Neuroblastoma: Fundamentals of Basic and Clinical Science

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Incidence

- 1/100,000 children
- Most common solid tumor in children less than 1yo (with exception to brain)
- Heterogeneous phenotype
  - Regress spontaneously in some types
  - Matures to benign
  - Aggressively malignant

Etiology

- Sporadic occurrence
- Beckwith-Weidemann syndrome
- Hirschsprung Disease
- Fetal alcohol syndrome
- In mothers taking phenytoin for seizure disorders
- Familial in 2% cases
  - Anaplastic activating kinase (ALK) oncogene on short arm of chromo 2p23

Treatment Strategies

- Surgery
- Radiation
- Chemotherapy
- Bone marrow transplant
- Children's Oncology Group- protocols to study multimodality therapy

Pathology

- Tumors originate along the pathway that neural crest cells migrate.
- Embryonal tumors of the sympathetic nervous system.
- Occur in the adrenal medulla, sympathetic chain paraspinal, organ of Zuckerkandl

History

- Rudolph Virchow- German pathologist described histology in 1864 in article, “Hyperplasia of Pineal and Suprarenal Glands”
- James Homer Wright- 1910 coined term “neuroblastoma” describing the rosettes of tumor cells around central neural fibrils
Differential Diagnosis

- Small blue round cells tumors of childhood
  Ewing sarcoma
  Non-Hodgkin lymphoma
  Rhabdomyosarcoma
- Dx neuroblastoma: Homer-Wright rosettes, scattered ganglion cells-immature to fully mature, immature chromaffin cells

Biology

- Secretion of catecholamine products
- Ability to regress or mature
- Spontaneous regression and in response to treatment
- Beckwith and Perrin: Autopsy studies revealed "neuroblastoma –in –situ" in the adrenal glands of children following death from nonmalignant cause

Pathology Classification

- 1984 Shimada et al: age linked classification system
- Favorable histology
- Unfavorable histology
- 1999 International NB Pathology Classification
- 2003 modified

Prognostic Evaluation of NB by INPC

- Histopath classification confirmed by Shimada
- Age <1.5 yo >5yo
- MKI- mitotic karyorrhexis index per 5K cells
  <100 low
  100-200 intermediate
  >200 high
- Schwannian stroma rich vs. poor
Ganglioneuroblastomas

- Ganglioneuromas
  Transitioning toward differentiation with residual microscopic neuroblastic cells.

Stroma rich tumors with mature ganglion cells considered benign

Nodular type worse prognosis

DNA content

- 23 chromosomes
- Normal diploid cell has 46 chromosomes (2 copies)
- Neuroblastomas:
  - 55% hyperdiploid (58-80 chromos)
  - 45% near diploid (35-57 chromos)
    or near tetraploid (81-103 chromos)

Chromosome content

- Most common chromosome deletion 1p (loss of a tumor suppressor gene)
  and MYCN amplification
- Near triploid tumors – favorable prognosis
- Near diploid or tetraploid – unfavorable
- Tumor ploidy no prognostic impact
  > 2yo...other factors dominate prognosis

MYCN proto-oncogene

- 64 kilodalton nuclear phosphoprotein forms a transcriptional complex with other nuclear proteins to develop nervous system tissues.
- Dominant oncogene that an cooperate with RAS to transform normal cells.
- Targeted expression of MYCN in transgenic mice results in NB

MYCN prognosis

- Amplification of MYCN associated with:
  advanced disease
  rapid tumor progression
  poor outcomes
- Detected by FISH (fluorescent in situ hybridization).
- Current NB protocols risk stratify by MYCN amplification.
Chromosome Abberations

- 70% NB have 1p deletions
- 1p Associated with MYCN amplification
- 1p deletions associated with age >1 year

- Deletions of 11q 14q inversely related to MYNC amplification.
- 17q gain most common finding in NB, associated with malignancy (unbalanced – extra copies 17q)

TrkA TrkB TrkC

- Tyrosine kinase receptors:
  A – primary receptor for nerve growth factor associated with favorable outcomes low MYCN
  B - primary receptor for brain derived NGF
  NB survives via autocrine/paracrine signals, associated with MYCN amplification
  C - associated with TrkA and has unknown mech but thought to be favorable.

Clinical Presentation

- Cervical NB – 1%
- Thoracic NB – 20% posterior mediastinum
- Retroperitoneal – 25% paraspinal
- Adrenal medulla – 50%
- Pelvic NB - 4% organ of Zuckerkandl

Presenting Symptoms

- Most commonly – abdominal mass
- Abdominal pain
- Respiratory distress
- Dysphagia
- Alteration of urination or defecation
- Horner’s syndrome

Presenting location of NB
Presenting Symptoms

- Excessive catecholamine secretion
  - diarrhea, wt loss, hypertension
- Dancing eye dancing feet syndrome
  - Opsoclonus, myoclonus, chaotic nystagmus, cerebellar ataxia
  - 66% of cases associated with mediastinal tumors

Age of Presentation
Evans Staging Replaced by INSS-International NB Staging System

<table>
<thead>
<tr>
<th>Age</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
<th>Total</th>
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<td>&lt;1 yr</td>
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<td>8.5</td>
<td>1.1</td>
<td>9.5</td>
<td>7.5</td>
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<tr>
<td>&gt;1 yr</td>
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<td>8.5</td>
<td>18.8</td>
<td>33.3</td>
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<td>TOTAL</td>
<td>17.7</td>
<td>18.0</td>
<td>18.9</td>
<td>42.9</td>
<td>9.5</td>
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Stage at Presentation
40% present with metastasis
- bone pain (cortex), anemia (marrow), lymph nodes.
- brain, spinal cord, heart, lungs in advanced stage.
- raccoon eyes- retro-orbital spread
- babies with “blueberry muffin” skin lesions

Site of Metastasis at Diagnosis

<table>
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<tr>
<th>Site of Metastasis</th>
<th>Stage IV</th>
<th>Stage V</th>
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<tbody>
<tr>
<td>Bone marrow</td>
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<tr>
<td>Bone</td>
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<td>Brain</td>
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<tr>
<td>Spinal cord</td>
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<td>0</td>
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<td>Heart</td>
<td>6.5</td>
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<tr>
<td>Lungs</td>
<td>16.0</td>
<td>16.0</td>
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<tr>
<td>Adrenal</td>
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<td>0</td>
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<tr>
<td>Skin</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Liver</td>
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<tr>
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<tr>
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<tr>
<td>TOTAL</td>
<td>85.7</td>
<td>74.1</td>
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</table>


Laboratory Findings

- Lactate Dehydrogenase
  - high levels = high cell activity = large tumor burden
  >1500 IU/L associated with poor prognosis
- Ferritin >150ng/ml poor prognosis
- Neuron-Specific Enolase >100ng/ml poor
- VMA/ HVA in urine of 90% with NB

Imaging

- Plain chest radiograph
- Ultrasound abdomen
- Chest CT
- Abdominal CT
- Head CT
- MRI for spine/ brain and mets to bone
** Mediastinal NB 

** MRI imaging of femur/spine mets 

** C: Intraspinal extension 

** D: Encasement of aorta/renal artery 

** MIBG scintigraphy 

- Metaiodobenzylguanidine (MIBG) taken up by chromaffin cells and stored in the similar to NE. 
- MIBG used as more sensitive than bone scan in detecting bony mets and extraskeletal disease. 
- Some advocate MRI over MIBG for bony mets 

** Look alike diseases 

- Acute primary ataxia- neurologic disease 
- Osteomyelitis or RA resembles non-neoplastic widespread bone disease. 
- VIP secretion 
- IBD 
- Histologically small round blue cell tumor: PNET, nonHodgkin lymphoma, Ewings sarcomas, rhabdomyosarcoma
**Low Risk Disease**

- Stage 1
- Stage 2A/B not MYCN amplified with > 50% resection

**TX:** surgery alone COG 90- POG 94% current study also supports this approach (2006)

- 4S with favorable histology

**TX:** biopsy with observation : 94-99%

**Intermediate Risk Disease**

Age to 12yo Stage 2A/B not MYCN amp

- Less than 50% resection (or biopsy only)
- Stage 3 not MYCN amp
- Stage 4 not MYCN amp w/favorable hist
- 4S disease symptomatic w/unfavorable hist

**TX:** Chemo cycloph, doxorub, carbo, etoposide

- 4-8 cycles : favorable-unfavorable

Radiation only for progressive disease or residual disease: 3yr EFS / OS : 85/95%
High Risk Disease

Any MYCN amplification (unless Stage 1 —completely resectable w/o +LN)
Age >1.5 yo
Stage 3 with unfavorable histology
Stage 4 unfavorable hist or DNA index>1
TX: biopsy/combination chemo (antitumor synergy for max tolerated dose)

Treatment Considerations

1. Combo chemo achieves synergy, variable mech action, overcomes drug resistance.
2. Maximum dose tolerated requires recovery period that may allow endothelium neovasc support for tumor growth/spread. Low dose therapy may more effectively inhibit angiogenesis.
3. Goldie-Coldman hypothesis- chemo more effective as adjuvant following resection.

Close only counts in horseshoes and .... oncology
Surgical Treatment

- Surgery only therapy for low risk disease.
- Low risk disease may spontaneously mature calling into question value of complete removal.
- Role of surgery in advanced local or metastatic disease less clear due to complex molecular genetics and biologic behavior of NB.

High Risk TX Outcomes

Multichemoagent toxicities...myelodysplastic syndrome, AML, myelosuppression, fever, neutropenia, mucositis...misery

BMT 3yr EFS: 34%
  Compared to no BMT 22% p=.034
  Add 13-cis-retinoic acid 3yr EFT: 46%
  compared to none 29% p=.027

TX: Locoregional Disease with Mets

- Bone marrow can usually provide tissue dx with determination of MYCN amp.
- If BM is not involved then surgical bx is recommended for histopath classification and appropriate risk stratification.
- Surgery for high risk disease results in benefit for local control, but no clear evidence that long term survival improved. COG still recommending surgery as soon as tumor resectable.

Surgery for Recurrent Disease

- Surgery recommended for recurrent disease that is localized.
- Surgery recommended for disease refractory to available chemo.
- No RCT to support surgery...never met an oncologist or tumor board that wouldn't recommend it.

Operative Principles

- Abdominal tumors require vascular control with thoracoabdominal incisions as needed to gain access to celiac axis or periaortic encasement. Subadventitial dissection to free.
- Piece-meal dissection to avoid torque injury to renal hilum leading to ischemia.
- Work distal perimeter to proximal blood supply with piece-meal division/ excision tumor.
Operative Principles

- Pelvic tumors- beware of the sacral plexus.
- Thoracic tumors- beware of the neuroforamina. No benefit of intraforaminal extraction in asymptomatic disease, only risk to spinal cord...employ the principle of “do no harm”

**Symptomatic spinal cord invasion is treated with chemo and a neurosurgical laminotomy/ectomy for progressive symptoms**

Population Screening for NB

- During the 1980s Japan performed mass screening of infants using urinary catecholamines. Picked up favorable lesions, Stage 1 felt to be in category of spontaneous regression.
- Presentation of advanced disease didn’t change in follow up studies.
- Screening fell out of favor.

Stage 4S Disease

Described in 1971
- small single primary tumor
- massive metastatic disease in liver
- skin nodules “blueberry muffin” lesions (not NAT)
- Spontaneous regression
- Massive hepatomegaly may require silo and limited chemo /radiation if infants dying of bulky disease.

TX: Opsoclonus-Myoclonus Syndrome

- OMS occurs in 4% of primarily thoracic tumors
- Random eye movements
- Progressive cerebellar ataxia
- Theoretically caused by autoantibodies to neural antigens
- Symptoms may persist after tumor resection
- TX: steroids, IVIG or chemo in trials

New Therapies

- Retinoids: 13-cis-Retinoic acid decrease proliferation of MYCN in cell lines and induce differentiation.
- Targeted therapy at apoptosis to reduce toxicity
  - Caspase 8p- regulates cell death (inactivated in NB)
  - TrK receptors induce cellular differentiation (blocking may induce apoptosis)
New Therapies

- Recombinant cytokines
  Interferon-alpha

- MIBG therapy
  I-MIBG taken up by tumor cells used in high risk cases, may be able to evaluate recurrent disease-guide extent of resection.

- Humoral mediated antibodies
  Murine antibodies to ganglioside antigen on NB cells

- Angiogenesis inhibitors: VEGF-trap/2
  affects tumor-associated neovascularization and spread