Opsoclonus-Myoclonus and Neuroblastoma
An introduction:

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**Today's Talk:**

1. High correlation of Neuroblastoma and OMA
   - Need for surveillance

2. What is Neuroblastoma?
   - How does Neuroblastoma present?
     - Not one disease – range of presentations
     - What ‘causes’ neuroblastoma?
     - Treatment: vary according to stage

3. Does Neuroblastoma cause OMA?
   - Or OMA cause Neuroblastoma?
     - Or neither?

4. Managing Neuroblastoma and OMA at the same time

Questions / Concerns?
Correlation of OMA and Neuroblastoma:

Neuroblastoma is rare:

>90% of cases are in children under 5yrs of age
Approximately 8-10 cases per million children (varies with age)
about 700 cases/ year in usa
Distribution between boys and girls about equal

OMA is very rare:

About 0.2 cases per million - 50X less common than neuroblastoma
--only about 2% of neuroblastoma cases involve OMA

Compare to childhood diabetes  3-400 cases per million.
Two Rare Diseases:

Neuroblastoma is detected in about 50-60% of all OMA patients even though both diseases are rare, This is a very high concordance.

OMA is a ‘paraneoplastic syndrome’ for neuroblastoma

*Association is not Causation:* We don’t know how OMA develops or if neuroblastoma induces OMA

*Surveillance:* But we do know that we need to look for Neuroblastoma in OMA patients
Opsoclonus-Myoclonus with no neuroblastoma - ? Other inflammatory signals? Infections, autoimmunity, other?

Possible connections:
cross reactive antibodies

GOOD:
Anti-tumor immune response
Clears cancer

BAD
Uncontrolled inflammation
Auto-immune antibodies
Cross-reactive to nerves?

Neuroblastoma

Activated Inflammation Signals

Immune response

B-cells

T-cells

Dendritic cells

macrophages

GOOD:
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Surveillance- Detection of Neuroblastoma:

**Radiology:**
MRI scans, CT scans – detects masses in chest/abdomen/pelvis

**Nuclear scans:**
MIBG – specific for most neuroblastoma *(not all)*
(Uptake of metaiodobenzylguanidine)

**Urine Tests:**
HVA/VMA – specific for metabolic products of most neuroblastomas *(not all)*

Should used combined modalities for first year (or until all negative) then decrease frequency of monitoring. MIBG alone is not sufficient. MRI is typical these days for anatomic imaging.
Biomarkers for OMS and Neuroblastoma:

Need: sensitive marker that corresponds to disease severity or recurrence.

New markers for neuroblastoma: circulating (blood) microRNAs, DNA, May reflect inflammatory response

Will these also be useful in OMA?
Neuroblastoma 101:

**NOT a Brain Tumor:**
Arises from peripheral sympathetic nervous system:

**Tumors in the abdomen and chest and pelvis**
- Paraspinal – 50% (chest and abdomen)
- Adrenal gland – 30%
- 20% other sites (pelvis, head, and neck)

95% of cases in children less than 5 years of age
Most in children less than 2 years of age

**Presentation varies dramatically:**
- Stage 1 – solitary tumor,
- Stage 2 spread to local lymphnodes
- Stage 3 larger tumor, + lymphnodes
- Stage 4 metastatic –
  - Bone, Bone marrow, liver
  - Skin, lymphnodes, kidney
  - Almost never to the lungs or brain
    (unlike other types of cancers)

Special Stage 4S – metastatic but regresses
- (more later)
Neuroblastoma is *not* a single disease: Treatments depend on spread and biology

Very low risk (stage 4s, infants): observation-regression

Low Risk (stage 1-2) no MYCN: observation, small chemo, ?radiation

Intermediate risk (larger tumors), histology: more chemo, surgery, radiation

High risk (metastatic), aggressive: Intensive chemo, immunotherapy, surgery Radiation, MIBG radiation, others

Differentiated

Less aggressive

Poorly differentiated

Undifferentiated

More aggressive
Neuroblastoma 101: treatments

1. **Low risk**: (most common for OMA patients)
   - Biopsy and observation
     - Intermittent MRI/MIBG and urine tests (interval 3-6 months, then yearly)
   - These tumors most often regress by themselves
   - Or ‘mature’ and don’t grow
   
   {Stage 4s (for special) - about 10% of cases
    - often spontaneously resolves and does not return.
    - This is the only case of a metastatic tumor that resolves by itself.}

2. **Intermediate risk**: larger tumors, spread to nodes
   - Biopsy, then chemotherapy
     - 4-8 cycles of **moderate** intensity chemotherapy (about 6 months)
   - Then observation

3. **High risk**: metastatic disease or multiple risk factors
   - Biopsy, then chemotherapy
   - More **intensive**, about 9-12 months, requires long term follow up
   - Risk for relapse
Take home points:

Neuroblastoma in OMA is typically:
**Low Risk**: a single lesion, no MYCN amplification, etc.
Observation, and frequent surveillance

Neuroblastoma can be MIBG negative- need additional imaging
Urine catecholamines also can be negative

Treatment of intermediate or high risk neuroblastoma requires chemotherapy and close follow up.

Surveillance includes MRI/CT scans, MIBG scans, Urine markers
Tumor doesn’t grow very fast (unlike leukemia)

Our understanding of immunology and ‘auto-immune’ responses to cancer is rapidly evolving.
New research into how cancer alters the immune system may be applicable to OMS in the future.
Some recent references:

Update on diagnosis, treatment, and prognosis in opsoclonus–myoclonus–ataxia syndrome

A prospective study of the presentation and management of dancing eye syndrome/opsoclonus–myoclonus syndrome in the United Kingdom

Outcome and Prognostic Features in Opsoclonus-Myoclonus Syndrome From Infancy to Adult Life
Pediatrics, 128, 2, e389-394, 2014

Opsoclonus myoclonus syndrome in neuroblastoma a report from a workshop on the dancing eyes syndrome at the advances in neuroblastoma meeting in Genoa, Italy, 2004
Cancer Letters 228 (2005) 275–282
Thank you !

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