OMS life Foundation

Opsoclonus Myoclonus Ataxia Family Symposium
April 11, 2015

Cincinnati Children's

Conference Agenda:

11:00AM	Mike Michaelis, OMSLife Foundation Welcome and Introductions
11:15AM	Donald L. Gilbert MD, MS Movement disorders
12:00PM	Dr. Allen DeSena, MD Neuro-immunology
1:00PM	Mike Michaelis, The OMSLife Foundation
1:15PM	Dr. Brian Weiss, MD Oncology
2:00PM	Wendi Lopez, PsyD Behavior, Learning at home and school
3:00PM	OMS Caregiver Panel Discussion

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Opsoclonus Myoclonus Ataxia Syndrome

Neurology/ Movement Disorder Overview

Donald L. Gilbert MD MS

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Disclosure

- None relevant to this talk
- Clinical trials (Tourette Syndrome): Psyadon, Otsuka, AstraZeneca

Story

- 21 month old completely healthy girl
- Walked on time
- Uses hands normally – stacks small toys
- Very social, not yet toilet trained but interested
- Points to objects and body parts
- Follows commands with gesture
- Has over 20 words

Story

- One morning she awoke with a cough and a fever
- Over the next two days she had tremors of her body and poor balance. She was fussy. Parents noted some unusual eye movements

Story

- She presented to small hospital, where she was admitted for a workup
- She underwent blood testing, 2 MRI scans, a 24 hour EEG, and a spinal tap
- All tests were normal

Diagnosis?

“Acute Cerebellar Ataxia”

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Story continued

The girl was sent home with her parents to wait for symptoms to improve

Story continued

The symptoms did not improve

Story continued

- The child's pediatrician was not sure what to do
- The child was sent to the ER and another MRI was performed, but discharged home again
- The pediatrician referred her for a second opinion

Story continued

- For 4 weeks she continued to get worse
- “Sometimes conditions get worse before they get better”
- She is very fussy, has stopped speaking, is very shaky, cannot or will not walk
- On the morning of her “second opinion” visit she spikes another fever

Story continued

- At the check in at the neurologists office, the medical assistant thinks she is having a seizure she is so shaky
- Her eyes are out of control, bouncing up and down really fast so she can't maintain eye contact with her parents
- She is so fussy her parents can't comfort her

Diagnosis?

~~Acute Cerebellar Ataxia~~

Opsoclonus Myoclonus (Ataxia) Syndrome

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Why is this diagnosis difficult?

Feature/ Symptom	Opsoclonus myoclonus	Acute Cerebellar Ataxia
Onset around age two	Yes	Yes
Presents with or after illness	Yes	Yes
Balance problems	Yes	Yes
Hand tremors	Yes	Yes
Eye problems	Yes	Yes

Lots of causes of acute balance problems in children

Category	Examples	Clinical features, diagnostic essentials
Acute		
Toxic Acute ingestion	Alcohol, anticonvulsants, antihistamines, benzodiazepines	**Toddlers – accidental ingestion; Adolescents – substance abuse. Mental status changes common, urine/serum toxicology screen in Emergency Department may detect unsuspected ingestions.**
Inflammatory	Acute cerebellar ataxia	**Symmetric cerebellar findings, gait impairment, truncal ataxia, titubation, nystagmus. Mental status normal. Usually post-infectious. Consider opsoclonus myoclonus ataxia syndrome.**
Trauma/Vascular	Stroke, vertebrobasilar dissection	**Consider after neck trauma or if hypercoagulable.**
Recurring		
Metabolic	Many inborn errors of metabolism may occur intermittently	**Can be triggered by intercurrent illness. Consider if child has preexisting intellectual disabilities, positive family history, consanguinity; or presents with encephalopathy and vomiting.**
Migrainous	Basilar migraine, benign paroxysmal vertigo	**In the young child, headache may not be prominent. Initial episode consider focal pathology and need for imaging.**
Episodic Ataxias	Episodic Ataxia 1, 2	**Bouts of dysarthria, gait ataxia, sometimes with characteristic provoking factors.**
Functional	Psychogenic / Functional Neurologic Symptom Disorders	**Gait disturbance or abnormal tremor-like movements which have fluctuating, on-off time course, variable direction, amplitude, and frequency, and otherwise do not conform to usual pattern of disease. Uneconomical gait, excessive sway without falling may be seen.**
Subacute		
Inflammatory	Acute Disseminated Encephalomyelitis (ADEM)	**Mental status changes; and multifocal neurologic deficits. MRI shows multiple discrete lesions involving white and gray matter.**
	Guillain Barre Syndrome, including Miller Fischer Variant	**Oculomotor paresis, bulbar weakness, hyporeflexia, radicular pain. Risk for respiratory/autonomic failure. Note – weakness localizing peripherally may masquerade as ataxia due to problems with limb control and gait. .**
	Opsoclonus myoclonus ataxia syndrome	**Truncal ataxia, multifocal myoclonus, opsoclonus (may be transient), behavioral irritability. Paraneoplastic (neuroblastoma) or post-infectious.**
Mass lesions	**Posterior fossa neoplasms**	**Headaches, vomiting, papilledema, cranial nerve palsies.**

Many Genetic Ataxias!

Why is this diagnosis difficult? Overlap

Feature/ Symptom	Opsoclonus myoclonus	Acute Cerebellar Ataxia
Onset around age two	Yes	Yes
Presents with or after illness	Yes	Yes
Balance problems	Yes	Yes
Hand tremors	Yes	Yes
Eye problems	Yes	Yes

Categories of disease causing myoclonus in children

Etiological Category	Clinical Features
Physiologic	Myoclonus occurs in certain settings in healthy persons. Examples include sleep (hypnic) jerks, hiccoughs, and benign infantile myoclonus with feeding.[15]
Benign, developmental	Myoclonus as a transient symptom during otherwise normal development. Examples include benign neonatal myoclonus and myoclonus of early infancy. See also chapter 6.
Startle syndromes	Quick, involuntary, stimulus-evoked reflex movements. An exaggerated startle response that may be further subdivided into hereditary, symptomatic, startle epilepsy, and neuropsychiatric startle syndromes (Latah syndrome, jumping Frenchman of Maine, anxiety-induced startle).[16]
Primary myoclonus disorders	Myoclonus occurs as the primary symptom. The cardinal example is essential myoclonus. [17,18]
Epileptic	Myoclonus is associated with clinical seizures and/or epileptiform discharges on EEG, supportive of a cortical origin.
Primary epileptic myoclonus disorders	Myoclonus as a seizure type or fragment, or myoclonus as a symptom in addition to seizures in an epilepsy syndrome without encephalopathy.[19,20]
Progressive myoclonic epilepsies and progressive encephalopathies with myoclonus	Myoclonus occurs as part of a multi-symptom, progressive neurologic disease.
Secondary myoclonus disorders	Myoclonus occurs secondary to some other identifiable, non-genetic cause or process. Examples include autoimmune diseases, infections/encephalitides, hypoxic ischemic injury (Lance Adams myoclonus), toxins, metabolic derangements such as uremia, acidosis. Also, secondary to medications, e.g. myoclonus triggered by the use of focal antiepileptic medications in patients with generalized epilepsies.[21-23] See Chapter also 22.
Psychogenic/ Functional	Pseudomyoclonus as a symptom of a Functional Neurological Symptom Disorder/Psychogenic Movement Disorder.[24-26] See also Chapter 23.

Many Genetic causes of Myoclonus

Disease	Gene (locus)/ Protein	Inheritance	Clinical Features	Age of onset
Primary myoclonus				
Hereditary Geniospasm[166]	possible linkage to 9q13-q21	AD	chin myoclonus/ tremor	childhood
Myoclonus Dystonia Syndrome : DYT11, DYT 15[15-17, 167-169]	SGCE; epsilon sarcoglycan; DRD2 Dopamine receptor 2	AD	bilateral myoclonus, tremor, dystonia, torticollis, depression, anxiety, Obsessive Compulsive disorder	5-15 years
Epileptic myoclonus without encephalopathy				
Juvenile Absence Epilepsy EJA1[170]	EFHC2; EF-HAND Domain (C-terminal)-containing protein 2	AD	Absence seizures, generalized tonic clonic seizures, myoclonic seizures	childhood, around puberty
Juvenile Myoclonic Epilepsy EJM[171-173]	GABRA1 and GABRD GABA receptors; CACNB4 Calcium Channels; CLCN2 Chloride Channels	AD	Morning myoclonic jerks, absence and GTC seizures	childhood and adolescence
Myoclonus plus encephalopathy				
Amish Infantile Epilepsy Syndrome[174]	SIAT9; sialytransferase-9	AR	failure to thrive, visual loss, startle myoclonus, epilepsy, no development, early death	infancy
Aromatic L-Amino Acid Decarboxylase Deficiency[480]	DDC; dopa-decarboxylase	AR	oculogyric crises, opisthotonus, dystonia, myoclonus, hyperreflexia, chorea, irritability	infancy
Combined Saposin Deficiency[181-182]	PSAP; prosaposin	AR	myoclonus, dyskinesias, seizures, organomegaly, respiratory failure	Infancy
Dentatorubral-pallidoluysian Atrophy (DRPLA)[183]	ATN1expanded trinucleotide repeat; atrophin 1	AD	seizures, ataxia, choreoathetosis, myoclonus, dementia	usually 30's, can occur in childhood
Gaucher Disease IIIA[185]				
Hyperornithinemia-Hyperammonemia-Homocitrullinuria				
Mitochondrial complex II deficiency[187]				
Myoclonic Epilepsy associated with Ragged Red Fibers M				
Neuronal Ceroid Lipofuscinosis 1[188]				
Neuronal Ceroid Lipofuscinosis 2[189]				
Neuronal Ceroid Lipofuscinosis 3[190]				
Neuronal Ceroid Lipofuscinosis 5[191]				
Neuronal Ceroid Lipofuscinosis 8[192]	CLN8	AR	Dementia, myoclonus, epilepsy, ataxia, atrophy	early childhood
Progressive Myoclonic Ataxias / Ramsay Hunt Syndrome[193]	None- the literature on this syndrome probably represents a collection of diagnoses, including some that now could have molecular diagnosis	AD/ other	Myoclonus, ataxia, tremor, GTCs, degeneration of dentate nucleus, globus pallidus, mitochondrial disease findings	Childhood
Progressive Neuronal Degeneration of Childhood with Liver Disease (Alpers Huttenlocher)[195]	POLG1 DNA mitochondrial polymerase gamma	AR	failure to thrive, visual loss, myoclonus, epilepsy, ataxia, early death	Infancy
Pyridoxine 5-Prime Phosphate Oxidase deficiency[197]	PNPO Pyridoxine Phosphate Oxidase	AR	myoclonus, neonatal epileptic encephalopathy, partial response to pyridoxine, seizure response to pyridoxal phosphate	infancy, usually preterm delivery
Rett Syndrome in Males[198-199]	MECP2	X linked	Severe encephalopathy, myoclonus, rigidity, death in 2 years	Infancy
Schindler Disease, infantile type[200]	NAGA; alpha-N-acetylgalactosaminidase	AR	visual loss, dementia, spasticity, myoclonus, brain atrophy	early childhood
Sialidosis I and II[201]	NEU1; Neuraminidase	AR	Storage phenotype - coarse facies retardation, coarse geatures features, asdif	can be early childhood
Spinocerebellar ataxia type 19[202]	Linkage 1p21-q23	AD	ataxia, myoclonus, tremor	usually adult, some child
Spinocerebellar ataxia type 2[203]	ATXN2 expanded trinucleotide repeat; ataxin 2	AD	Dementia, myoclonus, epilepsy, ataxia, atrophy, abnormal eye movements	usually adult, some infants
Progressive myoclonic epilepsy				
Myoclonic Epilepsy - Unverricht and Lundborg EPM1A[205]	CSTB; Cystatin B/Stefin B	AR	Myoclonus, ataxia, GTCs, Absence Seizures, Dysarthria, mental deterioration	Childhood
Epilepsy, Progressive Myoclonic EPM 1B[206]	PRICKLE1; Rest-interacting Lim Domain Protein	AR	Upward gaze palsy, Motor delays with ataxia early, seizures later childhood	Early childhood
Myoclonic Epilepsy – Lafora EPM2A[207]	EPM2A; Laforin	AR	myoclonus, epilepsy, apraxia, dementia, visual loss, psychosis	late childhood
Myoclonic Epilepsy – Lafora EPM2B[208]	NHLRC1; malin	AR	myoclonus, epilepsy, apraxia, dementia, visual loss, psychosis	late childhood
Action Myoclonus Renal Failure Syndrome[209]	SCARB2 (Scavenger Receptor, Class B, member 2)	AR	Progressive action myoclonus, finger tremor, ataxia, GTCs, nephropathy/renal failure	late teens

Story reprise

- The girl developed tremor and poor balance

Ataxia

- Problems in the timing of motor movements
- Inability to coordinate sequential parts of movement so that they are smooth and effective

The story reprise

- On more careful observation – she had many quick jerky movements of her body, her neck, and her limbs

Myoclonus

- Muscle jerks
- If they occur in the trunk muscles this can throw you off balance
- If they occur in the leg muscles they can also throw you of balance
- If they are small and frequent you can look like you have ataxia

The story

- Her eye movement problems were obvious at the second opinion – but may not have been so obvious every time doctors saw her

Eye movements

- Normal movements
- Fix your gaze on a target of interest
- Rapidly move your eyes to a new target

Cerebellar diseases and the eyes

- **Nystagmus** – poor gaze fixation. The eyes drift, the brain keeps trying to get back to the target so you have repeated eye drift/jerk drift/jerk movements that are very quick and fluttery
- **Opsoclonus** – brain activity controlling quick movements to targets is abnormal, so the quick movements happen in many directions very quickly – burst of quick eye movements

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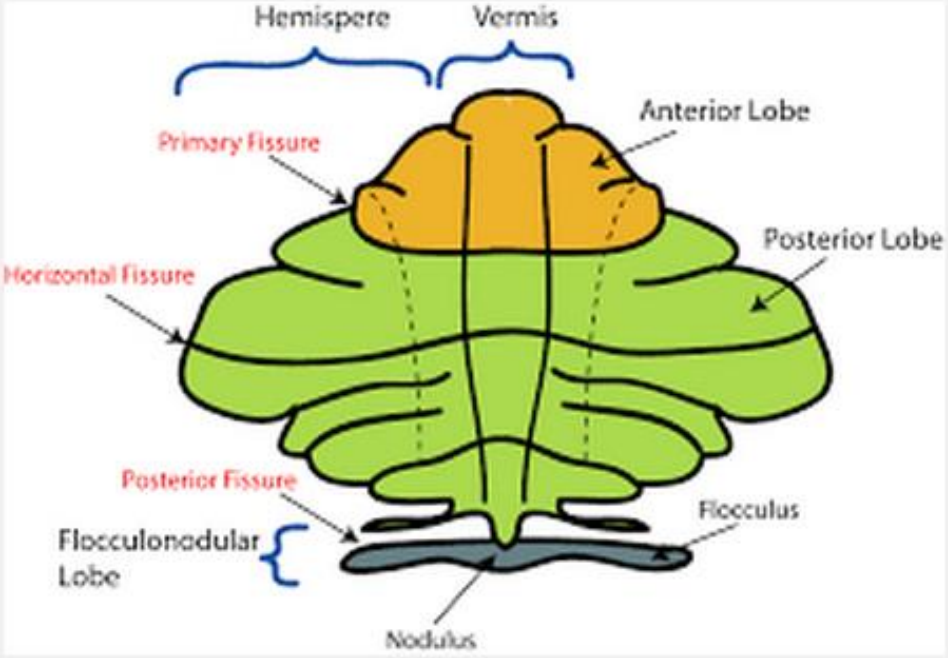
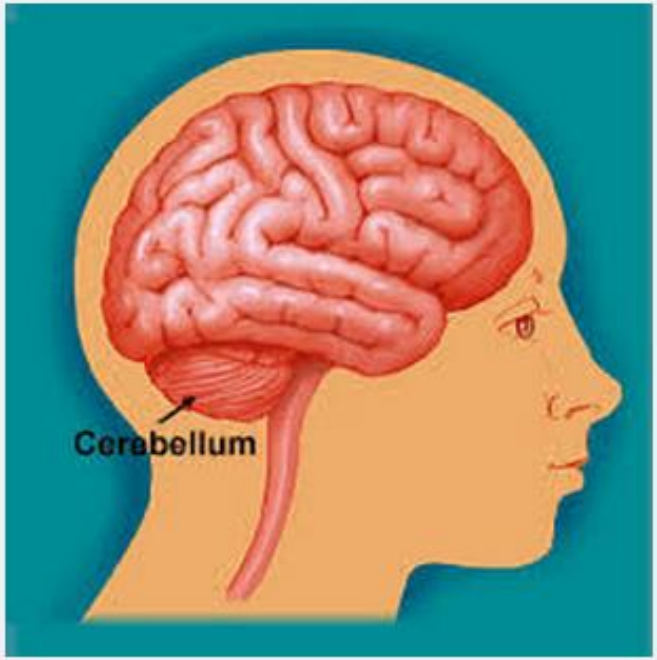
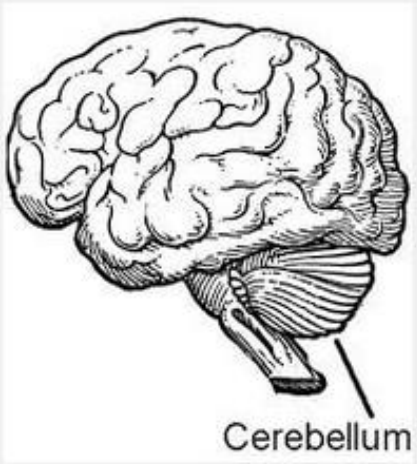
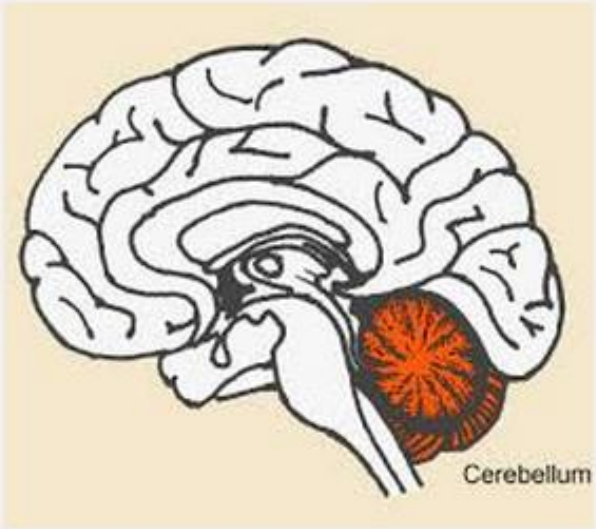
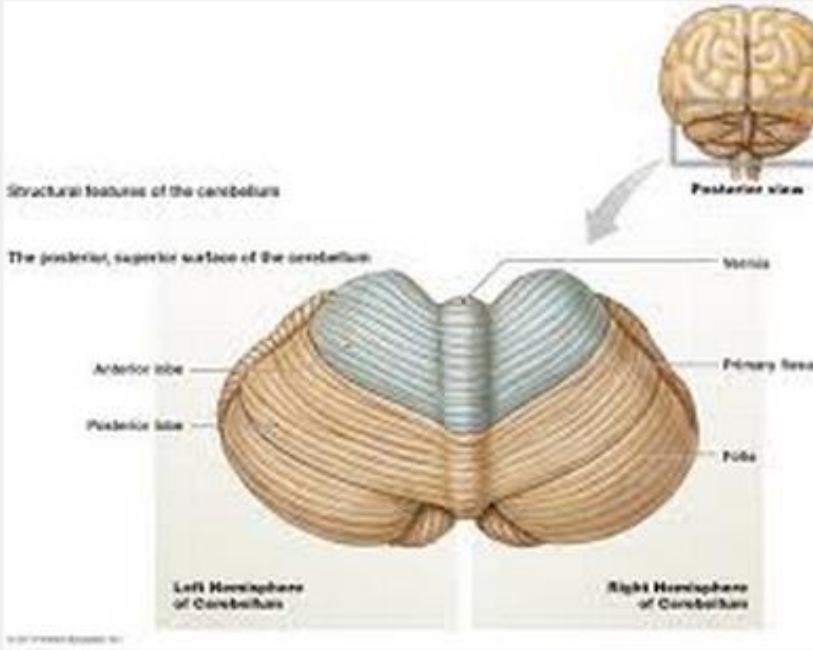

Hemispere
Vermis
Anterior Lobe
Primary Fissure
Posterior Lobe
Horizontal Fissure
Posterior Fissure
Flocculus
Flocculonodular Lobe
Nodulus

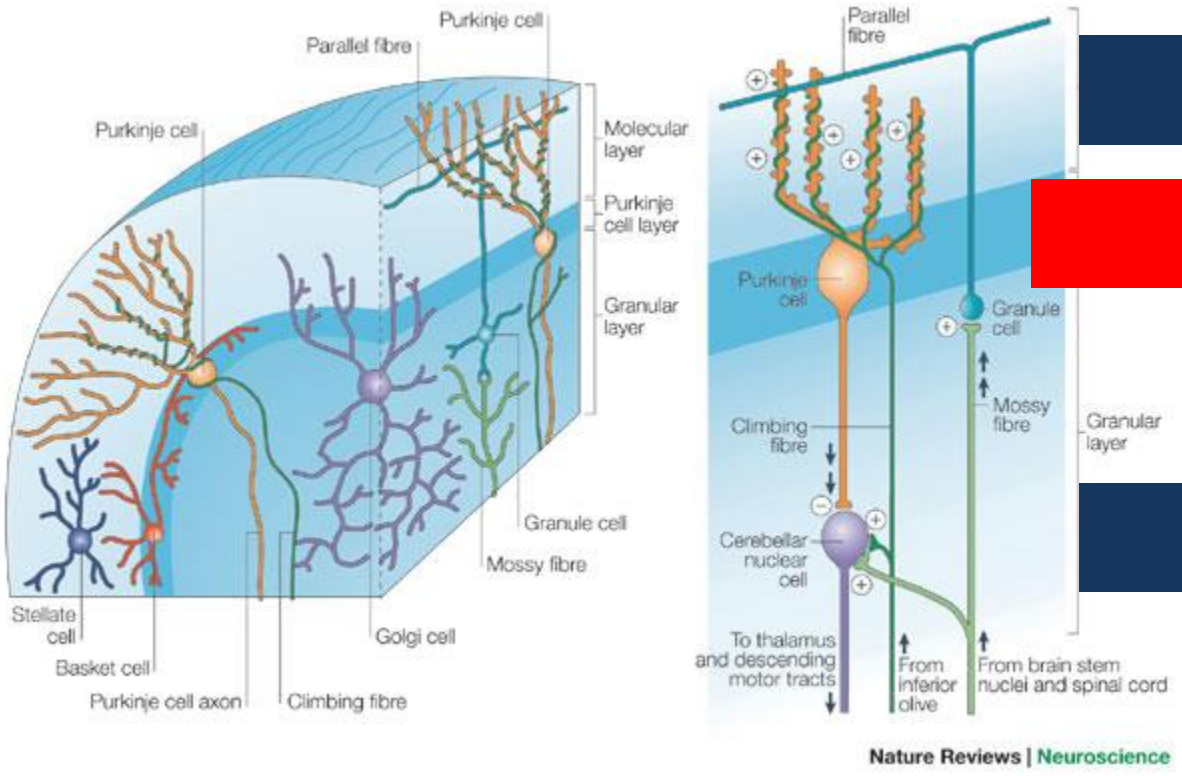

Cerebellum


Cerebellum


Cerebellum


Posterior view
Vermis
Anterior lobe
Posterior lobe
Fissure
Folia
Left Hemisphere of Cerebellum
Right Hemisphere of Cerebellum

3 cellular layers in cerebellum



Molecular

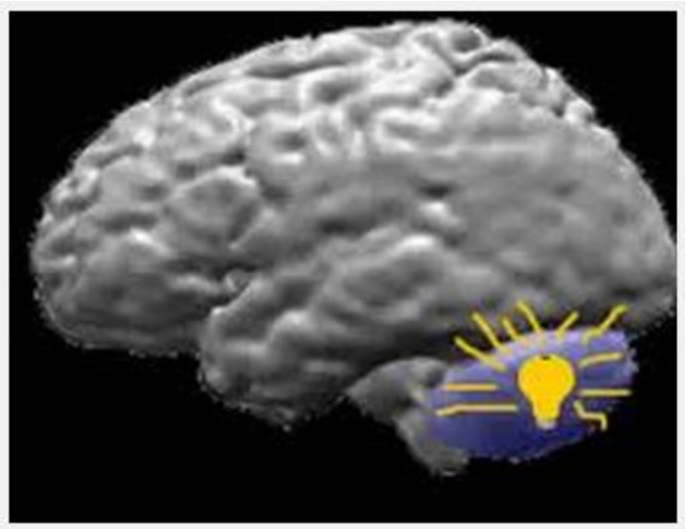
Purkinje

Granular

Apps R, Garwicz M. Nature Reviews Neuroscience 2005

Traditionally the cerebellum was thought to primarily control movement coordination

But the cerebellum is also important for:



- Impulse control
- Emotional regulation
- Social understanding

So the key to diagnosing OMAS is:

- The doctor has to recognize it
- Doctors, child neurologists especially, need to be well trained

Before discussing the immune system and neuroblastoma

Two other topics:

Types of Doctors

Navigating Web Information

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Who is my doctor?

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Primary Care Physicians

- The Go-To, front line doctors: Stay Here
- Pediatricians, Family Practitioners, affiliated NPs
- Diagnose common problems like ADHD (Am Acad Pediatrics: ADHD Toolkit)

Adult Neurologists

- Not ideal
- Note – in many communities the most accessible neurologist for a child to see is an adult neurologist

Child Neurologists

- Goal 1: Diagnosis. Ideally Specific. Should have a biological (cellular, genetic, molecular) basis, based on careful history and physical examination as well as from diagnostic testing: blood/urine/spinal fluid; MRI, Neurophysiology/EEG
- Goal 2: Rational, Evidence Based Intervention
- Often work in teams. We do not see ourselves as "pediatricians first" but we are still full medical doctors
- Prescribe medications
- Typically receive 12 months of adult neurology training

Child Neurologists

- Perspective: Children are not small adults
- We are actively involved on the genetics frontier
- We may or may not understand much immunology
- We understand that the diseases we see affect education but our training does not necessarily emphasize this in helpful ways
- The majority of us work in academic centers, not in private practice or in more rural areas

Child Neurologists

- Really rare diseases
  - There are a lot of really rare diseases we see
  - Some of these are partly managed in a few specialized centers around the country

Child Neurologists

- Most of what we treat is not curable

- There are increasing numbers of treatments but there are still chronic conditions for which we can provide little directly beneficial treatment

Neurosurgeons

- Goal 1: discern when and when not to operate
- Goal 2: Fix Problems
- Pediatric medicine training: minimal

Pediatric Physiatrists "PM&R"

- Goal: rehabilitation and adaptation to diseases and injuries of the brain
- Diagnosis has already been made, typically
- Multi-disciplinary – work with physical, occupational, speech therapists to improve function, independence, well being

Developmental Pediatricians

- Goal: manage the medical and psychosocial aspects of children's and adolescents' developmental and behavioral problems
- Emphasis more on disordered or atypical development, less on disease or brain injury
- Like physiatrists work collaboratively with therapy teams
- Very interested in schools

Psychiatrists

- Medication Treatment
- Work with a "med check" model for follow ups
- Interest/skill in therapy variable
- Can do a one-year fellowship in child psychiatry

Child Psychiatrists

- Medication Treatment
- Work with a "med check" model for follow ups
- May take particular interest in neurological condition that has high psychiatric comorbidity
- Interest/skill in therapy variable
- Badly Outnumbered because they are treating society, not just disease

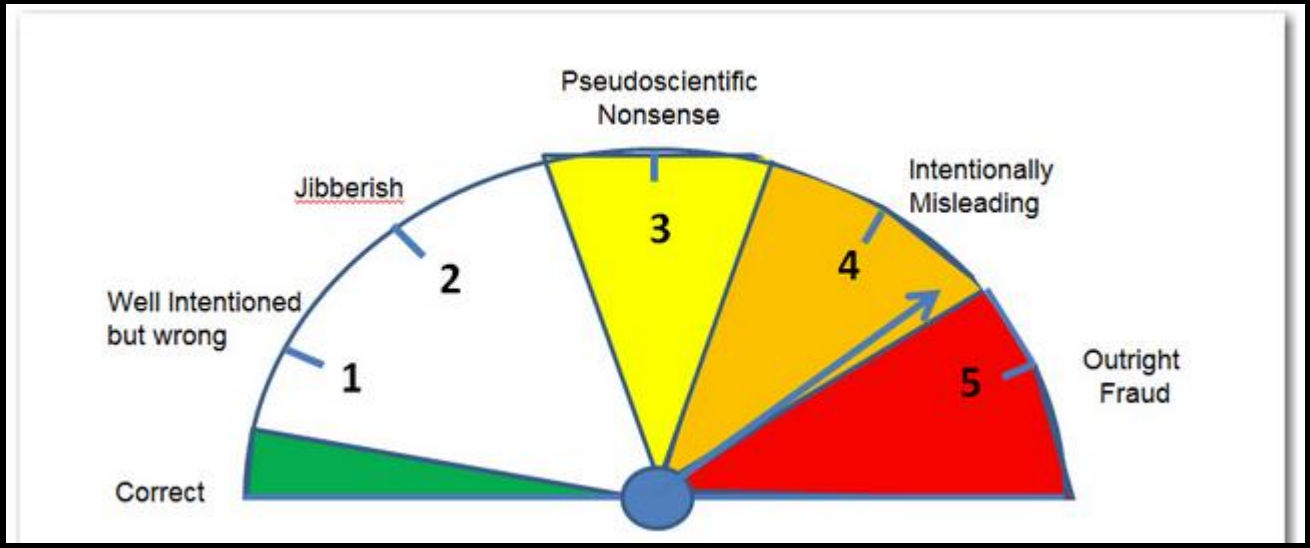
Psychologists

- Work with behavior as environmentally modifiable through evidence based techniques
- Work on problem solving, parenting techniques

The Way Forward

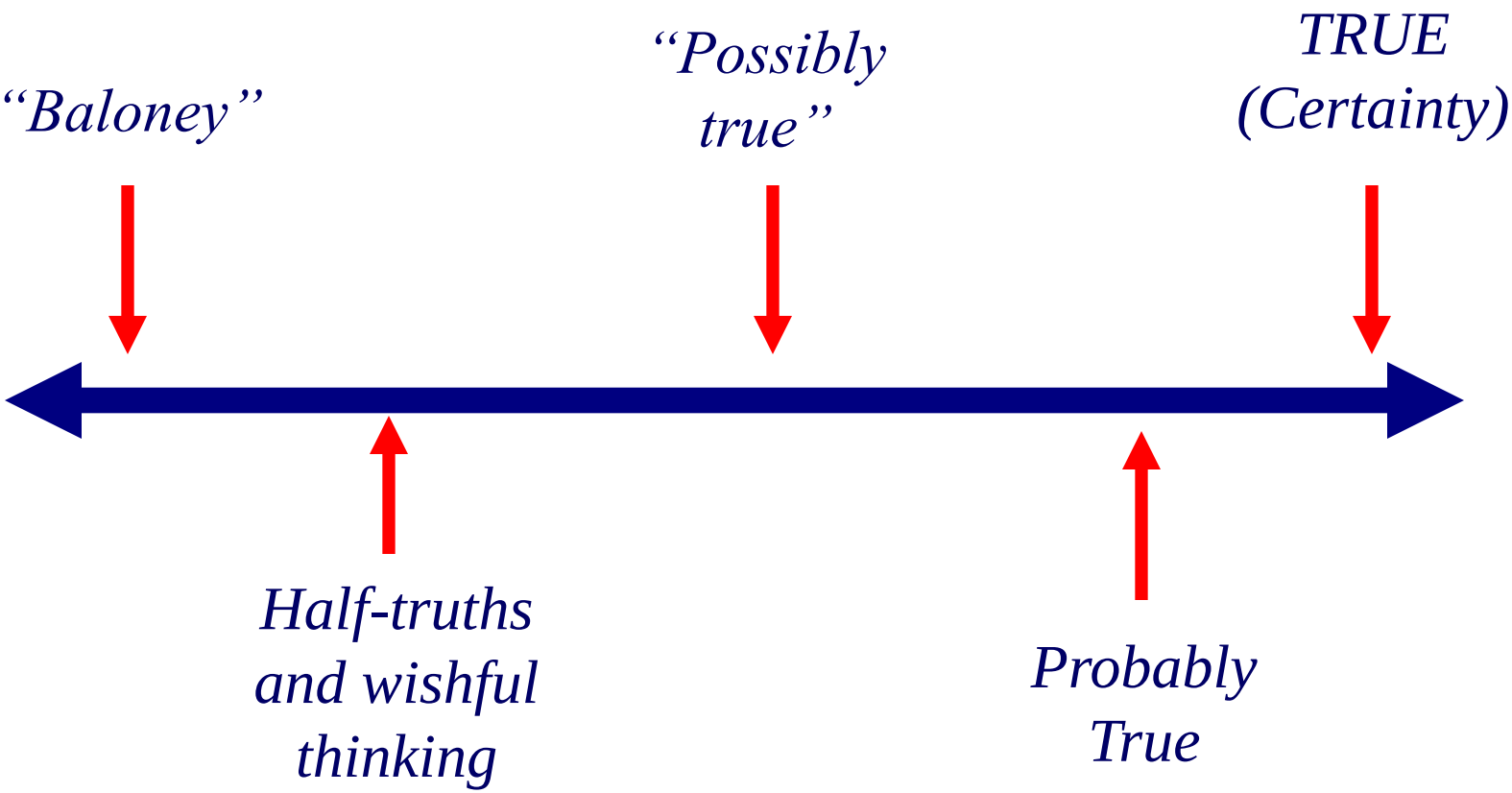
Navigating information successfully on your own

Tools for keeping yourself informed about new medical information


Pseudoscientific
Nonsense
Jibberish
Intentionally
Misleading
3
2
4
Well Intentioned
but wrong
1
5
Outright
Fraud
Correct


THE BALONEY METER

Information Metric v.1



Sources – PRETTY STRONG

- Major Medical Journals: NEJM, JAMA, LANCET,
- Major Specialty Journals: NEUROLOGY
- Medical Society Published, Evidence-Based Practice Guidelines and Patient Pages (examples in this talk)
- Advocacy organization websites with reputable medical advisory boards
- Hospitals with patient health topic pages, e.g. Cincinnati Children's, Mayo Clinic
- National Institutes of Health / National Library of Medicine
- Accredited Continuing Education

Websites you can trust usually end with

.org

.edu

.gov

Sources – beware of baloney

- Top Internet hits from your search
- Some Psychiatry Journals
- Journals your doctor has never heard of
- Network TV shows
- Lectures/Webinars/Blogs online by sincere but wacky doctors who tell lots of anecdotes
- Websites by unregulated purveyors of nutritional products and non-validated therapies that you have to pay directly for

How do we know if a treatment really works?

- Our best estimate of whether something really works is from Randomized Controlled Clinical Trials – look for this when you are on the internet seeking new treatments

6 studies found for: opsoclonus myoclonus

Modify this search | How to Use Search Results

List | By Topic | On a Map | Search Details

+ Show Display Options

Download | Subscribe to RSS

Include only open studies | Exclude studies with unknown status

Rank	Status	Study
1	Unknown †	Use of Rituximab in Opsoclonus-Myoclonus in Children With Neuroblastoma **Conditions:** Neuroblastoma; Opsoclonus-Myoclonus **Intervention:** Drug: anti-CD20 (Rituximab)
2	Recruiting	Study of Cytokines in Children With Opsoclonus-Myoclonus Syndrome **Condition:** Opsoclonus-myoclonus Syndrome **Intervention:**
3	Recruiting	Opsoclonus Myoclonus Syndrome/Dancing Eye Syndrome (OMS/DES) in Children With and Without Neuroblastoma (NBpos and NBneg)Opsoclonus Myoclonus Syndrome/Dancing Eye Syndrome (OMS/DES) in Children With and Without Neuroblastoma (NBpos and NBneg) **Conditions:** Opsoclonus Myoclonus Syndrome; Neuroblastoma **Interventions:** Drug: Dexamethasone acetate; Drug: dexamethasone and cyclophosphamide; Drug: dexamethasone and rituximab
4	Active, not recruiting	Cyclophosphamide and Prednisone With or Without Immunoglobulin in Treating Abnormal Muscle Movement in Children With Neuroblastoma

Story continues…

- Four years after her neuroblastoma was resected she is off all medication
- She runs but is clumsy, speaks less often and less clearly than her peers
- She attends school, has an IEP
- She has no more opsoclonus or myoclonus
- She is a bit feisty, but her behavior is OK
- She is making cognitive gains, slowly

Will she catch up?

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Questions?

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