OPHTHALMOLOGY
GRAND ROUNDS

Jordan Spindle MD
November 15th, 2012
HPI: 5 year old male brought to ER with right painless periocular swelling x 10 weeks. Mother states that the child had an unwitnessed fall at home and developed swelling around the right eye at that time. He was then brought to ER, diagnosed with a hematoma, no imaging was done. 1 month later he went to private pediatrician with continued swelling and was told that it would slowly resolve. After symptoms progressed she brought him back to ER 1 month later....
History

- POH: none
- Gtts: none
- PMH: none
- Birth History: none
- Meds: none
- All: nkda
- FH: no glaucoma/blindness
EXAM

- dVa sc: 20/20, 20/20
- Pupils: 3→2 ou, no apd
- EOMs: 10% supraduction OD, all other full
- CVFs: full ou
- Ttono: 20/18
PLE

- LLA: RUL fullness
- C/S: white and quiet ou
- K: clear ou
- A/C: formed and symm ou
- P/I: round and reactive ou
- L: clear ou
DFE

- V: clear ou
- C/D: 0.3/0.3, s and p ou
- M: flat ou, +flr ou
- V: wnl ou
- P: no holes/tears/heme seen ou
Differential Diagnosis
Differential Diagnosis

- Rhabdomyosarcoma
- Neuroblastoma
- Histiocytosis X
- Trauma
- Infectious (preseptal vs. septal)
- Orbital Varix
- Capillary hemangioma
- Ruptured dermoid cyst
- Lymphangioma
- Other mesenchymal tumor (Osteosarcoma, Ewing's sarcoma, etc).
What would you do next?
Medical Knowledge
CT

- Inferonasal globe dystopia with homogenous fairly poorly circumscribed, space occupying lesion in the superotemporal orbit. Subcutaneous homogenous lesion lateral to the lateral orbital wall with lytic bony change.
Next Step: Call the Plastics Fellow
To the OR!!
Patient Care, Interpersonal Skills and Communication Skills
Pre Op Labs

Hgb: 10
Platelets: 100k
WBC: 5

Frozen Section – inconclusive

Extended lid crease incision was done and orbital biopsy was taken.

Frozen Section – inconclusive, but favoring Rhabdomyosarcoma

Intralesional steroid injection was given in case diagnosis was Histiocytosis X

Surgical Findings:

- vascular tumor, gross bony lytic change of lateral orbital wall
The patient had excessive bleeding during the operation. Two drains were placed (one in orbit, one at brow incision site) and removed POD#2. Patient was admitted to PICU following surgery.

<table>
<thead>
<tr>
<th>Pre Op Labs</th>
<th>Post Op Labs</th>
<th>Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb: 10</td>
<td>Hgb: 4</td>
<td>2 units RBC’s</td>
</tr>
<tr>
<td>Platelets: 100k</td>
<td>Platelets: 20k</td>
<td>1 unit of platelets</td>
</tr>
</tbody>
</table>
Pathology Results shortly after arriving at Memorial Sloan-Kettering:

Metastatic Neuroblastoma
Neuroblastoma

First description of abdominal tumor termed then as "glioma" occurred in 1864 by German physician Rudolf Virchow.

Characteristics of tumors from the sympathetic nervous system and the adrenal medulla were noted by German pathologist Felix Marchand in 1891.

The tumor was named Neuroblastoma by James Homer Wright in 1910.
“Metastatic Neuroblastoma typically produces an abrupt ecchymotic proptosis that may be bilateral. A deposition of blood in the eyelids may lead to the mistaken impression of injury.”

“Commonly bone destruction is apparent, particularly in the lateral orbital wall or sphenoid marrow.”

**HAVE TO CONSIDER IN ANY PEDIATRIC PATIENT WITH ACUTE ORBITAL SIGNS**
Ophthalmic Findings

- Proptosis
- Periorbital ecchymosis
- Ptosis
- Horner's syndrome
- Anisocoria
- Opsclonus/Myoclonus
- Papilledema
- Retinal striae
- Other cranial nerve paralysis
- Blindness
Neuroblastoma

- Embryonal tumor arising during fetal or early postnatal life from sympathetic cells derived from the neural crest.

- It is the most common solid extracranial malignancy of childhood and the most common malignant tumor in infants.

- The overall incidence of neuroblastoma is 1 case per 100,000 children in the United States, or approximately 700 newly diagnosed patients per year.
Neuroblastoma

- The median age at diagnosis is about 16 months
- 95% of cases are diagnosed by 7 years of age
- The most common sites of origin of neuroblastic tumors are the adrenal region (48%), extraadrenal retroperitoneum (25%), and chest (16%). Less common sites are the neck (3%) and the pelvis (3%) and from ciliary ganglion
- Forty-eight percent of patients have metastatic disease at diagnosis
Neuroblastoma

- Some tumors disappear spontaneously without any therapy, while others progress with a fatal outcome despite the implementation of maximal modern therapy.

- However, strong prognostic factors can accurately predict whether children have “good” or “bad” disease at diagnosis, and the clinical stage is currently the most significant and clinically relevant prognostic factor.
<table>
<thead>
<tr>
<th>Tumor Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>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.</td>
</tr>
<tr>
<td>2A</td>
<td>Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.</td>
</tr>
<tr>
<td>2B</td>
<td>Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes negative microscopically.</td>
</tr>
<tr>
<td>3</td>
<td>Unresectable unilateral tumor infiltrating across the midline (beyond the opposite side of the vertebral column) with or without regional lymph node involvement, or midline tumor with bilateral extension via infiltration (unresectable) or lymph node involvement</td>
</tr>
<tr>
<td>4</td>
<td>Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S disease)</td>
</tr>
<tr>
<td>4S</td>
<td>Localized primary tumor (as defined for stage 1, 2A, or 2B disease) with dissemination limited to skin, liver, and/or bone marrow (limited to infants younger than 1 year, marrow involvement of less 10% of total nucleated cells, and MIBG scan findings negative in the marrow)</td>
</tr>
</tbody>
</table>

Source.—Reference 6.
International Neuroblastoma Staging System (INSS)
### Table 3: Children’s Oncology Group risk stratification for children with neuroblastoma

<table>
<thead>
<tr>
<th>Risk stratification</th>
<th>INSS stage</th>
<th>Age</th>
<th>Biology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>1</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>2A/2B (&gt;50% resected)</td>
<td></td>
<td>Any (&lt;365 days)</td>
<td>MYCN-NA, any histology/ploidy</td>
</tr>
<tr>
<td>4S</td>
<td></td>
<td>Intermediate</td>
<td>MYCN-NA, FH, DI &gt; 1</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td>0-12 years</td>
<td>MYCN-NA, any histology/ploidy*</td>
</tr>
<tr>
<td>2A/2B (&lt;50% resected or Bx only)</td>
<td>3</td>
<td>&lt;365 days</td>
<td>MYCN-NA, FH, DI &gt; 1*</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>&gt;365 days - 12 years</td>
<td>MYCN-NA, FH*</td>
</tr>
<tr>
<td>4S (symptomatic)</td>
<td></td>
<td>&lt;365 days</td>
<td>MYCN-NA, FH, DI &gt; 1*</td>
</tr>
<tr>
<td>Group 3</td>
<td>3</td>
<td>&lt;365 days</td>
<td>MYCN-NA, either UH or DI = 1*</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>&lt;365 days</td>
<td>MYCN-NA, FH, DI &gt; 1*</td>
</tr>
<tr>
<td>4S</td>
<td></td>
<td>&lt;365 days</td>
<td>MYCN-NA, either UH or DI = 1*; or unknown biology</td>
</tr>
<tr>
<td>Group 4</td>
<td>4</td>
<td>&lt;365 days</td>
<td>MYCN-NA, either DI = 1 or UH</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>365 - &lt;547 days</td>
<td>MYCN-NA, UH, any ploidy</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>365 - &gt;547 days</td>
<td>MYCN-NA, FH, DI &gt; 1</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2A/2B, 3, 4, 4S</td>
<td></td>
<td>Any</td>
<td>MYCN-amplified, any histology/ploidy</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>&gt; 547 days</td>
<td>MYCN-NA, UH, any ploidy</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>365 - &gt;547 days</td>
<td>MYCN-NA, UH or DI = 1</td>
</tr>
</tbody>
</table>

DI, DNA index; FH, favorable histology; MYCN-NA, MYCN not amplified; UH, unfavorable histology.

*If tumor contains chromosomal 1p LOH or unbalanced LOH, or if data are missing, treatment assignment is upgraded to next group.
Table 2

Descriptions of New INRG Tumor Stages

<table>
<thead>
<tr>
<th>Tumor Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>Localized tumor not involving vital structures, as defined by the list of IDRFs, and confined to one body compartment</td>
</tr>
<tr>
<td>L2</td>
<td>Local-regional tumor with presence of one or more IDRFs</td>
</tr>
<tr>
<td>M</td>
<td>Distant metastatic disease (except stage MS tumor)</td>
</tr>
<tr>
<td>MS</td>
<td>Metastatic disease in children younger than 18 months, with metastases confined to skin, liver, and/or bone marrow</td>
</tr>
</tbody>
</table>

Source.—Reference 8. Complete definitions of these stages are cited in the text. IDRFs = image-defined risk factors.
<table>
<thead>
<tr>
<th>INRG Stage</th>
<th>Age, months</th>
<th>Histologic category</th>
<th>Grade of tumor differentiation</th>
<th>MYCN</th>
<th>11q Aberration</th>
<th>Ploidy</th>
<th>Pretreatment risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1/L2</td>
<td></td>
<td>GN maturing; GNB intermixed</td>
<td></td>
<td>NA</td>
<td></td>
<td></td>
<td>A Very low</td>
</tr>
<tr>
<td>L1</td>
<td></td>
<td>Any, except GNB maturing or GNB intermixed</td>
<td></td>
<td>Amp</td>
<td></td>
<td></td>
<td>B Very low</td>
</tr>
<tr>
<td>L2</td>
<td>&lt;18</td>
<td>Any, except GNB maturing or GNB intermixed</td>
<td></td>
<td>NA</td>
<td>No</td>
<td></td>
<td>D Low</td>
</tr>
<tr>
<td></td>
<td>≥18</td>
<td>GNB nodular; neuroblastoma</td>
<td>Differentiating or undifferentiated</td>
<td>NA</td>
<td>No</td>
<td>Yes</td>
<td>E Low</td>
</tr>
<tr>
<td>M</td>
<td>&lt;18</td>
<td></td>
<td></td>
<td>Amp</td>
<td>Hyperdiploid</td>
<td></td>
<td>N High</td>
</tr>
<tr>
<td></td>
<td>&lt;12</td>
<td></td>
<td></td>
<td>NA</td>
<td>Diploid</td>
<td></td>
<td>F Low</td>
</tr>
<tr>
<td></td>
<td>12 to &lt;18</td>
<td></td>
<td></td>
<td>NA</td>
<td>Diploid</td>
<td></td>
<td>I Intermediate</td>
</tr>
<tr>
<td></td>
<td>&lt;18</td>
<td></td>
<td>Amp</td>
<td></td>
<td>Hyperdiploid</td>
<td></td>
<td>J Intermediate</td>
</tr>
<tr>
<td>MS</td>
<td>&lt;18</td>
<td></td>
<td>NA No</td>
<td></td>
<td>Yes</td>
<td></td>
<td>O High</td>
</tr>
<tr>
<td></td>
<td>≥18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P High</td>
</tr>
</tbody>
</table>

Adapted from Cohn et al.40

GN, ganglioneuroma; GNB, ganglioneuroblastoma.

Please define GNB + GN in the abbreviations footnote.
Prognosis

- Age at diagnosis
- Location of Tumor
- Microscopy
- Stage
Prognosis

- **Tumor Grade** – estimation of proliferative activity
- **DNA ploidy** – Hyperploidy is found in earlier stages of the disease and have better prognosis than diploid.
- **Cytogenetics** - N-MYC oncogene (amplification) tend to grow more quickly and are associated with a worse prognosis than children without the amplification.
- **Oncogene amplification** – ferritin, NSE, LDH
5 year Survival Rates

- Low Risk Disease: 95%
- Intermediate Risk Disease: 80-90%
- High Risk Disease: 10-40%
Role of the Ophthalmologist

1) Diagnosis and Staging by virtue of distant spread

2) Monitoring and Managing visual involvement
   ○ Decompression, strabismus, etc.

3) Monitoring response to both medical and surgical interventions
   ○ Stability of proptosis, vision, EOMS, fundus

4) Long term supportive treatment
Incidence, Ocular Manifestations, and Survival in Children with Neuroblastoma: A Population-Based Study

STEVEN J. SMITH, NANCY N. DIEHL, BRIAN D. SMITH, AND BRIAN G. MOHNEY

- PURPOSE: To determine the incidence, ophthalmic manifestations, and survival among children with neuroblastoma in a defined population.
- DESIGN: Population-based retrospective cohort.
- METHODS: The medical records of all pediatric (<19 years) residents of Olmsted County, Minnesota, diagnosed with neuroblastoma from January 1, 1969, through December 31, 2008, were retrospectively reviewed.
<table>
<thead>
<tr>
<th>Case No. (Year of Diagnosis)</th>
<th>Age at Diagnosis (Months)</th>
<th>Gender</th>
<th>Presenting Symptoms</th>
<th>Primary Site</th>
<th>Ophthalmic Site/Manifestations</th>
<th>Ophthalmic Complications</th>
<th>Treatment</th>
<th>F/U Duration (Months)</th>
<th>Final Outcome</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (1969)</td>
<td>42.6</td>
<td>F</td>
<td>Bilateral periorbital ecchymosis</td>
<td>R adrenal</td>
<td>Bilateral orbits/painful proptosis</td>
<td>Scleral hemorrhage</td>
<td>Chemotherapy</td>
<td>5.2</td>
<td>Pt deceased</td>
<td>IV</td>
</tr>
<tr>
<td>2 (1970)</td>
<td>21.5</td>
<td>M</td>
<td>Decreased appetite, listless, anorexia, hematuria</td>
<td>L adrenal</td>
<td>Right orbit/phtosis, right subconjunctival hemorrhage secondary to right temporal mass</td>
<td>Sluggish pupillary response</td>
<td>Radiation and chemotherapy</td>
<td>3.1</td>
<td>Pt deceased</td>
<td>IV</td>
</tr>
<tr>
<td>3 (1971)</td>
<td>16.5</td>
<td>F</td>
<td>Fever, rhinorrhea, cough, swollen L inguinal nodes</td>
<td>L adrenal</td>
<td>None</td>
<td>N/A</td>
<td>Resection, L adrenal and L inguinal nodes</td>
<td>309.6</td>
<td>Remission</td>
<td>IV</td>
</tr>
<tr>
<td>4 (1971)</td>
<td>4.6</td>
<td>F</td>
<td>Fever, vomiting, palpated RUQ mass</td>
<td>R adrenal</td>
<td>None</td>
<td>N/A</td>
<td>Resection, R adrenal mass and L supravacuicular mass</td>
<td>454.6</td>
<td>Remission</td>
<td>IVS</td>
</tr>
<tr>
<td>5 (1976)</td>
<td>29.7</td>
<td>F</td>
<td>Listless, purpura, thrombocytopenia, anemia</td>
<td>L adrenal</td>
<td>Bilateral orbits/right proptosis with ecchymosis and ptosis. Neurologic deficit, temporal lobe nodule</td>
<td>Difficulty depressing and abducting the right eye</td>
<td>Resection of L adrenal, L metastatic lymph nodes, L nephrectomy, Radiation and chemotherapy.</td>
<td>3.9</td>
<td>Pt deceased</td>
<td>IV</td>
</tr>
<tr>
<td>6 (1977)</td>
<td>34.8</td>
<td>F</td>
<td>Irritability, dehydration, fever, lethargy</td>
<td>L adrenal</td>
<td>Bilateral orbits/left proptosis with inward and medial displacement of the left globe, Bilateral metastasis.</td>
<td>Left esotropia with III, IV, and VI nerve palsies</td>
<td>Resection of L adrenal, L kidney, and L peri-aortic lymph nodes. Radiation and chemotherapy.</td>
<td>8.7</td>
<td>Pt deceased</td>
<td>IV</td>
</tr>
<tr>
<td>7 (1981)</td>
<td>24.5</td>
<td>M</td>
<td>Fatigue, fever, poor appetite, swollen L testicle</td>
<td>L adrenal</td>
<td>Left orbit/left proptosis and ecchymosis</td>
<td>N/A</td>
<td>Radiation and chemotherapy</td>
<td>3.5</td>
<td>Pt deceased</td>
<td>IV</td>
</tr>
<tr>
<td>8 (1987)</td>
<td>29.5</td>
<td>M</td>
<td>Bilateral periorbital ecchymosis, tender abdomen, ataxic gait</td>
<td>R abdomen</td>
<td>Bilateral orbits/bilateral periorbital ecchymosis.</td>
<td>N/A</td>
<td>Resection of R abdominal mass and peri-aortic lymph nodes</td>
<td>9.1</td>
<td>Pt deceased</td>
<td>IV</td>
</tr>
<tr>
<td>9 (1988)</td>
<td>37.9</td>
<td>M</td>
<td>Hydronephrosis, noted abdominal mass</td>
<td>R abdomen</td>
<td>None</td>
<td>N/A</td>
<td>Resection of abdominal mass. Chemotherapy.</td>
<td>245.4</td>
<td>Remission</td>
<td>III</td>
</tr>
<tr>
<td>10 (1990)</td>
<td>36.2</td>
<td>F</td>
<td>Decreased appetite, irritability, palpable LUQ mass</td>
<td>Abdomen</td>
<td>None</td>
<td>N/A</td>
<td>Chemotherapy</td>
<td>17.5</td>
<td>Pt deceased</td>
<td>IV</td>
</tr>
<tr>
<td>11 (1993)</td>
<td>31.3</td>
<td>F</td>
<td>Ataxia, irritability, fever, urinary incontinence</td>
<td>R adrenal</td>
<td>None</td>
<td>N/A</td>
<td>Resection of R adrenal tumor. Chemotherapy.</td>
<td>142.1</td>
<td>Remission</td>
<td>III</td>
</tr>
</tbody>
</table>

*Continued on next page*
RESULTS:
- 14 patients
- Average age at diagnosis: 22.5 months (0.4–42.6)

Ophthalmic Involvement:
- 6 patients (43%)
  * 4 bilateral, 2 unilateral
- Proptosis and Ecchymosis: 67%
- 9 month survival for those with orbital involvement was 17%
Patient update…

Currently being treated at Memorial Sloan-Kettering Cancer Center. Initial Systemic Workup revealed diffuse mets in bone marrow, multiple calvarial and skull base osseous metastases, as well as to right orbit. Primary was found thoracic paraspinal region.

He has been through a lot….

1. Bone Marrow Biopsy
2. Placement of Leukaphoresis catheter
3. 3 cycles of chemotherapy
4. Posterior Thoracotomy with excision of neuroblastoma from the superior posterior mediastinum
5. Chest tube placement
6. Insertion of double lumen right sided mediport
7. 4 cycles of chemotherapy with Cyclophosphamide/Doxorubicin/Vincristine
Reflective Practice

This case demonstrated the importance of a differential diagnosis when common entities are encountered. Expedited diagnosis and treatment is also important to patient and family when dealing with the unknown.
Core Competencies

- **Patient Care**: The case involved thorough patient care and attention to patient’s complaints. Once diagnosed, the patient received proper management and care.

- **Medical Knowledge**: This presentation allowed us to review the presentations, proper evaluation/work up, and different treatments.

- **Practice-Based Learning and Improvement**: This presentation included a current literature search of developing associations and current treatment modalities.

- **Interpersonal and Communication Skills**: The patient was treated with respect and every effort was made to communicate with the patient in a timely manner for the proper follow-up.

- **Professionalism**: The patient was treated in the proper manner. He was also referred to the proper specialist to treat her condition.

- **Systems-Based Practice**: The patient was discussed in detail with pediatric oncology colleagues in regard to follow up and treatment.
References

- Basic Science and Clinical Series: Orbit, Eyelids, and Lacrimal System: pages: 79-80
5 year old male with 2 month history of left periorbital edema misdiagnosed as a hematoma by emergency department and pediatrician. Urgent biopsy diagnosed as Rhabdomyosarcoma by first pathologist. Second opinion revealed final diagnosis of metastatic neuroblastoma subsequently found to be thoracic paraspinal primary. Patient is status post thoracotomy and currently undergoing chemotherapy.