Opsoclonus Myoclonus Ataxia
Family Symposium
November 11, 2014
WELCOME!

11 – 1105 am  Welcome and Introductions  Tim Lotze, M.D.
Dept of Child Neurology

1105 - 1140 am  Past, present, and future of OMA  Tim Lotze, M.D.

1140 am – 1215 pm  Tumors and OMA  Jason Shohet, M.D.
Dept of Oncology

1215 - 1250 pm  Rehabilitation Needs of OMA  Desi Roge, M.D.
Dept of Physical Medicine and Rehabilitation

1250 - 120 pm  Lunch - OMS Life and Pablove  Mike Michaelis and Naveen Viswanatha

120 - 155 pm  Neurocognitive Outcomes  Karen Evankovich, Ph.D.
Dept of Psychology

155 - 230 pm  Community and School Support  Diane Murrell, LCSW
Dept of Social Work

230-3 pm  Panel Q and A
Overview

• History of Opsoclonus Myoclonus Ataxia
• The Cerebellum
• OMA and other autoimmune encephalopathies
• Biomarkers in disease
• OMA Etiology
• OMA Natural History
• OMA Current Treatment
• Future Directions
Kinsbourne Syndrome

- 1962: Marcel Kinsbourne
- Other names:
  - Myoclonic Encephalopathy of Infants
  - Dancing Eyes-Dancing Feet syndrome
  - Dancing Eyes syndrome Nystagmus
  - OMA and OMS
The Cerebellum

• “Little brain”

• Functions

  - Motor control: coordination, precision, timing

  - Attention

  - Language

  - Emotional responses
Opsoclonus Myoclonus Ataxia Syndrome

• Opsoclonus = “dancing eyes”

• Myoclonus = muscle jerks

• Ataxia = falling and poor coordination

• Encephalopathy = constant altered behavior

• Commonly misdiagnosed initially as acute cerebellar ataxia
OMA Cause and Effect

• Neuroblastoma (~50% of cases)
  - Theorized that some may have had tumor that spontaneously dissolved

• Infectious trigger (more common in older)
  - Mycoplasma pneumoniae
  - Salmonella enterica
  - Rotavirus
  - Cytomegalovirus
  - Human herpesvirus 6
  - Hepatitis C

• Demyelinating disease (MS; rare)

• No clear cause
Other autoimmune diseases of the central nervous system

• NMDA Receptor antibody encephalitis
• Antibody related dementias and epilepsies
• Hashimoto’s Encephalopathy
• Multiple Sclerosis
• Neuromyelitis Optica
Other neurological paraneoplastic syndromes

• Adults >>> kids
• NMDA Receptor Antibody Encephalitis - teratoma
• Myasthenia gravis – thymoma
• Limbic encephalitis– lung cancer
The Importance of Biomarkers in Disease

- What is the diagnosis?
- What is the cause?
- What is the best treatment?
- Is this a relapse?
- What is the prognosis?

a measurable indicator of some biological state or condition
The Immune System and Autoimmunity

Macrophage  T-Cell  B-Cell

Activated T-Cell  Plasma Cell
Variability in Course of OMS

• Monophasic
  - Complete Remission

• Multiphasic
  - Relapsing – Remitting

Symptoms

Time

Ataxia
Opsoclonus
Encephalopathy

Mild Ataxia
Intermittent Opsoclonus

Residual problems
Neuropsychiatric Manifestations

• Acute Period
  - Irritability
  - Sleeplessness
  - Rage
  - Staring spells

• Chronic Relapsing Period
  - Obsessive Compulsive
  - Oppositional Defiant
  - ADHD
  - Mood Disorders
  - Cognitive Impairment
  - Language Disorders (expressive > receptive)
Behavioral, Language, Cognitive Outcomes

• 105 US cases of OMS

• 52% of patients had relapses

• Residual Behavioral, Language, Cognitive concerns
  - Sleep issues: 46% insomnia, 77% nighttime awakening
  - 58% OCD spectrum, 65% ODD, 79% rage attacks, 47% hyperactive, 29% Depression, 19% ADHD.
  - Language: 50% only ½ of speech was intelligible
  - 41% resource education, 24 % mainstream, 35% combined

Tate ED et al J Pediatr Oncol Nurs. 2005 Jan-Feb;22(1):8-19
Behavioral, Language, Cognitive Outcomes

• Boston Children’s/London Study
  - 54 subjects with Neuropsychological evaluation(s)
    • 29 @ 2 evals
    • 37 with formal IQ eval
      • FSIQ 90 (VIQ 90; PIQ 85)
  - IQ not related to +/- tumor, gender, time to tx
  - IQ related to relapse #, no remission, higher OMA score
  - Some correlation b/w IQ and amount of treatment received
Treatment Options

• Surgical Removal of Tumor
  - Two year monitoring in tumor negative (MRI + MIBG)

• Immunomodulation
  - Cytoxan vs. rituximab
  - Steroids
    • Pred vs. Dexamethasone vs. ACTH
  - IVIG
  - Cellcept and Imuran
Cytoxan

- Chemotherapeutic agent with immunomodulatory effects

<table>
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<tr>
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<th>Complete Response of OMA</th>
<th>No Response</th>
<th>Total</th>
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<tbody>
<tr>
<td>Cytoxan</td>
<td>22 (78%)</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>No Cytoxan</td>
<td>17 (47%)</td>
<td>19</td>
<td>36</td>
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<tr>
<td>Total</td>
<td>39</td>
<td>25</td>
<td>64</td>
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Steroids (Prednisone vs Dexamethasone)

• Many doses used in different treatment regimes
• No head to head comparison trials
• Prednisone daily and tapered slowly
• Dexamethasone given as a monthly pulse
• Both have been able to achieve remissions
• Relapses may occur when tapering
ACTH

• Works by stimulating adrenal gland production of corticosteroids

• Side effects are similar to Prednisone/Dexamethasone

• Can be difficult to administer and expensive
IVIG

• 81% positive response to IVIG + CTX + pred vs. 26% response to CTX + pred alone
  - Response = decrease OMA symptoms/score

• 34% relapse rate across all subjects
  - Relapse = not able to wean steroid or increase OMA symptoms/score

Say What?
Rituximab

• Finding of expanded B cells in CSF prompted trials with Rituxan

• Antibody against B-cells

• Largest trial: 12 pts severe dz.
  - ACTH, IVIG, Rituximab.
  - 17% relapse rate.
  - No long term neurocognitive data yet.
Response to IVIg, ACTH + Ritux

A) Clinical Response

B) Motor Components

- Gait ataxia
- Opsoclonus (at rest)
- Action myoclonus
Adjunctive/Supportive Care

• Neuropsychological evaluation
• Physical/Occupational/Speech Therapy
• Behavioral Support
• Sleep Hygiene
Treatment Recommendations

• Rituximab x 2 doses (redose?)

• IVIg monthly

• Dexamethasone monthly pulse dose

• Consider ACTH and cyclophosphamide
Future Directions

• Establish patient registry
  - Define natural history including long term outcomes
  - Define relapse

• Cause and Effect Studies
  - Genetics
  - Environmental triggers
  - Vitamin D
  - Gut microbiome
  - Biomarker studies

• Clinical trials
  - Current and future therapeutics
  - Cognitive and physical rehabilitation
Thanks!

OMS Life
Autoimmune Reaction

Neuroblastoma

Virus

Antigen

Antigen-Presenting Cell

Activated T Cell

Th

Ts

Cytotoxic T Cell

Brain Injury

Antibodies

B Cell

Activated B Cell

Cytokines

Resting T Cell
Current clinic demographics

- 16 patients
  - F:M = 2.2 : 1
  - Current median age: 5 years
  - 10 with neuroblastoma; 1 with ganglioneuroma
Long Term Outcomes with OMS

• Published reports very similar
  - neurocognitive function
  - Relapsed/residual motor symptoms

• Not related to findings on imaging
  - Rarely signs of cerebellar atrophy
  - No studies published with functional imaging evaluation*

• Some evidence that neurocognitive function worse in those with relapses

Howard K. et al J. Pediatr 2001;139;552-559
Genetics and OMS

• German study: 13 out of 82 OMS parents (15.8%), but only two out of 100 controls (2.0%) had a history of autoimmune disease

• Autoantibodies detected in 12 out of 28 OMS parents (42%) and in 4 out of 50 controls (8%)
  - anti-myelin (5), anti-GAD- (1) and anti-axonal (1) autoantibodies

• May explain why only a subset of NBL pts develop OMS
Pathophysiology behind OMS

• Imaging rarely with changes
  - Cerebellar vermis (Ataxia)
  - Pons (Opsoclonus)

• Handful of autopsies
Pathophysiology behind OMS

• Autoimmune Disease
  - Response to immunomodulatory agents
  - Genetic predisposition
  - Presence of lymphoid infiltrate in tumor

• Leading Hypothesis
  - “Onconeural antigens: antigens shared by brain and tumor
  - Molecular mimicry leads to “friendly fire” attack on the brain
  - No specific universal antibody has been found

Pathophysiology behind OMS

• Evidence of Immune Dysregulation – B cells in CSF
  - CSF B Cells have been found to be increased
  - CSF T helper to Cytotoxic T Lymph ratio is reduced
  - CXCL10 an inflammatory chemokine found to be elevated in the brain, recruiting lymphocytes across the BBB
  - Cytokine BAFF found to be elevated in CSF compared to serum
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Response to IVIg, ACTH + Ritux

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CSF B Cell Reduction

% CSF CD19+ B cells

P < 0.0001

-93%

Pre-rituximab
Post-rituximab

D

Clinical-Immunological Relation

% of baseline

Time from initiation of rituximab (months)

Total score
Serum IgM
Blood B cells

% Reduction