Neuroblastoma

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Main Topics

- Definition.
- Incidence.
- Etiology and pathogenesis.
- Molecular Cytogenetics.
- Pathology (Macro/Microscopic).
- Clinical Manifestations.
- Metastatic Spread.
- Diagnostic imaging.
- Differential Diagnosis.
- Staging
- Therapy (Risk adapted/Relapse).
- Special Forms.

Definition:

- Malignant embryonal tumor of precursor cells of sympathetic ganglia and adrenal medulla.

- Entity characterized by:
  - Occasional spontaneous regression and differentiation to benign tumor especially in infants less than 12 months of age.
  - Usually extremely malignant course in children in the advanced stage

Incidence

- Eight percent of all neoplasia in children.
- Most frequent malignant neoplasia in infants.
- Mean age at diagnosis is 2.5 years.
- Rarely observed in adolescents and adults.
- Boy-girl ratio of 1.1:1.0.

Etiology and Pathogenesis

- Etiology is unknown.
- Familial occurrence as well as sibling and twin disease with different stages of neuroblastoma within the same family are rarely described.
- Association with neurofibromatosis, Hirschsprung disease, heterochromia iridis.
- Tumor cell chromosomal changes and various karyotypic abnormalities in the majority of patients are detectable.

Pathology

- **Macroscopic features**: Pale gray, soft tumors with necrosis and calcification; in large tumors the demarcations are unclear; and the tumors are highly invasive into surrounding structures.
- **Microscopic features:** High variability with various differentiation stages of sympathetic nervous tissue ranging from undifferentiated neuroblastoma to ganglioneuroblastoma, to differentiated ganglioneuroma. Differentiation with **(1) EM:** for cytoplasmic neuro structures (neurofilaments, neurotubules, and neurosec. Granules) **(2) IHC:** Immunoperoxidase & NSE **(3) Fluorescence testing** for intracellular catecholamines. **Histologically**, It must be differentiated from other *small blue round-cell tumors* e.g. PNET, Retinoblastoma, Ewing's Sarcoma, lymphoma etc.

Molecular Cytogenetics

MYCN amplification and expression of neurotropic receptors (*TRK1*, *-2*, *-3*), neuropeptides (vasoactive intestinal polypeptide, VIP, somatostatin, SS), DNA index, and chromosomal changes (deletion 1p suppressor gene on chromosome 11, deletion 14, etc.) are prognostic factors.

Cytogenetic Prognostic Criteria

Cytogenetic prognostic criteria

Age at diagnosis	*MYCN*	DNA	*TRK1*	Stage	Prognosis (survival rate)
<12 months	Usually normal	Hyper-diploid	High	1, 2, 4S	95%
>12 months	Usually normal	Diploid	Low	3, 4	50%
1—5 years	Commonly amplified	Diploid	Low	3, 4	25%

Clinical Manifestations

- **Primary locations:** Any area with sympathetic tissue (Abdomen 65%, Adrenal Medulla, posterior mediast., pelvis, H&N, other areas, and rarely undetectable 1ry).
- **Symptoms & Signs:**
  - **Common:** Wt. loss, fever, abdominal disturbances, Irritability, pain in joints and bones, pallor.
  - **Associated with Catecholamine production:** Paroxysmal attacks of sweating, flushing, and pallor, HTN, palpitation, & headache.
  - **Paraneoplastic syndromes:** e.g. VIP syndrome (in 5 – 10% of cases characterized by intractable diarrhea with low S. potass. levels.
  - **Local: Eyes:** periorbital edema, swelling, proptosis, ... **Neck:** LN, Horner syndrome. **Chest & post medias.:** cough & dysnea (tracheal compression), muscle weakness, parathesia, bladder dysfunction, and constipation (d.t. n. comp., necessitating emergency decomp.). ..... *Continue*

Clinical Manifestations

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Abdomen: **Retroperitoneal mass**: firm, irregular, and often crossing the midline. **Paravertebral & presacral :** tends to grow into the intervertebral foramina causing neurological dysfunction. **Liver:** In infants, marked hepatomegaly (known as pepper eye). **Skin:** Subcutaneous nodules mainly seen in neonates or infants with disseminated neuroblastoma; blue → red → white d.t. catecholamines release. **Bone:** pain (sometimes is the first sign), lytic lesions involving mainly skull and long bones. **Bone marrow:** involved in 50% of patients, peripheral thrombocytopenia and/or anemia indicates advanced stage disease.

- **Metastatic Spread:** Lymphatic and/or hematogenous, often initially present in: 40–50% of children less than 1 year of age and 70% of children more than 1 year of age. In children with local neuroblastoma 35% have involvement of lymph nodes Metastatic spread mostly in bone marrow, bone, liver and/or skin, rarely in brain, spinal cord, heart, lung

Laboratory Findings

- **Urinary catecholamine metabolites (Tyrosine metabolism):** High levels of vanillylmandelic acid **(VMA)** in 95%, homovanillic acid **(HVA)** in 90% and 3-methoxy-4-hydroxyphenylglycol **(MHPG)** in 97% of patients. Other metabolites of catecholamine metabolism for differentiation of pheochromocytoma, olfactory neuroblastoma, and melanoma. Urinary catecholamine metabolite analyses useful: follow-up tumor marker.
- **Bone marrow Aspiration and biopsy:** at two or more locations for detection of bone marrow involvement

Diagnostic Imaging

- **Conventional X-ray**
  - **Thoracic X-ray:** for mediastinal tumor
  - **Abdominal X-ray:** often calcifications visible in the tumor
  - **Skeletal survey:** for cortical bone metastases (differential diagnosis: bone tumor, Langerhans histiocytosis, infectious disease of bone, battered-child syndrome, metastatic spread of other neoplasia.
- **Methylisobenzyl guanidinium (MIBG) scintigraphy**
  - Radiolabeled specific and sensitive method for evaluation of the primary tumor and focal metastatic disease
- **Ultrasound, computed tomography and/or magnetic resonance imaging**
  - Provision of detailed information on tumor size, extension, metastases of abdominal, hepatic, skeletal, pulmonary, mediastinal and central nervous system involvement

Differential Diagnosis

1. Osteomyelitis
2. Rheumatoid arthritis
3. Signs of VIP syndrome: infectious or autoimmune intestinal disorders
4. In opsoclonus or ataxia: neurological disorders
5. In infants with hepatomegaly: storage diseases

Staging

Stage	Description
I	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)
IIA	Localized tumor with incomplete gross excision; representative, ipsilateral nonadherent lymph nodes negative for tumor microscopically
IIB	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically
III	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
IV	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin or other organs (except as defined for stage 4S)
IVS	Localized primary tumor (as defined for stages I, IIA, or IIB) with dissemination limited to skin, liver or bone marrow (limited to infants aged less than 1 year)

Treatment

Depends on:

1. Age.
2. Stage.
3. Molecular features.

Modalities:

1. Surgery.
2. Chemotherapy.
3. Radiation therapy

Treatment

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- **Surgery**
  - Initial surgery for staging and eventually tumor excision without injury to vital structures; and for biopsy.
  - Often radical resection becomes possible after chemotherapy and/or radiotherapy.
- **Chemotherapy (CTH)**
  - Combinations of chemotherapy: cyclophosphamide/ifosfamide, cisplatin, and doxorubicin according to international protocols
  - The course of therapy is divided into an induction phase and a consolidation phase
- **Radiotherapy (RT)**
  - It's a radiosensitive disease.
  - **RT Limitations:** Age, long-term sequelae, combination with CTH.
  - **Indications:** Shrinking large tumor masses, decompression of intraspinal tumors, or palliative treatment.

Treatment: *Risk Adapted*

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Item \ Risk Group	Low	Intermediate & high
Definition:	- Stage I, II, and IVS. - No MYCN amp. - Favorable histology.	- Stage II: Age 1-21 ys, with MYCN amp. & Unfav. Histo. - Stage III, IV, VS: Age 0-21 ys. With MYCN amp. Or: age 1-21 ys with unfav. Histo.
Generally		- Mostly, good response to induction CTH. - Poor prognosis for persistent bone &/or BM involvement
Treatment of different scenarios	- Radical resection after CTH &/or RT - Stage IVS in infants (<12 mo.) can have surgery without CTH or RT (high cure rates: 90%). - Rapid prog. hepatomegaly: CTH or low-dose RT (1.5-6 Gy) are mostly used. (to improve dysnea). - For Intraspinal compression: CTH alone &/or laminectomy.	- Induction CTH → tumor resection → maint. CTH and/or RT. - Persistent disease: 1) MRD by MIBG: use retinoids for induction of neuroblast differentiation, or monoclonal Ab against neuroblastoma cell Ag (3F8, GD2a). 2) HD-CTH → auto BMT supp.

Treatment: *Relapse*

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- **CTH:** For curative or palliative goals: topotecan, paclitaxel (Taxol), irinotecan or etoposide
- **Radiolabeled MIBG therapy** as experimental option

Prognosis

- **Generally speaking, it depend on:**
  - **Age:** Favorable if < 18 mo. at diagnosis.
  - **Stage:** including poor prognosis with LN involvement.
  - **Primary site:** Favorable if in thorax, presacral, or cervical.
  - **Pathological features:** Histology; Favorable vs unfavorable, molecular cytogentics: MYCN amp. DNA ploidy, and TRK-1 exp statuses.
- **As for different risk groups:**
  - **Low-risk group:** > 90 % long-term survival.
  - **Intermediate and high-risk groups:** ORR (CR+PR) is 70%. After consolidation therapy (including double HD-CTH w auto BMT support) event-free survival (EFS) is 50%.

Special Forms

Form / Item RT	Ganglioneuroblastoma	Ganglioneuroma	Olfactory Neuroblastoma	Neuroblastoma of organ of Zuckerkandl	Pheochromocytoma
Age	Older children & adolescents.	Adolescents and young adults.	Older children and adults	----------	Children > 10 ys and adults
Location	Adrenal medulla and post. Mediastinum.	----------	Mid-line base of skull	Mid-line tumor	Mostly adrenal gland, 20% bilateral.
Histology	Typical neuroblastoma	Benign tumor	----------	Typical neuroblastoma	Arising from chromium cells of neural crest
Macroscopically	Often large tumors	Encapsulated			
Clinical manifestations	----------	----------	Unilat. nasal obs. Epistaxix, rhinorrhea, pain .	----------	Paroxysmal attacks of flushing, pallor, sweating, headache .....
Prognosis			2/3 of pt. are cured		
Treatment	As Neuroblastoma	Resection	Resetion +/- RT	As neuroblastoma	Resection + prophylaxis against HTN crisis

ThankYou