



Opsoclonus-Myoclonus Syndrome: A Neuroimmunologic Enigma

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OMS overview

- Onset can be explosive or subacute over several weeks
- General first-line therapies are ACTH/steroids +/- IVIg +/- Cyclophosphamide +/- Rituximab
- Many patients appear to be exquisitely steroid-responsive
- There are “super-responders” and non-responders for all therapies
- Long-term neurobehavioral issues are common – 50-80%

Known Neuroimmunologic Disorders

Multiple Sclerosis

Acute Disseminated Encephalomyelitis

Idiopathic Transverse Myelitis

Idiopathic Optic Neuritis

Chronic Relapsing Idiopathic Optic Neuritis (CRION)

Neuromyelitis Optica

Isolated CNS Vasculitis

Autoimmune Encephalitis (e.g. anti-NMDA receptor antibody encephalitis, “limbic encephalitis,” autoimmune epilepsy, etc)

Hashimoto’s encephalopathy (SREAT – steroid responsive encephalopathy associated with thyroiditis)

Opsoclonus-Myoclonus Syndrome

Neuroimmunologic Disorders Regarded as Chronic, Relapsing with a Known/Presumed Degenerative Phase

Multiple Sclerosis (MS)

Acute Disseminated Encephalomyelitis

Idiopathic Transverse Myelitis (TM)

Idiopathic Optic Neuritis (ON)

Chronic Relapsing Idiopathic Optic Neuritis (CRION)

Neuromyelitis Optica (NMO)

Isolated CNS Vasculitis (CNS-V)

Autoimmune Encephalitis (e.g. anti-NMDA receptor antibody encephalitis, “limbic encephalitis,” autoimmune epilepsy, etc)

Hashimoto’s encephalopathy (SREAT – steroid responsive encephalopathy associated with thyroiditis) (HE)

Opsoclonus-Myoclonus Syndrome (OMS)

Known Possible Association with Tumors/Neoplasms

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Opsoclonus-Myoclonus Syndrome

Figuring out a Neuroimmunologic Disorder

- Clinical findings and syndrome
 - Depth of findings, variability of symptoms
- Self-limited or not?
- Imaging correlate
- Spinal fluid or blood biomarker
- Other ancillary biomarkers (EEG, OCT, VEP, etc)

OMS – The search for biomarkers

- What is a biomarker?
 - a measurable substance in a person whose presence is indicative of some phenomenon such as disease, infection, or environmental exposure
- Biomarkers can be an imaging marker, a blood test, spinal fluid test, or neurophysiologic test
- Ideally, something that is objective evidence of disease that can be measured and repeated

Imaging Markers?

- The imaging is “normal” in the vast majority of cases
 - EEG/evoked potentials data does exist that implicates some degree of cortical involvement
- Several isolated cases have reported lesions in the pons
- The fastigial nucleus of the cerebellum has been implicated as possible key lesion site
- Several cases followed long-term exhibit progressive cerebellar atrophy
- One study of two patients showed hyperperfusion in the cerebellum (especially centrally) in SPECT (single photon emission computed tomography) in an acute case and hypoperfusion throughout cerebellum in a chronic OMS case

Autopsy Data

- One adult case showed diffuse loss of cerebellar Purkinje cells and dentate neurons
- Another adult case showed similar findings plus some evidence of demyelination and IgG deposits along Purkinje cells and various parts of the cerebellum
- Another case series of 3 OMS patients noted perivascular concentrations of lymphocytes throughout multiple areas in the brain

Infections associated with OMS/OMA

- West Nile virus
- HHV-6
- HIV
- E. coli sepsis
- Leptospirosis
- Influenza A
- Hepatitis C
- Mycoplasma
- HPV-vaccine related
- Salmonella
- Enterovirus
- Borrelia Burgdorferi
- Streptococcus
- EBV
- CMV

- Reports of infections can only suggest association, difficult to 100% determine causation

OMS – Infections?

Antibodies associated with OMS/OMA

- GABA-A, GABA-B antibodies
- Anti-Hu (anti-neuronal nuclear antibody type 1)
- GQ1b antibodies
- GAD (glutamic acid decarboxylase antibodies)
- Glycine receptor antibodies
- Anti-Ri (anti-neuronal nuclear antibody type 2)
- Anti-NMDA receptor antibodies
- Anti-VGCC antibodies
- NB-binding antibodies
- Cerebellar neuron binding antibodies (neuronal surface)
- Celiac antibodies
- Anti-neuroleukin antibodies

- In a larger study of about 55 OMS patients, Pranzatelli did not find anti-Hu, Ri, Yo Ab
- Another earlier study notes that there is autoantigen diversity – so the sera of various OMS patients reacts with one or more antigens

OMS - Antibody markers?

The B cell...

CSF B-Cell Expansion in Opsoclonus–Myoclonus Syndrome: A Biomarker of Disease Activity

Michael R. Pranzatelli, MD,^{1,2*} Anna L. Travelstead, BS, MT (ASCP),³ Elizabeth D. Tate, FNP-C, MN,¹
Tyler J. Allison, BS,¹ and Steven J. Verhulst, PhD⁴

Role of BAFF in Opsoclonus-Myoclonus syndrome, a bridge between cancer and autoimmunity

Lizzia Raffaghello,^{,1} Verena Fuhlhuber,^{†,1} Giovanna Bianchi,^{*} Massimo Conte,[‡] Franz Blaes,[†]
Claudio Gambini,[§] and Vito Pistoia^{*,2}*

BAFF/APRIL system in pediatric OMS: relation to severity, neuroinflammation, and immunotherapy

Michael R Pranzatelli^{1*}, Elizabeth D Tate¹, Nathan R McGee¹, Anna L Travelstead², Jerry A Colliver³,
Jayne M Ness⁴ and Richard M Ransohoff⁵

Take-Home Messages from Pranzatelli's work

- An abundance of evidence (to varying degrees) of elevation in various cytokines, chemokines (in addition to B cells in general), most of which implicate at least a prominent role of B cell biology in the pathogenesis
- Various markers relate well to steroid responses, IVIg, rituximab, and/or ACTH responses
- A single unifying molecular mechanism remains elusive

Why is this important?

- Clinical

- Acute: establishing a reliable biomarker will “clinch” the diagnosis, likely lead to earlier intervention
- Acute/Chronic: A reliable antibody marker for any patient opens up different therapeutic avenues

- Research

- A reliable marker for OMS patients, whether they be acute or chronic would be important when testing new/novel interventions

Disease	Clinical Syndrome(s)	Diagnostic Test (blood, CSF)	Imaging Marker - Acute	Imaging Marker - Relapses	Subtypes Yes/No	Mono or Polyphasic	
MS	Yes	No	+++	+++	Yes	Poly	
ADEM	Yes	No	+++	+	No	Mono*	
TM	Yes	No	++	++	Yes/No	Mono*	
ON	Yes	No	+++	N/A	No	Mono	
CRION	Yes	No	+++	+++	No	Poly	
NMO	Yes	Yes*	+++	+++	No*	Poly	
CNS-V	Yes	No	++	++	No	<i>Mono/Poly</i>	
AE	Yes	Yes*	+/-	---	Yes*	<i>Mono/Poly</i>	
HE	Yes	Yes*	+/-	---	No	<i>Mono/Poly</i>	
OMS	Yes	No	---	---	?	<i>Mono/Poly</i>	

What is a relapse?

- “to suffer deterioration after a period of improvement...”
- “to fall back or slip into a former state...”
- “the return of an illness after a period of improvement...”
- “recurrence of a past medical condition...”

A Neuroimmunologist's definition of a relapse

- A relapse is a new and/or sustained neurological event secondary to *immune-mediated inflammation*
- But... how do we prove there is immune-mediated inflammation going on??

The Problem of Uhthoff and His Phenomenon

- Wilhelm Uhthoff reported on patients who had optic neuritis that had **recurrence** of their **same symptoms** that was reversible
- Menses, exercise, infection, fever, psychological stress, and high ambient air temperatures reduce the rate of nerve conduction
- Symptoms can persist **until stressors are eliminated**
- In this phenomenon, **NO NEW IMMUNE-MEDIATED DAMAGE IS OCCURRING**

But that's an MS thing... Does it happen in other diseases..?

- Short answer: Yes....and.... No
- The mechanism of Uhthoff's as it relates to symptom recurrence is specific to MS and demyelinating diseases, BUT patients that have CNS insults (stroke, traumatic brain injury, etc) can have re-exacerbation of old symptoms during times of infection and other stressors

So, are infection-induced relapses in OMS true immune-mediated relapses?

- Unknown
- Pranzatelli's work would argue/suggest 'Yes' but markers of inflammation that are elevated during relapses may be a consequence of the processes rather than the cause, in addition, if an infection is going on, I would expect inflammatory markers to be elevated
- Conversely, many patients appear to respond to therapies being given for their immunomodulatory properties (steroids, IVIg) but that's not to say they don't have other effects on the body

Acute vs Chronic Immunomodulatory Therapies

- Acute
 - Steroids
 - IVIg
 - Plasma exchange
 - Cyclophosphamide
- Chronic
 - Rituximab, other anti-CD20 therapies
 - Mycophenolate mofetil, azathioprine, many others* (used in varying degrees in other autoimmune conditions)

The more things change...

- Historical MS patients treated with pulsed doses of steroids, IVIg, cyclophosphamide did horribly compared to their modern-day counterparts
- Largely, these treatments are temporary bridging agents BUT if there is a *chronic, relapsing autoimmune process* – one could argue a more aggressive therapy should be considered

Why?

- Time is tissue
- Determining what is sequelae of the initial OMS event vs ongoing autoimmune insult is particularly challenging

Other B-cell therapies

- Anti CD20
 - Afutuzumab
 - FBTA05
 - Fletikumab
 - Ocaratuzumab
 - Ocrelizumab
 - Ofatumumab
 - Tositimomab
 - Veltuzumab
- Anti BAFF
 - Belimumab
 - Tabalumab
- Anti Plasma cell
 - Bortezomib
 - Carfilzomib

Bortezomib for chronic relapsing thrombotic thrombocytopenic purpura: a case report

Sean Yates,¹ Karen Matevosyan,¹ Cynthia Rutherford,² Yu-Min Shen,² and Ravi Sarode¹

Non B-cell therapies

- Natalizumab?
 - Works by blocking adhesion of lymphocytes to endothelial walls (blood vessels) preventing their entry into the CNS
- Odulimomab?
 - Directed against alpha chain of LFA-1 (found on all T cells, B cells, macrophages, and neutrophils – recruited to site of infection)
- Toralizumab?
 - Anti CD154 – important for T cell co-stimulation, eliminates/reduces germinal centers (prevents antibody-mediated maturation (B cells))
- Alemtuzumab?
 - Anti CD52 – protein present on all mature lymphocytes – “deletion of immune system”

Other Aggressive therapies for autoimmune conditions

- High-dose immunoablative cyclophosphamide
- Allogeneic stem cell transplantation

Clinical Trials

- European Trial: Dexamethasone vs Dexamethasone + Cyclophosphamide vs Dexamethasone + Rituximab. Each patient escalates from the first to each of the next treatments if not adequately responding (recruiting now)
- Children's Oncology Group (USA): NBL-associated OMS/OMA – steroids/cyclophosphamide + IVIg vs steroids/cyclophosphamide alone - adding IVIg improved short-term improvement, little effect long-term

Moving Forward

- Introducing novel therapeutic approaches for OMS?
- Are their subtypes of OMS?
 - Similar syndromes with various causes with distinct mechanisms vs unifying mechanisms across different cases?
- Are all relapses immune-mediated? Some?
- Are the cognitive/behavioral changes reflective of an ongoing immune-mediated process vs repercussions of the initial event?

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