Neuroblastoma

BIO 404/504 - Physiology-Medical Practice
Dr. Eric Toolson
TA Bethaney Fehrenkamp
Students: Emily Mazzei, Nada Kherbik, Patricia Viola, and Parwana Ebrahimi
Spring 2015
Neuroblastoma (NB) is the most common extracranial solid tumor seen in child.

Over half of children diagnosed present with metastatic disease.

Neuroblastomas arise from cells of neural crest that form the adrenal medulla and sympathetic ganglia.

(Maris et al, 2007)
Epidemiology

- 8% to 10% of all childhood cancers
- 10% cases per 1 million live births
- Most common malignant tumor of infancy
- Median age at diagnosis is 19 month
- There is no geographic or racial variations

(Brodeur and Maris, 2006)
Epidemiology

- Adrenal gland - 40%
- Abdominal - 25%
- Thorax - 15%
- Cervical - 5%
- Pelvis sympathetic - 5%
Signs and Symptoms

It can vary depending on the site of the tumor, the size, the metastatic stage and whether or not the tumor secrete hormones. Some of the symptoms are listed below:

- Metastasis spread to the bones around the eyes can lead to **periorbital ecchymosis** (bruise around the eyes) or **proptosis** (eye ball to stick out).
- A tumor in the abdomen or pelvis can reflect symptoms in other parts of the body. If it is pressing against or growing into the blood or lymph vessels, it can stop fluids from getting back to the heart leading to **swelling legs**.
- The pressure from a growing tumor can also affects the child’s bladder or bowel causing **urination** or **constipation**.
- **Coughing** and **breathing problems** can be cause by pressure on the throat or trachea.
- Metastasis to the bone marrow can lead to not have enough erythrocytes (red blood cells), leukocytes (white blood cells), or blood platelets. The decrease of erythrocytes leads to **anemia**, the decrease of leukocytes can lead to **recurrent infection** and the decrease of platelets leads to **hemorrhagic emergencies**.

(American Cancer Society, 2015)
Diagnosis Screening

The diagnosis of neuroblastoma is indicated by the presence of distinctive histology/pathological features of tumor tissue or the presence of tumor cells in a sample of bone marrow taken from the child, accompanied by increased concentrations of urinary catecholamines.

(Cohn, 2007)

Figure 1. Skeletal scintigraphy is used to identify metastasis sites.
Figure 2. CT scan of the abdomen

- Neuroblastoma mass crossing the middle of the body
- Tumor surrounding one of the main abdominal blood vessels
- Left kidney being compressed by the tumor
Diagnostic Exams

- Clinical/physical
  - Signs and Symptoms

- Image exams
  - X-ray
  - CT-scan
  - Ultrasound
  - MRI scan
  - Radionuclide Bone scan

- Histologic exams
  - Biopsy
  - Tissue diagnosis
Diagnostic Exams

- **Laboratory exams**
  - Routine investigations
  - Hemoglobin - Anemia in bone metastases
  - Vanillylmandelic acid (VMA)- test and catecholamine 24 hour urinary and serum
  - Homovanillic acid (HVA)
  - Two bone marrow aspirates
  - Serum ferritin (>142ng/ml) (directly related to the amount of iron stored in the body)
  - Serum lactate dehydrogenase (LDH) (1500 IU/ml)
  - Liver function test (LFT) (>100ng/ml)
Staging

International Neuroblastoma Staging System

- **Stage 1**: Localized tumor
- **Stage 2A**: Unilateral tumor with incomplete resection; identifiable lymph node negative for tumor.
- **Stage 2B**: Unilateral tumor with complete or incomplete resection; with ipsilateral lymph node positive for tumor; identifiable contralateral lymph node negative for tumor.
- **Stage 3**: Tumor infiltrating across midline involvement; or unilateral tumor with contralateral lymph node involvement; or midline tumor with bilateral lymph node involvement.
- **Stage 4**: Dissemination of tumor to distant lymph nodes, bone marrow, bone, liver, or other organs except as defined by Stage 4S.
- **Stage 4S**: Age <1 year old with localized primary tumor as defined in Stage 1 or 2, with dissemination limited to liver, skin, or bone marrow (less than 10 percent of nucleated bone marrow cells are tumors).

(American Cancer Society, 2015)
International Neuroblastoma Staging System (INSS)

Figure 3. Representation of the stages.

(NANT, 2015)
Pathogenesis

• Embryogenesis
  o Develop from residual microscopic neuroblastic nodules
  o Origin of extraadrenal neuroblastomas is unknown

• Molecular
  o Chromosomal deletion (1p,11q,14p)-50%
  o Amplification of oncogene MYCN (N-MYC) found in 25% of NB cells.
  o Gain of chromosome 17q material
  o Alterations in total DNA content
  o Expression of neurotrophic factors:
    - NGF and BDNF and receptors
  o Tumors of NB origin are classified according to the balance between neural type cells and schwann-type cells

(Park et al, 1993)
Figure 4. Genetic model of neuroblastoma development. (Brodeur, 2003)
Physiology and Pathology of NB

• The sympathetic nervous system consists of two main components
  o Sympathetic neurons organized in ganglia
  o neuroendocrine chromaffin cells: which form the adrenal gland.

• The sympathetic nervous system is the major derivative of the neural crest and develops in a process firmly controlled by restricted microenvironments encountered by neural crest cells during their migration within an embryo.

• The critical factor involved in this process is bone morphogenic proteins (BMPs) released from the dorsal aorta, which begin the differentiation of neural crest cells to sympathoadrenal lineage.

• Developed sympathoneural phenotype is activated by induction of multiple transcription factors, such as Phox2B, MASH-1, GATA3, Hand2 and myelocytomatosis viral oncogene neuroblastoma (MYCN) gene.

(Cazarnecka et al, 2012)
Physiology and Pathology of NB

• Immature sympathetic neurons obtain expression of TrkA receptor and become dependent on its ligand, nerve growth factor (NGF), for their survival.

• The developed sympathetic neurons reach the adrenergic phenotype associated with the ability to create and release their main neurotransmitter; norepinephrine
  o As a result, the enzymes involved in the synthesis of this catecholamine, tyrosine hydroxylase (TH) and dopamine-hydroxylase (DBH), are considered the most characteristic sympathetic markers.

• Although, development of the adrenergic phenotype is considered as the end stage of sympathetic neuron differentiation, in their small subset innervating sweat glands, periosteum and skeletal muscle vasculature, this process proceeds further and the neurons undergo a “cholinergic switch”.

(Cazarnecka et al, 2012)
Physiology and Pathology of NB

- Sympathetic Neurotransmitters in Neuroblastoma - Between Physiology and Pathology
  139 neurons acquire additional cholinergic features:
  - Expression of the enzyme involved in acetylcholine synthesis, choline acetyltransferase, and the ability to release this neurotransmitter.
  - The neurons have both adrenergic and cholinergic characteristics. Subsequently, however, their adrenergic properties are lost and the neurons become purely cholinergic.

- All these stages of sympathetic differentiation are reflected in various phenotypes of neuroblastomas.

(Cazarnecka et al, 2012)
Figure 5. Development of the sympathoadrenal lineage of the neural crest. As cells of the neural crest (represented by green and red cells) migrate, they undergo epithelial–mesenchymal transition (EMT). Some cells (red) migrate towards the dorsal aorta as they commit to the sympathoadrenal lineage. (Cheung, 2013)
Histology

- Microscopically, these tumors are arranged in sheets and pseudorosettes of:
  - small round blue cells
  - tumor cells immunostain for neuroendocrine markers such as chromogranin
Figure 6. Histology of neuroblastoma.

(Ohio State University, 2015)
Figure 7. Sympathetic neuron differentiation and neuroblastoma development.
(Cazarnecka et al, 2012)
Biochemistry of Neuroblastoma

• Neuroblastoma cells produce excess catecholamines (any of various amines such as epinephrine, norepinephrine, and dopamine) that contain a dihydroxy benzene ring, that are derived from tyrosine, and that function as hormones, neurotransmitters, or both.

• Patients with neuroblastoma have Urinary catecholamine metabolites.

• There is a correlation between the level of catecholamine and the stage of neuroblastoma.

• High level of vanillylmandelic acid (VMA)

• Ratio dopamine (DA)/ (VMA) showed to be useful for discrimination of stage 4 versus stage 4s.

(Strenger et al, 2007)
Treatment

- Surgery
- Radiation
- Chemotherapy
- Stem cell transplant

(Matthay et al, 1999)
Treatment

- Surgery establishes the diagnosis, stage of tumor, excise the tumor (if localized), and provide tissues for the biologic/pathologic studies.
- Stage I NB patients have a disease free survival rate of greater than 90% with surgical excision alone.
- Chemotherapy is indicated only in the case of recurrence in children; unless they show MYCN gene amplification and unfavorable histology.
- Radiotherapy increases local control in children with advanced stage IV or bulky stage III tumors.
  - External beam radiation therapy
  - MIBG radiotherapy (metaiodobenzylguanidine) is an analogue of norepinephrine that is concentrated in sympathetic nervous tissue via the noradrenalin transporter of neuroblastomas.

(Matthay et al, 1999)
Treatment

Figure 8. Probability of Event-free Survival among Patients Who Entered Both Phases of the Study and Who Were Randomly Assigned to Receive a Bone Marrow Transplant plus 13-cis-Retinoic Acid, Transplant without 13-cis-Retinoic Acid, Continuation Chemotherapy plus 13-cis-Retinoic Acid, or Continuation Chemotherapy without 13-cis-Retinoic Acid. Follow-up began at the time of the second randomization (34 weeks after diagnosis). Overall event-free survival was significantly better in the group treated with transplantation plus 13-cis-retinoic acid than in the group assigned to continuation chemotherapy without 13-cis-retinoic acid (P=0.02).

(Matthay et al, 1999)
Figure 9. Probability of Event-free Survival among Patients Assigned to Receive 13-cis-Retinoic Acid or No Further Treatment. Follow-up began at the time of the second randomization (34 weeks after diagnosis). The difference in survival between the two groups was significant at three years (P=0.027). (Matthay et al, 1999)
Case study of Neuroblastoma

An 18-month-old girl presents with difficulty sleeping, increased crying, and abdominal pain. The mother had a normal, full-term delivery, and has no major past medical history. The parents note that the child was healthy until around the last month, when she began waking up at night complaining of pain. They also note that she has been increasingly irritable and less willing to walk over the past 2 to 3 weeks. They deny fever, vomiting, diarrhea, or constipation. She has not lost any weight that they have noticed, although her appetite has been decreasing. After two days with swollen eye, they took her into the Emergency room because the swollen eye has persisted.
Case study of Neuroblastoma

Mother claims her daughter has been sleeping more and has been sick 3 times in the last month, but her daughter does go to daycare during the day. Mother claims that 2 nights ago when her daughter was playing with her uncle, her uncle lightly tossed her on to the bed and her daughter let out a loud shriek and took a while to calm down.

Signs at the Emergency room:

Temporal Temperature: 38.8 Celsius (normal: 36.0-38.0)
Heart Rate: 155 bpm (normal: 75-130)
Blood Pressure: 115/70 mm Hg (normal 95-105/56-68)
Respirations: 40 (normal 25-35)
Oxygen Saturation: 90

(Pediatric surge pocket guide, 2009)
Case study of Neuroblastoma - Emergency Room Doctor

- **What are the first things to do at the ER?**
  “We would do a CT or MRI of the head, along with Urinalysis and blood work to check for electrolyte and blood abnormalities”.

- **If during examination the doctor notes mass on the abdominal, when do you start to think it maybe neuroblastoma?**
  “We would worry about a space occupying lesion in the head with the irritability and swollen eye. A pediatric emergency MD might think of neuroblastoma right off the bat. The rest of us would consider it after a tumor was visualized on CT or MRI of head and abdomen”.

- **When do you have a clear diagnosis of neuroblastoma?**
  “This is a diagnosis that would be suggested by imaging”.
Case study of Neuroblastoma - Emergency Room Doctor

- Do you ask for CT, MRI, other test at the ER, or refer her immediately to a specialist?
  “I would order CT or MRI right away after talking to a radiologist”.

- How often do you see neuroblastoma Patients at ER?
  “Almost never, but I have done mostly adult patients in my career”.

- Why is this cancer happening with young children from evolutionary medicine point of view?
  “One possibility is that childhood cancers are more likely than not to involve imprinted genes. Parent of origin effects seem to be involved in many childhood tumors, This evolutionary phenomenon needs more study.”
Case study of Neuroblastoma -
Emergency Room Doctor

- Picture of Kylie Howard* during the E.R. appointment showing swelling eyes and periorbital ecchymosis.

*permission to use photos of Kylie was given by her mother.
Case study of Neuroblastoma - Neurosurgeon

● Who usually make the referral to the Neurosurgeon?

“This is typically a tumor of children. The pediatrician is the typical source of referral”.

● Should this patient see a Neurosurgeon or a Pediatric neurosurgeon?

“This patient should see a pediatric specialist ideally, however in our group this varies based upon the comfort level of the individual neurosurgeon. I have an interest in pediatrics and will typically consult our pediatric specialist for more input”.

● What would be the prognosis of Neuroblastoma of this specific case?

“These tumors can be devastating. The child is too young for adjuvant radiation therapy and so will only get chemotherapy. I would need to know more about the location of the tumor size etc to determine prognosis”.
In the case above, at which stage the Neurosurgeon will get involve?

“The neurosurgeon is consulted immediately. It is our job to obtain tissue for pathology. Many medulloblastomas now have very promising genetic analysis which can lead to dramatically different outcomes. In some case a major debulking of tumor volume may be indicated. In some cases only a small tissue sample is obtained lest the surgery leave the patient with significant neurological deficit”.

What is the order in this case of chemotherapy, and radiation therapy, and surgery? And why the order in these steps of treatments is important?

“In general surgery is done first. There may be need for further surgery – for placement of cerebrospinal fluid diversionary shunt for example. Chemotherapy will follow. This child is likely too young for radiation”.

Case study of Neuroblastoma - Neurosurgeon
Case study of Neuroblastoma - Neurosurgeon

Kylie after brain surgery

- Brain surgery was done because 2 tumors exploded in the head causing hemorrhaging which clogged the pathway for any of the fluid or blood to drain out of the brain.

- The tube on top of the head was placed to drain any extra fluid that remained in the brain.
Case study of Neuroblastoma - Neurosurgeon

- Another surgery needed to be done due to another massive brain bleed

- The brain bleed was on the top right of the head, pressing on the part that controls the left side of her body

- A piece of her skull had to be removed to allow the brain to swell, and was placed inside her stomach, until the swelling went down and could be placed back in her head
Case Study of Neuroblastoma

- Neuroblastoma is a rare cancer that does not get very much attention and therefore has very limited funding and research.

- This will lead to not having the right treatment and localized chemotherapy

- Unfortunately due to the limitation of research and drugs available Kylie relapsed and her little body couldn’t fight anymore.

- We chose this topic to bring awareness to this rare disease
In Honor of Kylie Rowand
Acknowledgements

• This case is based on real facts about Kylie Rowand and the chronological sequence was made up for our group.

• We interviewed several professionals to answer some questions to help our understanding this disease.

• We would like to thank Dr. Joe Alcock MD (Associate Professor at University of New Mexico - Department of Emergency Medicine) and Dr. Suguna Pappu, MD, PhD (Assistant Professor of Neurosurgery at University of New Mexico - Department of Neurosurgery) for being so nice and neighbourly to answer our questions.
References


