

Opsoclonus Myoclonus Ataxia Family Symposium

November 11, 2014



**Texas Children's
Hospital®**

BCM®

Baylor College of Medicine



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

- 1927: Orzechowski K. De l'ataxie dysmetrique des yeux : Remarques sur l'ataxie des yeux dite myoclonique (opsoclonie, opsochorie).
- 1962: Marcel Kinsbourne
- Other names:
 - Myoclonic Encephalopathy of Infants
 - Dancing Eyes-Dancing Feet syndrome
 - Dancing Eyes syndrome Nystagmus
 - OMA and OMS



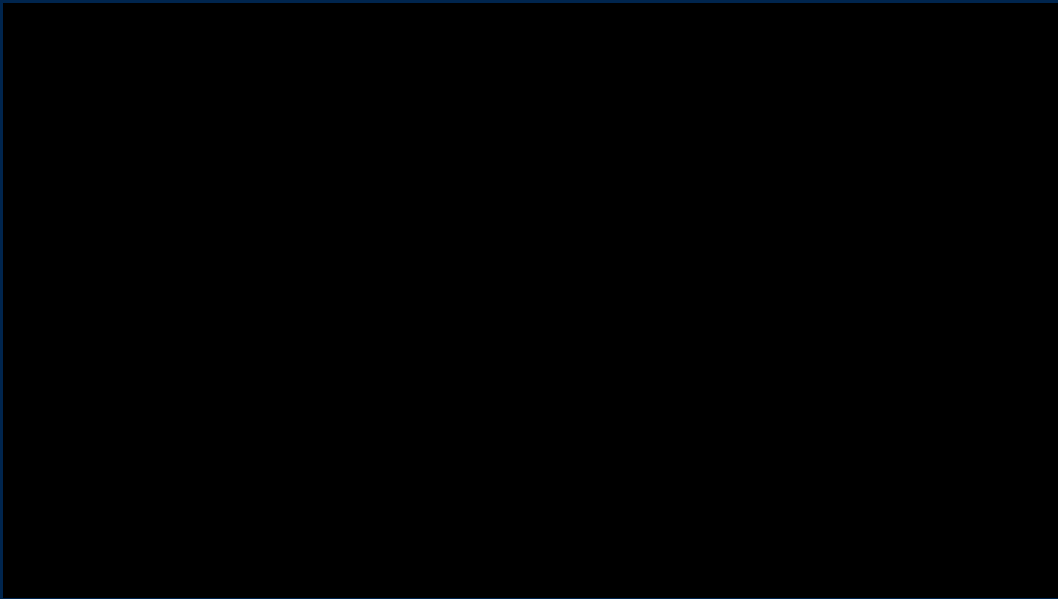
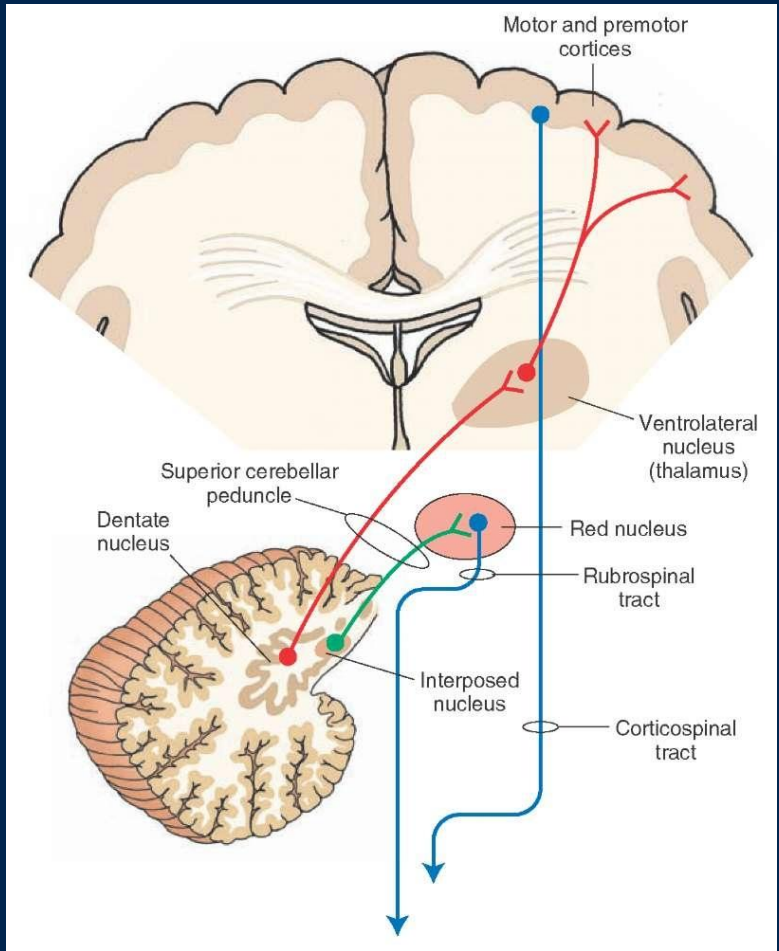
The Cerebellum

- “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

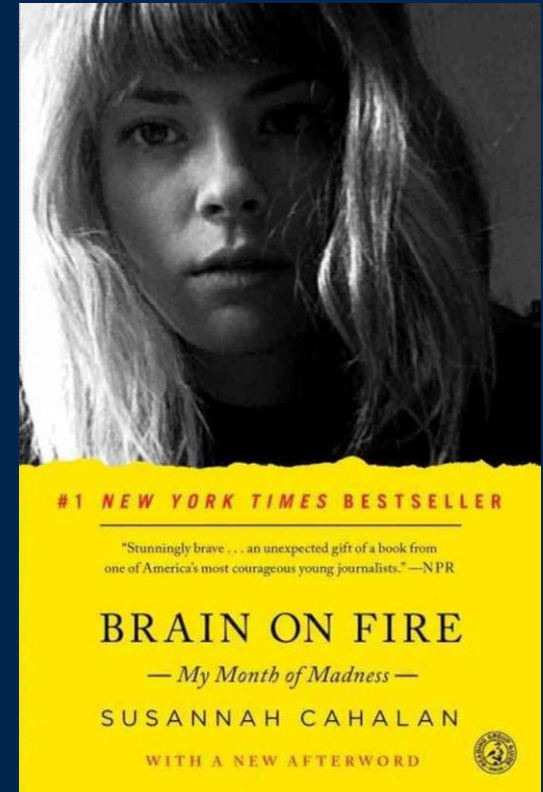
OMA Cause and Effect

- 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

a measurable indicator of some biological state or condition

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



The Immune System and Autoimmunity

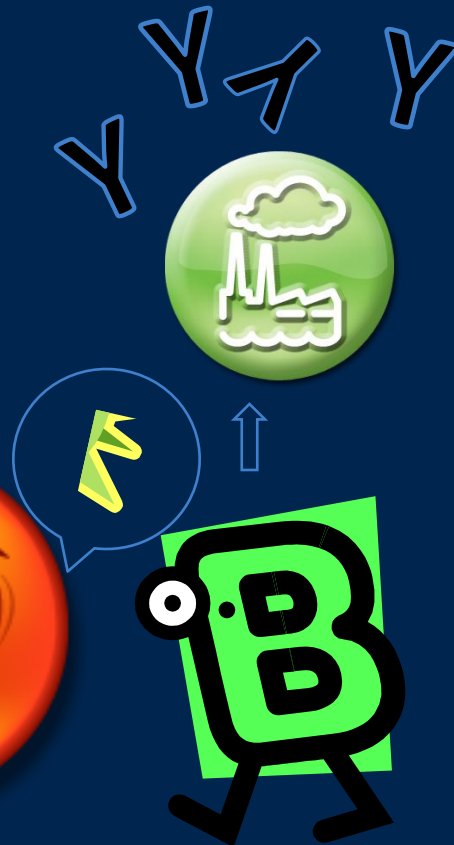
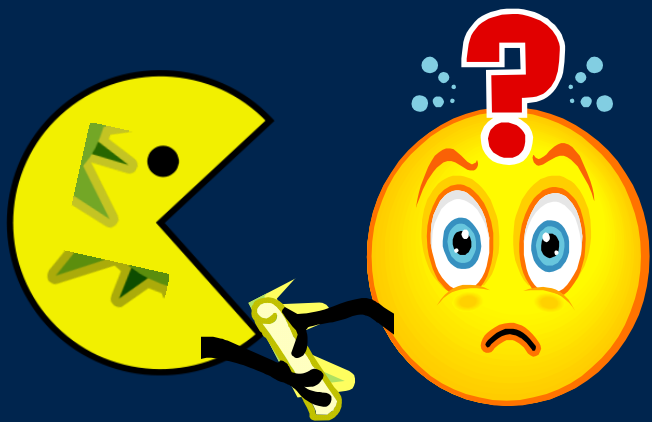
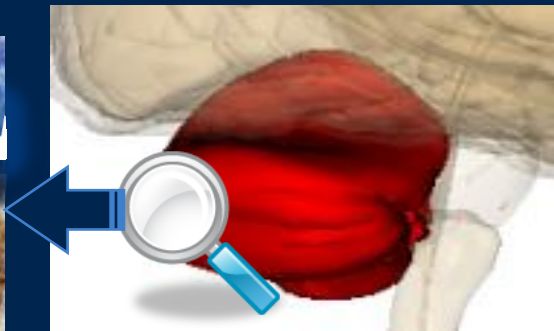
Macrophage T-Cell B-Cell



Activated T-Cell



Plasma Cell



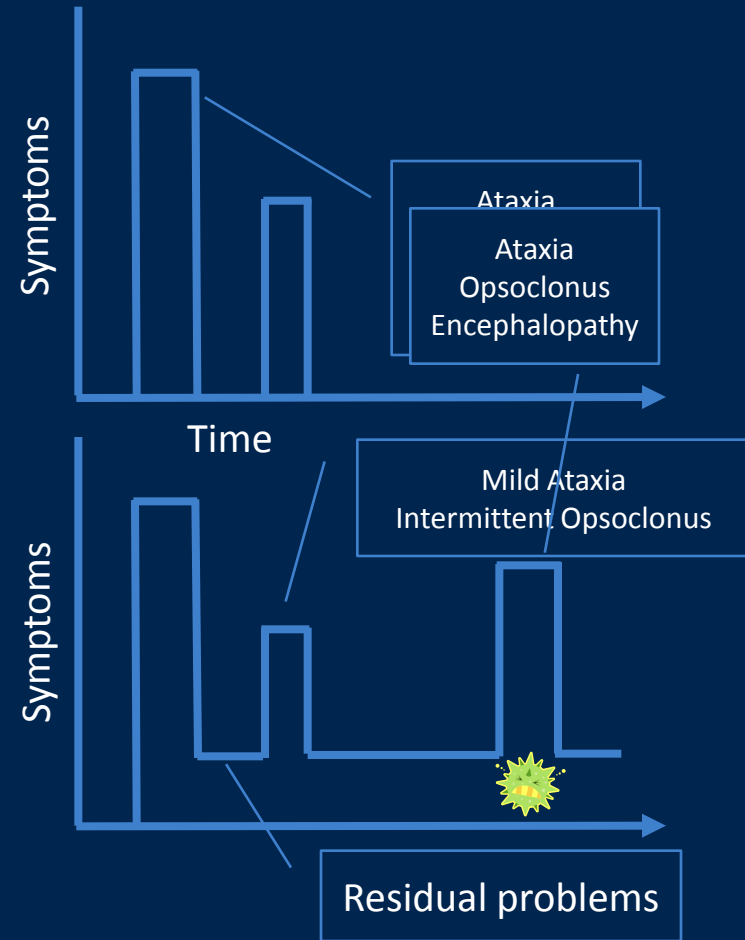
Variability in Course of OMS

- Monophasic

- Complete Remission

- Multiphasic

- Relapsing – Remitting



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

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

- Cytosan vs. rituximab
- Steroids
 - Pred vs. Dexamethasone vs. ACTH
- IVIG
- Cellcept and Imuran

Cytosan



- Chemotherapeutic agent with immunomodulatory effects

	<u>Complete Response of OMA</u>	No Response	Total
Cytosan	22 (78%)	6	28
No Cytosan	17 (47%)	19	36
Total	39	25	64

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

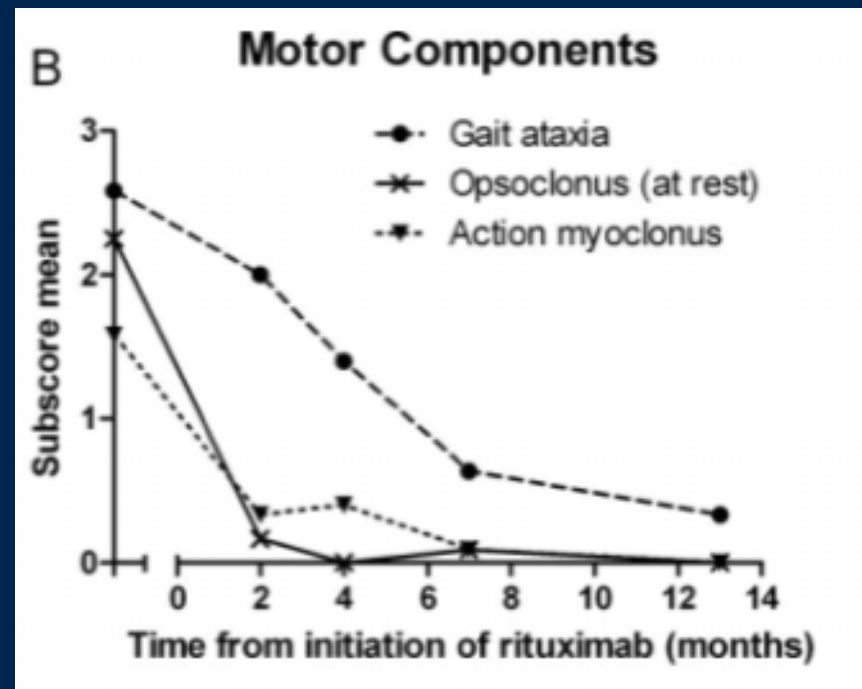
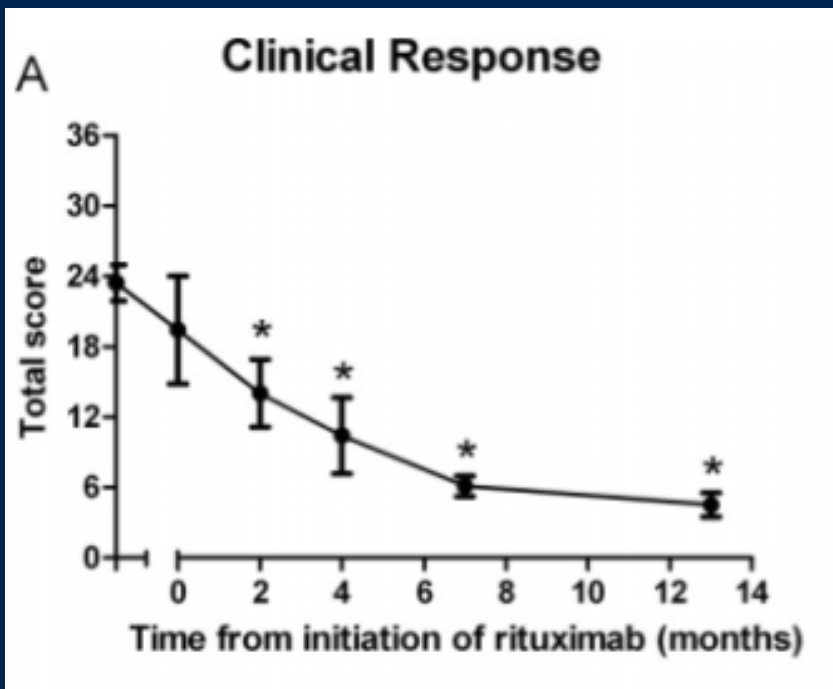


Rituximab

- 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



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

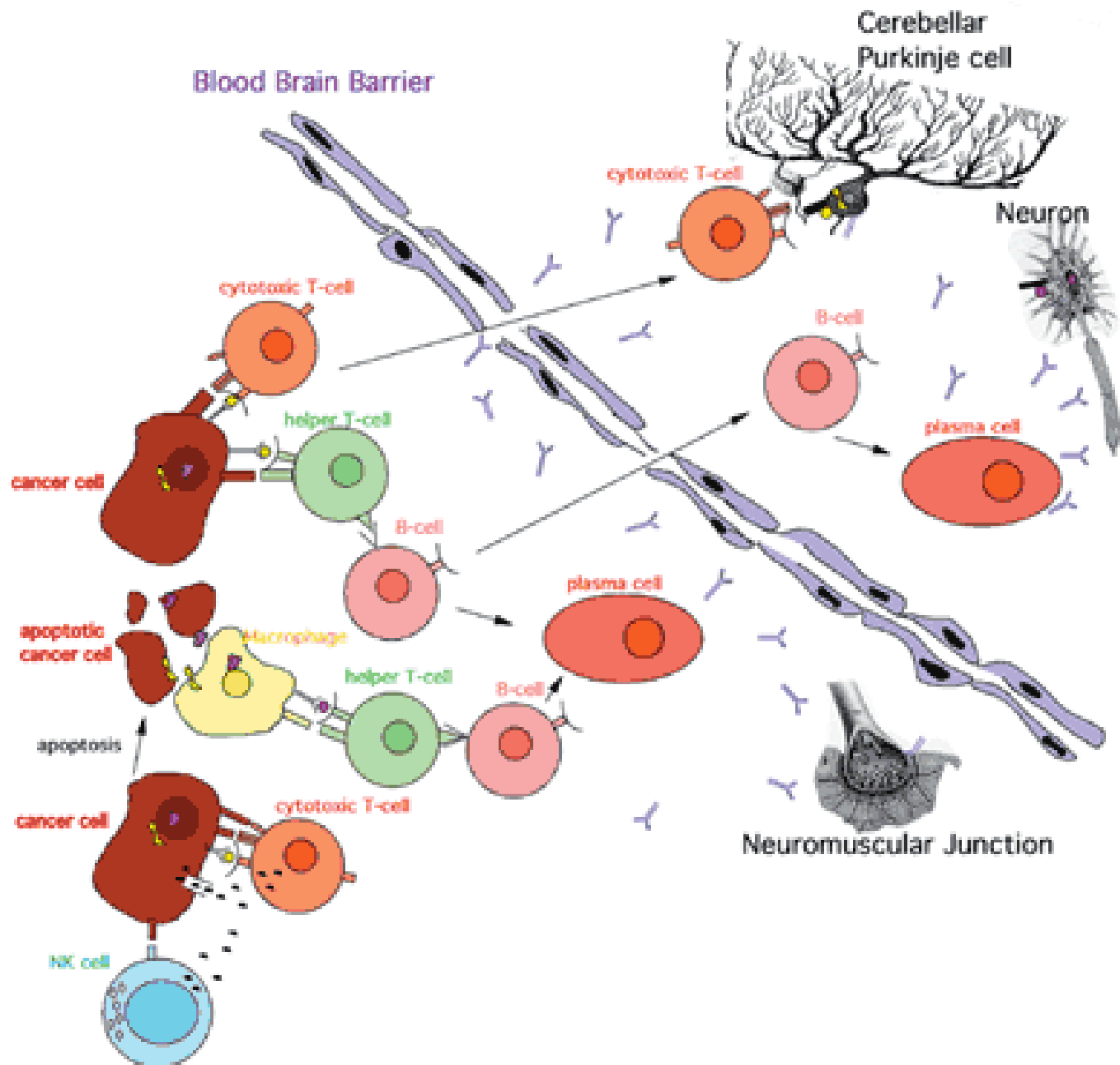
Future Directions

- 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

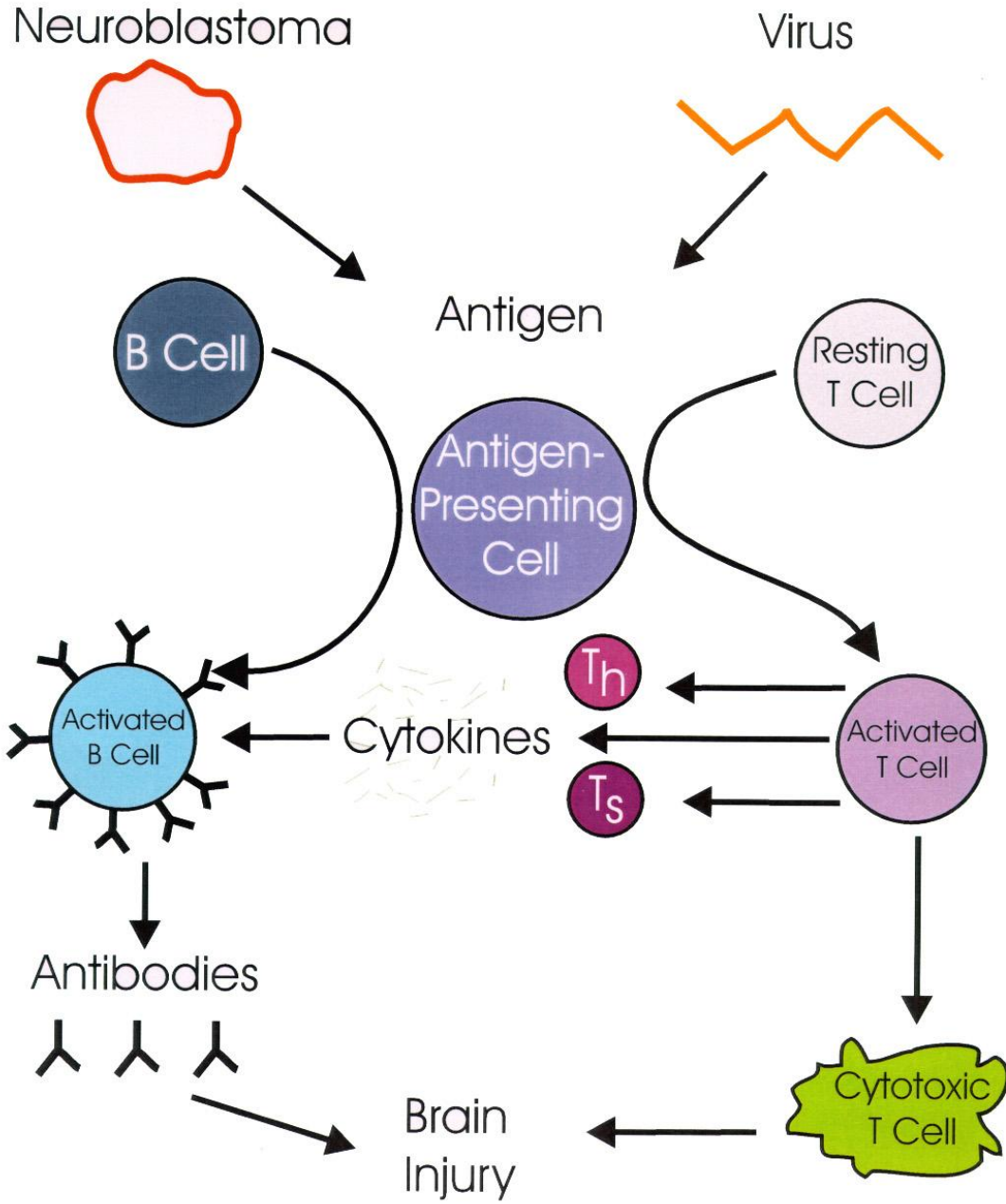


Thanks!
OMS Life

Assumed pathogenesis of paraneoplastic neurologic syndromes



Autoimmune Reaction



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

De Grandis et al Neuropediatrics. 2009 Jun;40(3):103-11.

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

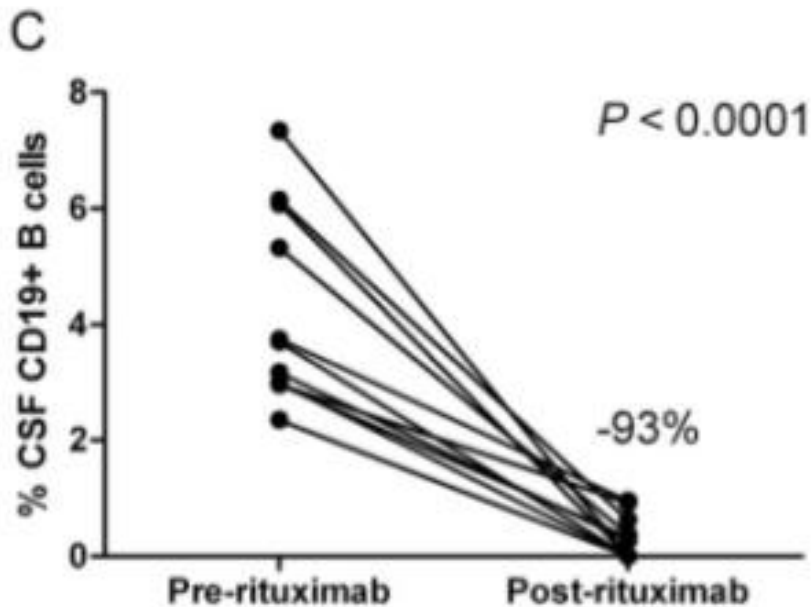
- Evidence of Immune Dysregulation – B cells in CSF
 - CSF B Cells have been found to be increased
 - CSF T helper to Cytotoxic T Lymph ratio is reduced
 - CXCL10 an inflammatory chemokine found to be elevated in the brain, recruiting lymphocytes across the BBB
 - Cytokine BAFF found to be elevated in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

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Response to IVIg, ACTH + Ritux

CSF B Cell Reduction



Clinical-Immunological Relation

