of diagnosis:

- Stage of the disease
- Patient age
- Histologic appearance of the tumor
- Presence or absence of amplification of the MYCN oncogene
- Quantitative DNA content of the tumor (DNA index or ploidy).

Children's Oncology Group neuroblastoma risk strata

Risk	Stage	Age	MYCN status	DNA ploidy	INPC	Other
Low*	1	Any	Any	Any	Any	
	2a/2b	Any	Not amp	Any	Any	Resection ≥50 percent
	4s	<365 days	Not amp	DI >1	FH	Asymptomatic
Intermediate•	2a/2b	0-12 years	Not amp	Any	Any	Biopsy or resection <50 percent
	3	<547 days	Not amp	Any	Any	
	3	≥547 days - 12 years	Not amp	Any	FH	
	4	<365 days	Not amp	Any	Any	
	4	365 - <547 days	Not amp	DI >1	FH	
	4s	<365 days	Not amp	Any	Any	Symptomatic
	4s	<365 days	Not amp	DI = 1	Any	Asymptomatic or symptomatic
	4s	<365 days	Not amp	Any	UH	Asymptomatic or symptomatic
	4s	<365 days	Missing	Missing	Missing	Too sick for biopsy
HighΔ	2a/2b	Any	Amp	Any	Any	Any degree of resection
	3	Any	Amp	Any	Any	
	3	≥547 days	Not amp	Any	UH	
	4	<365 days	Amp	Any	Any	
	4	365 - <547 days	Amp	Any	Any	
	4	365 - <547 days	Any	DI = 1	Any	
	4	365 - <547 days	Any	Any	UH	
	4	≥547 days	Any	Any	Any	
	4s	<365 days	Amp	Any	Any	Asymptomatic or symptomatic

INPC: International Neuroblastoma Pathology Classification; FH: favorable histology; UH: unfavorable histology; Amp: amplified; DI: DNA Index.
* Low risk groups as defined in Children's Oncology Group trial ANBL00B1.
• Intermediate risk group as defined in Children's Oncology Group trial ANBL0531.
Δ High risk group as defined in the Children's Oncology Group trial ANBL0532.

- **Low-risk disease :**
- Patients in the low-risk category generally have low stage disease (eg, stage 1, 2A, or 2B,) and tumors are MYCN non-amplified, hyperdiploid and have favorable histology.
- In general, **tumor outcomes** for children with low-risk neuroblastoma are **excellent**.

- **Surgery** is the mainstay of treatment for low risk tumors although some infants and children need additional **chemotherapy** and others can be **observed** without surgery.

Intermediate-risk:

- According to the Children Oncology Group risk classification schema, intermediate-risk disease includes those children **younger than 18 months** of age **with stage 3 disease without MYCN amplification** (regardless of histology), and **stage 3 disease in children older than 18 months without MYCN** amplification and with favorable histologic features. In addition, this stratum also includes infants with stage 4 disease without MYCN amplification, and a subset of infants with 4S disease who have diploid tumors or unfavorable histology, and no MYCN amplification.
- The standard approach for these patients includes **chemotherapy** with **resection when possible**.
- **Radiation** therapy is **rarely** indicated but should be considered for those with **tumor progression** or tumor-related life threatening or organ-threatening complications unresponsive to chemotherapy.
- The **duration** of chemotherapy is **typically 12 to 24 weeks**; optimization of chemotherapy according to risk factors is a focus of current clinical investigations.

- **High-risk disease:**
- Patients at the highest risk for disease progression and mortality are those who are older than 18 months year of age and have disseminated disease, or localized disease with unfavorable markers such as MYCN amplification .
- Historically, the long-term **survival** probability for children with high-risk disease was **less than 15 percent**. Better results have been achieved using an **aggressive multimodality** approach that includes **chemotherapy**, **surgical resection**, **high-dose chemotherapy** with **hematopoietic stem-cell rescue**, and **radiation therapy** .
- However, current survival rates remain unacceptably low (approximately 40 percent), and the improved outcome has come at a cost of significant early and late toxicity.

•Treatment outcome:

- Infants **less than one** year of age have **a better survival** rate (five-year survival rate of 83 percent, 55 percent, and 40 percent for those younger than one year, one to four years, and five to nine years, respectively).
- For patients with **low-risk tumors** (stage 1 or 2 disease, infants with stage 4S disease and favorable biologic factors), **surgery** alone is the **primary treatment**. Two-year event-free survival rates are between 85 and 100 percent . Patients who **relapse** generally can be salvaged with further **surgery or chemotherapy**.

- Among patients with stage 3 neuroblastoma (intermediate- or high-risk, depending upon other prognostic factors), outcome varies according to age at diagnosis and histologic features.
- The treatment of patients with intermediate-risk neuroblastoma requires the addition of moderate-dose intensity chemotherapy to surgery, with local RT having a limited role. Long-term survival rates are over 90 percent .
- Children with high-risk disease (older than 18 months of age with disseminated disease at diagnosis, or disseminated or localized disease with unfavorable biologic and histologic markers such as MYCN amplification) do **poorly even** with **intensive** multimodality strategies that include high-dose therapy with autologous hematopoietic stem cell rescue.
- Long-term survival rates are approximately 40 percent.

- **Thanks for your attention**