Opsoclonus Myoclonus Ataxia (OMA) Syndrome and Oncology

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Neuroblastoma

- 2nd most common solid tumor in pediatrics (behind brain tumors)
- Most common solid tumor in < 1 year olds
- Contribute 15% of cancer-related deaths
- ~650 cases/year in US
- Median age 22 months
  - 36% < 1 year
  - 79% < 4 years
- 2/3 of patients present with metastases
- Less than 5% are > 10 years
Neuroblastic Tumors with OMA

• Gambini et al, Virchows Arch 442:555, 2003:
  – 10/15 (66%) Ganglioneuroblastoma, intermixed
  – 4/15 (27%) Neuroblastomas of NB with OMA had abundant interstitial or perivascular lymphoid infiltrates
  – 1/15 (7%) Ganglioneuroma
Other Clinical Features

Tate et al, Neurology A447, 2003:
88 cases (41% with NB)

- Irritability and mood disturbances
- Facial palsy described rarely; drooling common
- Head tilt and strabismus in 33%
- Seizures in 10%
- Early symptoms: falling, body jerks, drooling
- Later symptoms: opsoclonus, hypotonia, speech problems
- Misdiagnosis as acute cerebellitis (brain inflammation) common
OMA with Neuroblastoma

- > 50% of OMS = paraneoplastic syndrome
- 2-3% of neuroblastoma present with OMS
- Prognosis of tumor is excellent
  - 90% 2 year survival
- Prognosis for OMS
  - 70-80% with neurologic sequelae
  - Motor and speech delay, behavioral difficulties, cognitive deficits
- Favorable disease stage correlates with worse neurologic outcome
POG Experience with OMA
(Russo et al, MPO 28:284, 1997)

• 29 children with NB and OMA, 1983-1993
• Stage A 18, stage B 3, stage C 7, stage D 1
• MYCN amplification (High Risk) in 0/17
• Treatment NB
  – surgery alone 19/29
  – surgery + chemotherapy 10/29
• Treatment OMA
  – Steroids 26 (prednis. 12/ ACTH 14)
  – IVIG 6
POG Experience with OMA (cont)

Outcome of OMA

• Resolution OMA 18/29 (62%)
  – 37% with surgery alone in one study
• Persistent neurologic deficit in 20/29 (69%)
  – speech delay
  – cognitive
  – motor
  – behavioral
• Complete recovery in 9 patients, of whom 6 received chemotherapy as part of treatment
CCG Experience with OMA
(Rudnick et al, MPO 36:612. 2001)

• Questionnaire study 1980-1994 all NB with serum banked
• Demographics, presentation, treatment, survival and neurologic outcome
• Sera tested for variety of anti-neuronal antibodies (case-control)
• OMA in 21/675 patients (3%)
Presentation of OMA

- Opsoclonus, Myoclonus and Ataxia 13 (60%)
- Two of the above 6 (30%)
- Either opsoclonus or ataxia alone 2 (10%)

- Time to diagnosis of NB <6 months 18 (85%)
- Time to diagnosis of NB ≥6 months 3 (15%)
Treatment: 15 resolved OMA

• Treatment of OMA
  – Steroids 10
  – Steroids + ACTH 1
  – ACTH alone 2
  – IVIG + steroids/ACTH 5
  – None 3

• Treatment of Tumor
  – Surgery + chemotherapy 12 (57%)
  – Surgery alone 9 (43%)
Survival of Patients with OMA

OMA  N=21

Non-OMA  N=654

P=0.004
Survival with OMA
Age >1 and Stage-stratified

Stratified P=0.261
Survival with Loco-regional Neuroblastoma and OMA

- OMA, Stage I, II, III >1
  N=18
- Non-OMA, Stage I, II, III, >1
  N=134

P=.0222
Patient characteristics in OMA different than non-OMA

- Age: Only 1/21 OMA patients <1 yr at Dx
- Advanced stage (3+4) in 43% OMA vs. 75% non-OMA
- Male:female: 0.5 in OMA vs. 1.22 in non-OMA*
- Abdominal primary in 69% vs. 79%*
- MYCN amplification in 6% vs. 23%*
- Histology unfavorable in 18% vs. 52%*

*None of these differences significant after stratification for stage and age
## Relative Risk of Neurologic Sequelae

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<th>N</th>
<th>N-Sequelae</th>
<th>RR</th>
<th>P-value</th>
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<tr>
<td>Age &lt;2</td>
<td>12</td>
<td>10</td>
<td>1.14</td>
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<td>≥2</td>
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<td>4</td>
<td>0.78</td>
<td>0.3</td>
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<td>Stage 1+2</td>
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<td>11</td>
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<td>3+4</td>
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<td>3</td>
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<td>OMA to Dx &lt;6 mo.</td>
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<td>13</td>
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<td>≥6 mo.</td>
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<td>1</td>
<td>0.71</td>
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<td>Primary abdominal</td>
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<td>non-abd</td>
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Relative Risk of Neurologic Sequelae cont

<table>
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<th>Treatment</th>
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<td>Rx OMA steroids</td>
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<td>IVIG + steroids</td>
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<td>4</td>
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<tr>
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<td>1</td>
<td>0.52</td>
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<td>Rx tumor: surgery</td>
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<td>1.14</td>
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<td>Surgery + chemo</td>
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<td>Antineuronal Ab +</td>
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<td>Ab -</td>
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<td>3</td>
<td>1.43</td>
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Lymphocytic infiltrates and follicles in neuroblastoma with OMA

(Cooper et al, MPO 36;623, 2001)
Lymphocyte Infiltrates

- Gambini et al, Virchows Arch 442:555, 2003:
  - 12/15 (80%) cases of NB with OMA had abundant interstitial or perivascular lymphoid infiltrates
  - 91 age- and stage-matched NB without OMA had much less lymphoid infiltration
Antineuronal Antibodies

• Dalmau et al, Cancer 75:99, 1995:
  – 4/71 NB had anti-Hu Ab, but antigens present on more than half the tumors without Ab
  – Seropositive patients had longer survival

• Connolly et al J Pediatr 130:878, 1997:
  – 9 children with OMA (3 NB) and 41 controls
  – All OMA had anti-neuronal Ab; none of controls
Antineuronal Antibodies  
(Antunes et al. JPHO 2000; 22:315)

- Sera from 16 children with OMA associated with NB, and 48 age-stage matched controls
- Human cerebellum and rat brain IHC
- Western Blot using neurons, Purkinje cells, HuD, NBL cells
- 81% of OMA Vs. 21% of controls had IgG anti-neuronal Ab
COG OMA Study: ANBLOOP3
Specific Aims

• Outcome using chemotherapy + prednisone
• Determine in a randomized study whether IVIG improves response of OMA
• Determine whether chemotherapy, prednisone and IVIG improves functional outcome compared to historical control
• Investigate the biology of OMA
  – Antineuronal antibodies, CSF, MRI, Tumor biology
• Better define the long-term prognosis
ANBL00P3 Schema

OMA & NB
Age <21
No prior Rx
New Dx

Cytoxan* & Prednisone
+ IVIG

NR-1 mo.
+ ACTH

NR-3 mo.
+ IVIG

*Stage 3/4: A3973 or A3961 + Prednisone ± IVIG

NR - 6 mo.: Off protocol therapy
OMA summary

• Neurologic and developmental sequelae in about 70%
• Survival >90%
• Low stage in 80%
• Anti-neuronal antibodies in >80%
• Unknown if more immunosuppressive treatment can prevent late sequelae
OMA and Oncology

Questions?