Opsoclonus-Myoclonus and the Neuroimmunology of Neuroblastoma

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• Prof Dale believes he has no conflict of interest in this presentation
Overview: OMAS

• Clinical syndromes: Opsoclonus Myoclonus Ataxia Syndrome (OMAS) and other
• The trigger
  – Neural crest tumor, infections, idiopathic
  – Tumour histology and immunology
• Autoantibodies
  – Cell surface paradigm, and the evidence (or not) for autoantibodies in OMAS
• Other immune mechanisms
• Treatment
• The natural history and 21st century outcomes
Questions

1. Is OMAS a single entity (a disease) or a syndrome?
2. How does the tumour initiate OMAS?
3. Is OMAS a cell surface antibody associated syndrome? Or other immune mediation?
4. What is the brain region affected in OMAS?
5. What is the treatment approach and are we changing the natural history of disease?
Clinical spectrum of paraneoplastic disease associated with NBL

• Opsoclonus myoclonus ataxia spectrum

• Other uncommon:
  – Narcolepsy/catalepsy
  – Digestive
OMAS: The clinical syndrome

• A highly recognisable syndrome in its complete form...beware the ‘forme frustes’ or incomplete forms...

• 4 key features
  – Opsoclonus (can be transient)
  – Myoclonus (may be misinterpreted as tremor)
  – Ataxia
  – Irritability, behavioural change, sleep problems, cognitive and developmental regression
Demographics

• Any age from infancy to adult
• But peak 1-3 years (median 16 months in Japanese cohort, 18 months in UK cohort)
OMAS triggers: Case 1

18 month old
Previously well

Identified abdominal neuroblastoma
OMAS triggers: Case 2

6 year old girl
Previously well

Sore throat one week before onset
No neural crest tumour
OMAS triggers: Case 3

8 year old girl
Previously well

Fever and Enterovirus pcr positive in CSF

No neural crest tumour

Ocular flutter, myoclonus, ataxia

Good outcome 2 weeks after steroids IVIG
OMAS %associa+ons%UK%cohort%n=101%

Brunklaus et al Pediatrics 2011

OMAS associations UK cohort n=101

OMAS Japanese cohort n=23

Hasegawa et al. Brain Dev 2015
OMAS and Neuroblastoma

• OMAS occurs in 2-3% of all Neuroblastoma cases

• Neuroblastoma found in ~40% of OMAS cases

Rudnick et al. Med Pediatr Oncol 2001
Tumor detection

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Percentage tumours detected</th>
</tr>
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<tbody>
<tr>
<td>CT</td>
<td>100%</td>
</tr>
<tr>
<td>MRI</td>
<td>100%</td>
</tr>
<tr>
<td>MIBG</td>
<td>75%</td>
</tr>
<tr>
<td>Urine catecholamines</td>
<td>24%</td>
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</table>

Thoracic 33%
Abdominal/Pelvic 67%

Brunklaus et al 2012
The tumour

• Neural crest tumours found in 40-50% of OMAS cases (higher rates more recently with better imaging)
• Can be neuroblastoma, neurogangliomas, other neural crest tumours
• Can have low metabolic activity (catecholamine secretion), relevant to ‘tumor detection’
Mechanisms of neuroblastoma regression (and initiation of OMAS)

Garrett and Bagatell, Nat Rev Clin Oncol 14
Less metastatic disease in OMAS

Rudnick et al. Med Pediatr Oncol 2001
Survival:
Better NBL survival in OMAS v non-OMAS

Regardless of staging, children with OMAS-NBL are more likely to survive than NBL without OMAS

Rudnick et al. Med Pediatr Oncol 2001
Neuroblastoma with OMAS have more inflammatory infiltration of tumour

Blinded review:
Diffuse is 50% microscopic view

Lymphocytes: CD20 (B cells), also CD4 and CD8 (T cells)

Cooper et al Med Clin Oncol 2001
Tumour immunology

Immune reactivity against tumour is protective for patient survival

Immune reactivity against tumour can promote auto-reactive immune response
The paraneoplastic hypothesis

Tumour induction of autoimmunity. McKeon and Pittock, 2011
## Autoantibodies

<table>
<thead>
<tr>
<th>Detail</th>
<th>Onconeuronal antibodies</th>
<th>Cell surface antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examples</td>
<td>Anti-Hu, Ma</td>
<td>Anti-NMDAR, anti-AQP4</td>
</tr>
<tr>
<td>Antigen localisation</td>
<td>Intracellular</td>
<td>Cell surface</td>
</tr>
<tr>
<td>Epitope</td>
<td>Linear, or conformational</td>
<td>Conformational</td>
</tr>
<tr>
<td>Pathogenicity</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Dominant immune mechanism</td>
<td>T-cell, degeneration</td>
<td>Humoral (B cell, antibody)</td>
</tr>
<tr>
<td>Therapeutic reversibility</td>
<td>Usually not</td>
<td>Yes, often</td>
</tr>
</tbody>
</table>

- **Pathogenicity**: No, Yes
- **Therapeutic reversibility**: Usually not, Yes, often
Autoantibody detection: principle
Recent developments

• Paradigm:
  – autoantibodies that are important in CNS disease bind to the extracellular domain of important cell surface antigens such as neuronal receptors
Proof of an autoantibody binding to cell surface neuronal antigen

IgG binds to cell surface of live cultured hippocampal rat neurones. Performed by Fabienne Brilot. Dale et al, Brain 2012
Evidence of ‘cell surface antibody’ in OMAS

• Serum IgG binding to live cultured rat cerebellar granule cells in 10/14 OMAS (Blaes et al 2005). Unknown antigen.

• Mostly IgG3 (Beck et al 2007)

• ‘Idioapthic OMAS’ more likely to have cell surface IgG binding than OMAS-NBL (Blaes et al 2008)

• IgG has some functional effects on cell survival (Korfei et al 2005)
Evidence of ‘cell surface antibody’ in OMAS

- IgG binding to live cultured rat cerebellar/brainstem/cortical neurones in only 4/35 sera from OMAS (denritic, extrasynaptic antigen)

Panzer et al 2015
**Description of opsoclonus myoclonus with specific cell surface autoab**

<table>
<thead>
<tr>
<th>Cell surface antibody</th>
<th>Finding</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA-A receptor</td>
<td>2/18 patients with GABA-A receptor antibodies had opsoclonus myoclonus</td>
<td>Petit-Pedrol et al 2014</td>
</tr>
<tr>
<td>GABA-B receptor</td>
<td>1/20 patients with GABA-B receptor antibodies had opsoclonus myoclonus</td>
<td>Hofberger et al 2013, Kruer et al 2014</td>
</tr>
<tr>
<td>NMDA receptor</td>
<td>Case report</td>
<td>Kurian et al 2010</td>
</tr>
<tr>
<td>Novel cell surface antigen</td>
<td>NMDAR negative patients with teratoma associated opsoclonus</td>
<td>Armangue et al 2014</td>
</tr>
</tbody>
</table>

**SUMMARY:** Most OMAS patients are negative for known cell surface antibodies: NMDAR, LGI1, Caspr2, Glycine R (Panzer et al 2015)
## Onconeuronal or intracellular autoab in OMAS

<table>
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<tr>
<th>Autoantibody</th>
<th>Finding</th>
<th>Ref</th>
</tr>
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<tbody>
<tr>
<td>Immunohistochemistry against cerebellar neurones</td>
<td>Cerebellar, purkinje cell binding common</td>
<td>Antunes et al 2000 Jen et al 2012</td>
</tr>
<tr>
<td>Variable binding using immunohistochemistry and western blot</td>
<td>Different patients have different staining patterns</td>
<td>Panzer et al 2015</td>
</tr>
<tr>
<td>Anti-Hu, Ri, Yo</td>
<td>0/59 positive</td>
<td>Pranzatelli et al 2002</td>
</tr>
<tr>
<td></td>
<td>Occasional anti-Hu positive</td>
<td>Antunes et al 2000</td>
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<tr>
<td></td>
<td></td>
<td>Honnorat et al 2013</td>
</tr>
<tr>
<td>Anti-GAD</td>
<td>Case report</td>
<td>Markakis et al 2008</td>
</tr>
<tr>
<td>Other intracellular antigens</td>
<td>Neuroleukin</td>
<td>Candler et al 2006</td>
</tr>
</tbody>
</table>

**SUMMARY:** Patients with OMAS often have IgG binding to cerebellar/other tissue, but no common antigens.
Autoantibodies: summary

- Novel Cell surface antibody present in minority of patients.
- No syndrome specific cell surface antibody to date
- Intracellular IgG binding to cerebellar tissue common
- No common intracellular antibody finding
- OMAS may have heterogenous immunobiology
Other immune factors

Garay and McAllister 2010
Other B cell (humoral factors)

<table>
<thead>
<tr>
<th>Finding</th>
<th>Detail</th>
<th>Reference</th>
</tr>
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<tr>
<td>Intrathecal oligoclonal bands</td>
<td>Detected in 35%</td>
<td>Pranzatelli et al 2011</td>
</tr>
<tr>
<td>CSF B cell expansion</td>
<td>B cell expansion</td>
<td>Pranzatelli et al 2004</td>
</tr>
<tr>
<td>Elevation of B cell associated chemokines</td>
<td>CXCL13, BAFF</td>
<td>Pranzatelli et al 2013 Raffaghello et al 2013</td>
</tr>
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</table>

SUMMARY: evidence of broader Humoral immune activation
# T cell associated findings

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<th>Detail</th>
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</tr>
</thead>
<tbody>
<tr>
<td>T cell CD4 count in CSF and blood</td>
<td>Some reduction</td>
<td>Pranzatelli et al 2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sottini et al 2009</td>
</tr>
<tr>
<td>Th2 associated chemokines</td>
<td>Elevation of serum CCL17 and CCL22</td>
<td>Pranzatelli et al 2013</td>
</tr>
<tr>
<td>CSF neopterin, marker of interferon species</td>
<td>Elevated in 33%</td>
<td>Pranzatelli et al. 2004</td>
</tr>
<tr>
<td>T cell mediated chemokines</td>
<td>Elevated CSF Interferon gamma inducible protein 10 (CXCL10): CXCL10</td>
<td>Pranzatelli et al 2013</td>
</tr>
</tbody>
</table>

**SUMMARY:** Evidence of T cell activation and T cell involvement
The ‘brain region of attack’

<table>
<thead>
<tr>
<th>Feature</th>
<th>Proposed region involved</th>
</tr>
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<tbody>
<tr>
<td>Opsoclonus</td>
<td>‘Omnipause’ neurones of brainstem</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Brainstem</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Cerebellum or connections</td>
</tr>
<tr>
<td>Irritability</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Sleep dysfunction</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>Cortex, cerebellum</td>
</tr>
</tbody>
</table>

SUMMARY: generally considered a predominant brainstem-cerebellar syndrome
The ‘region of attack’

Acute MRI normal
5/5 follow-up MRI showed pan-cerebellar atrophy
Hayward et al 2001

MRI at follow-up
Voxel-based morphometry shows reduced cerebellar grey matter (but also posterior cortical regions)
Anand et al 2015
CSF neurofilament elevated in (untreated) OMAS

Neurofilament light chain is a marker of neuronal/axonal injury.

OMAS targets neurones/axons and not glia. Pranzatelli et al, J Neuroimmunol 14
Natural history and treatment of OMAS
Outcomes
(UK treated cohort over 53 years)

Median follow-up 7.3 years (range 3-32)
Chronic-relapsing course predicted poor outcomes

Brunklaus et al Pediatrics 11
Autoimmune CNS disease: Treatment

Remove tumour if present/relevant (inadequate alone)

1\textsuperscript{st} line therapy for acute disease: Methyl-prednisolone PLUS oral steroids, IVIG or plasma exchange

\downarrow

2\textsuperscript{nd} line therapy for acute disease: Rituximab, cyclophosphamide

\downarrow

Treating chronic disease, preventing relapse: 2\textsuperscript{nd} line agents and/or steroid sparing agents (azathioprine/mycophenolate mofetil) or rituximab
Therapeutic principles

In OMAS:

1. Untreated neuroinflammation results in permanent damage and permanent neurodisability
2. Induce a complete remission and tolerate no residual symptoms or signs
3. Avoid relapse, treat any relapses rapidly and completely
Scenario 1

Start corticosteroid (ACTH, IVMP, oral prednisolone)
+/- IVIG or plasma exchange

Scenario 1:
Rapid improvements back to normal
Slow wean oral prednisolone months

Monitor
Tolerate no symptoms or signs and no relapses
Scenario 2

Start corticosteroid (ACTH, IVMP, oral prednisolone)
 +/- IVIG or plasma exchange

Scenario 2:
Incomplete improvements
Use rituximab or cyclophosphamide

Monitor
Tolerate no symptoms or signs and minimise relapses (very slow alternate day steroid over years)
The evidence: therapeutic decision making

• There are no randomised controlled trials!

• All data is retrospective or prospective unblinded uncontrolled, or cohort studies
Therapeutic decision making

Conventional: corticotropin +/- IVIG

Multimodal: Corticotropin PLUS rituximab, cyclophosphamide or steroid sparing

SUMMARY: Combination therapy improves outcomes
Rituximab improves impairment

- Rituximab improves outcome scores
- Reduces CSF B cells

Pranzatelli et al, J Pediatr Hematol Oncol 06
Early rituximab therapy is better than late therapy

Better outcomes in OMAS patients given rituximab early (<1 year) compared to late (> 1 year)

Dale et al, Neurology 14
Outcomes improving with more aggressive immune therapy

15 new patients treated 2002-2012 (BLUE)

Compared to 24 ‘old patients’ treated in same institution reported in 2002 (RED)

More contemporary aggressive immune therapy improves outcomes in adaptive behaviour, intelligence and motor ability

Mitchell et al. JCN 15
Summary, and comparison with anti-NMDAR encephalitis

<table>
<thead>
<tr>
<th></th>
<th>OMAS</th>
<th>Anti-NMDAR encephalitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age onset</strong></td>
<td>Infancy, childhood</td>
<td>Infancy-young adulthood</td>
</tr>
<tr>
<td><strong>Movement disorder</strong></td>
<td>Opsoclonus, myoclonus, ataxia</td>
<td>Stereotypy, chorea, dystonia, akinesia</td>
</tr>
<tr>
<td><strong>Other features</strong></td>
<td>Cognitive and speech regression, behaviour disorder</td>
<td>Memory and speech dysfunction, behaviour disorder, seizures</td>
</tr>
<tr>
<td><strong>Paraneoplastic</strong></td>
<td>~40%</td>
<td>~5% (children), ~50% adults</td>
</tr>
<tr>
<td><strong>Regional target</strong></td>
<td>Neurones: Cerebellum, brainstem, cerebral cortex</td>
<td>Neurones: cerebral cortex, basal ganglia, brainstem</td>
</tr>
<tr>
<td><strong>Antigenic target</strong></td>
<td>Unknown</td>
<td>NMDA receptor</td>
</tr>
<tr>
<td><strong>Autoimmune process</strong></td>
<td>Not clear, likely humoral, possibly heterogenous</td>
<td>Autoantibody, humoral</td>
</tr>
</tbody>
</table>
### Summary, and comparison with anti-NMDAR encephalitis

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<thead>
<tr>
<th></th>
<th>OMAS</th>
<th>Anti-NMDAR encephalitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td>ACTH/corticosteroid, IVIG, cyclophosphamide, rituximab</td>
<td>Steroid, IVIG, cyclophosphamide, rituximab</td>
</tr>
<tr>
<td><strong>Relapses</strong></td>
<td>~50%</td>
<td>~15%</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Cognitive, behavioural, motor</td>
<td>Cognitive and behavioural</td>
</tr>
</tbody>
</table>

IN BOTH DISORDERS: Uncontrolled evidence that EARLY, AGGRESSIVE TREATMENT OF SEVERE DISEASE IMPROVES OUTCOMES AND REDUCES RELAPSES
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