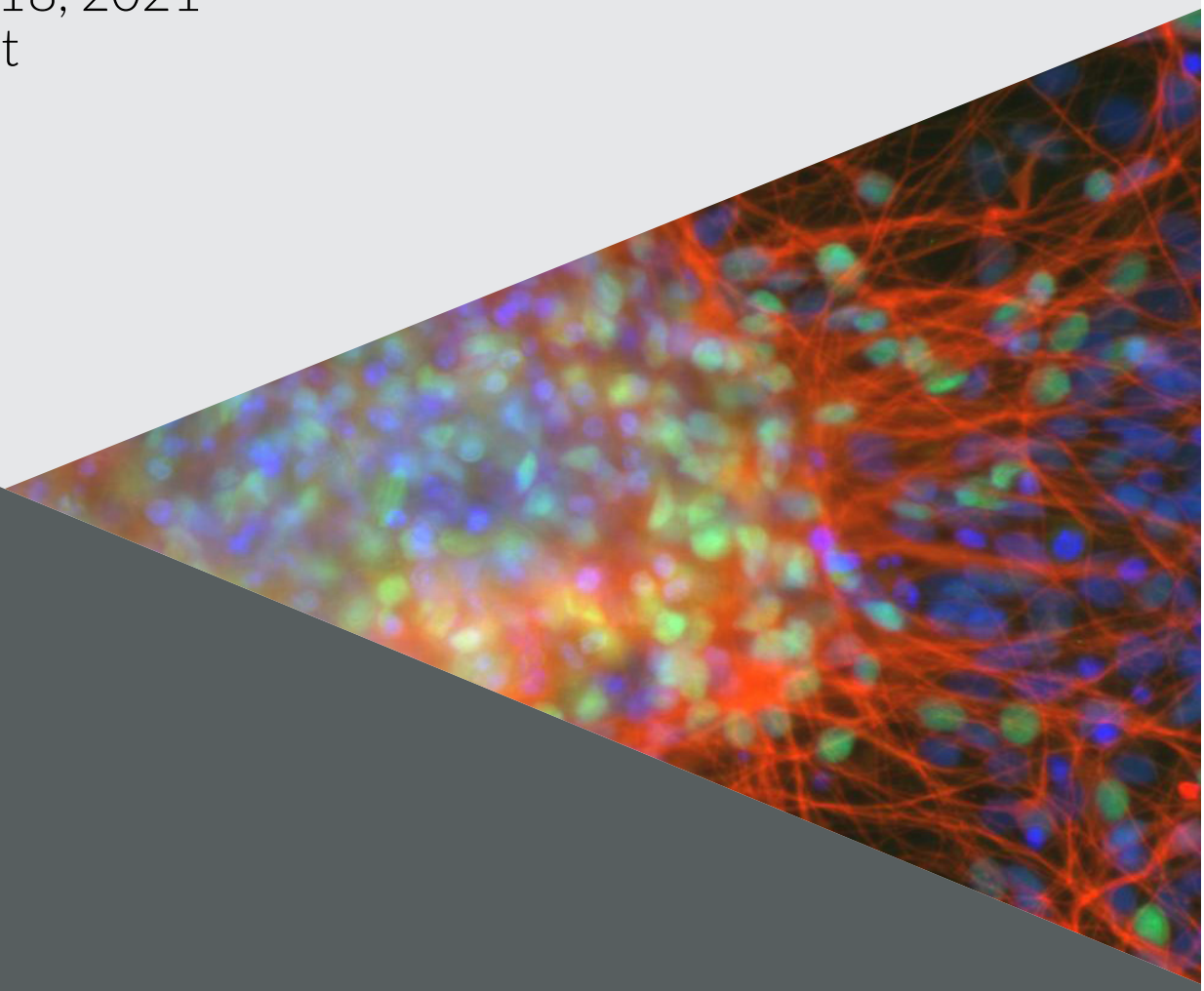
MULITPLE SCLEROSIS CENTER

4TH ANNUAL

MS and CNS Neuroimmunology Symposium: Advances and Updates

September 18, 2021
virtual event



Oregon Health & Science University
Multiple Sclerosis Center
Portland, OR 97239

www.ohsu.edu/ms

OHSU

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AGENDA

9:00 a.m.	**Opening remarks** Vijayshree Yadav, MD, MCR, FANA, FAAN *Department of Neurology, OHSU and VA Portland Health Care System*
9:10 a.m.	**Amyotrophic Lateral Sclerosis: Update on Diagnostic Criteria, Guidelines and Therapies** Wendy Johnston, MD, FRCPC *Department of Medicine/Division of Neurology, University of Alberta*
9:55 a.m.	**Disease Modifying Therapy Update for MS** Elizabeth Silbermann, MD *Department of Neurology, OHSU and VA Portland Health Care System*
10:40 a.m.	**Break/Exhibit Hall**
10:55 a.m.	**Technology Innovation in MS Rehabilitation** Mike Jones, PhD, FACRM *MS Rehabilitation and Wellness Program, Shepherd Center*
11:40 a.m.	**Autoimmune Epilepsy Diagnosis and Management** Marissa Kellogg, MD, MPH *Department of Neurology, OHSU*
12:25 p.m.	**Lunch break/Exhibit Hall**
1:15 p.m.	**Longitudinal Extensive Transverse Myelitis: An Imaging Perspective** Gary Nesbit, MD, FSNIS *Dotter Department of Interventional Radiology, OHSU*
2:00 p.m.	**Stimulating Remyelination for the Treatment of MS** Dennis Bourdette, MD, FAAN, FANA *Department of Neurology, OHSU*
2:45 p.m.	**Closing remarks** Vijayshree Yadav, MD, MCR, FANA, FAAN *Department of Neurology, OHSU and VA Portland Health Care System*
3:00 p.m.	**Adjourn Meeting**

FACULTY DISCLOSURE INFORMATION

In accordance with the requirements of the ACCME's Standards for Integrity and independence in Accredited Continuing Education, each instructor and member of the planning committee has been asked to disclose any relevant financial relationships with ineligible companies (defined as: any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients). All of the relevant financial relationships listed for these individuals have been mitigated.

PROGRAM PLANNING COMMITTEE

Dennis Bourdette, MD, FANA, FAAN	Nothing to disclose
Vijayshree Yadav, MD, MCR, FANA, FAAN	Nothing to disclose

INSTRUCTORS/MODERATORS

Dennis Bourdette, MD, FANA, FAAN	Nothing to disclose
Wendy Johnston, MD, FRCPC	An investigator and scientific advisory board member for Biogen receiving grant support and honoraria. An investigator and scientific advisory board member for Mitsubishi-Tanabe Canada receiving grant support and honoraria. An investigator and scientific advisory board member for Cytokinetics receiving grant support and honoraria. An investigator for Alexion, Annexion, and AI-S Pharma receiving grant support.
Mike Jones, PhD, FACRM	Nothing to disclose
Marissa Kellogg, MD, MPH	Nothing to disclose
Gary Nesbit, MD, FSNIS	Nothing to disclose
Elizabeth Silbermann, MD	Nothing to disclose

ACKNOWLEDGEMENTS

GRANT SUPPORT

Paralyzed Veterans of America

Portland VA Health Care System MS Center of Excellence West

EXHIBITORS

Biogen

Bristol Myer Squibb

National Multiple Sclerosis Society

Novartis

Sanofi Genzyme

CREDIT STATEMENT

Accreditation
Oregon Health & Science University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit
OHSU School of Medicine designates this live activity for a maximum of 4.75 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

SPEAKER BIOGRAPHIES

Dennis Bourdette, MD, FAAN, FANA is Chair and Professor Emeritus and Founder of the MS Center in the Oregon Health & Science University (OHSU) Department of Neurology. He is nationally recognized for his important discoveries in the field of multiple sclerosis, having authored over 250 publications related to MS. Dr. Bourdette received his medical degree at the University of California at Davis, was a neurology resident at OHSU and joined the OHSU faculty in 1985. Dr. Bourdette is a fellow of the American Neurological Association and the American Academy of Neurology.

Wendy Johnston, MD, FRCPC is Professor of Neurology at the University of Alberta, Director of the Amyotrophic Lateral Sclerosis Clinic at the Kaye Edmonton Clinic and a member of the ALS Canada Board of Directors. After obtaining her BSc summa cum laude at University of Toronto, M.D. at Queens University Kingston Ontario, she completed neurology residency at McGill University Montréal and a neuromuscular fellowship at the Montréal Neurologic Hospital and Institute under George Karpati. Dr. Johnston, at Oregon Health & Sciences University, Portland Oregon, founded the Amyotrophic Lateral Sclerosis (ALS) and Neuromuscular programs, and was Director of the Muscular Dystrophy Association and ALS clinics. Research included investigational drug trials in ALS, and investigator initiated research in muscle disorders and ALS, including in collaboration with Dr. Linda Ganzini, studies on attitudes to assisted suicide in patients with ALS, quality of life and end-of-life issues in ALS published in diverse journals including The New England Journal of Medicine, and Neurology. At the University of Alberta Dr. Johnston established an ALS clinical and research group that includes a large multidisciplinary clinic and collaborative research programme. In addition to clinical trials in ALS, her research continues to evaluate quality of life and end-of-life issue in ALS and studies are underway to evaluate information-seeking strategies of those affected by ALS. Dr. Johnston is the past Chair of the Canadian ALS Clinical research group (CALS) and has served on various expert panels regarding Medical Assistance in Dying (MAiD) preparedness and implementation, as well as advising the Attorney General of Canada.

Mike Jones, PhD, FACRM is director emeritus of the Virginia C. Crawford Research Institute and former vice president for research and technology (1996-2021) at Shepherd Center. Mike received his Ph.D. in child psychology (with an emphasis in applied behavior analysis) from the University of Kansas, where he also served as associate director of the Research and Training Center on Independent Living. Mike began his career working with children and youth with

autism and developmental disabilities, with a focus on design and management of programs to support management of difficult behaviors (aggressive and self-injurious behavior). Prior to joining Shepherd Center, he was executive director of the Center for Universal Design and Associate Professor of design and technology at North Carolina State University. Mike's professional interests address the design and management of programs and services that promote independent living and full inclusion of people with disabilities. His research includes applications of universal design, information and communication technology, behavior management strategies, and independent living philosophy to promote health, wellness, and community participation.

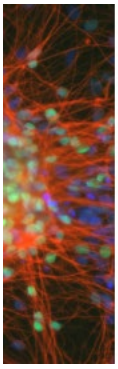
Marissa Kellogg, MD, MPH is an epileptologist and Assistant Professor of Neurology at Oregon Health & Science University (OHSU) and the incoming Director of the Portland VA Epilepsy Center of Excellence (ECoE) (effective November 2021). She completed her undergraduate training at Yale University, her medical training at Rutgers New Jersey Medical School, her neurology residency training at OHSU, and her fellowship in epilepsy/EEG at Stanford University. She is the Epilepsy Clinic Director at OHSU, Global Health Neurology Program Director, and the Vice Chair of the OHSU Neurology Diversity, Equity & Inclusion (DEI) committee. She also serves on the OHSU School of Medicine DEI committee, and on the Medical Board of the NORSE Institute (a national non-profit dedicated to promoting awareness, education, and research regarding New Onset Refractory Status Epilepticus). She is the OHSU Site Principle Investigator for the Marinus RAISE drug trial evaluating the efficacy of a neurosteroid in the treatment of refractory status epilepticus. Her clinical and research interests include psychiatric comorbidities of epilepsy, status epilepticus, NORSE, epidemiology of epilepsy and its comorbidities, telehealth, clinical trials research, global neurology, and promoting DEI in neurology.

Gary Nesbit, MD, FSNIS is a Professor in the Dotter Department of Interventional Radiology, with joint appointments in the Departments of Neurology and Neurosurgery at Oregon Health & Science University. Following Medical School at the University of Minnesota, radiology residency and neuroradiology fellowship at the Mayo Clinic, he served in the Navy at the Naval Medical Center, San Diego. He joined OHSU as an Interventional Neuroradiology fellow and Radiology faculty in 1994, was Neuroradiology division chief from 1996-2006, and has practiced a combination of pediatric and adult diagnostic and interventional neuroradiology throughout his 30-year career. He has published over 130 peer-reviewed manuscripts in both disciplines and recently published a chapter on pediatric cerebrovascular disease in the Handbook of Clinical Neurology. He has been invited as a speaker regionally, nationally, and

internationally on a variety of topics. He has also served as a principle or co-investigator on numerous trials in conjunction with the Oregon Stroke Center and other divisions of the Departments of Neurology, Neurosurgery, Otorhinolaryngology, and Radiology and continues to enjoy the collaborative environment at OHSU.

Elizabeth Silbermann, MD earned her undergraduate degree in Neuroscience at Brown University and her medical degree at Warren Alpert Medical School, Providence, RI. She completed a residency in neurology at Washington University School of Medicine in Saint Louis, MO and a Sylvia Lawry Physician Fellowship through the National MS Society in Neuro-immunology at Oregon Health and Science University at the Portland VA. She is currently an assistant professor at the Portland VA and OHSU. She was recently awarded a CDA-2 to study the relationship between vascular risk factors and microvascular damage in multiple sclerosis.

Vijayshree Yadav, MD, MCR, FANA, FAAN is a board-certified neurologist who is fellowship trained in MS and Neuro-immunology and honored with a Masters degree in Clinical Research from OHSU. She currently is an Associate Professor of Neurology at OHSU and Staff Neurologist at the Portland VA Medical Center (PVAMC). She is the Director of the MS Center at OHSU, and has been the MS and Neuroimmunology Fellowship Director at OHSU and PVAMC since 2017. Her research interests include improving health using complementary therapies such as dietary modification and supplements and conducted novel MS research evaluating effects of low fat diet intervention and role of an antioxidant, lipoic acid in MS for more than a decade. Her research has been funded by National Institute of Health, Department of Veterans Affairs, National MS Society, McDougall Foundation, and Nancy Davis Foundation without walls and she is well-published and presenter at local and national meetings.



Acknowledgment

Grant support

Paralyzed Veterans of America
Portland VA Health Care System, MS Center of Excellence West

Exhibits

National Multiple Sclerosis Society
Biogen
Bristol Myers Squibb
Novartis
Sanofi Genzyme

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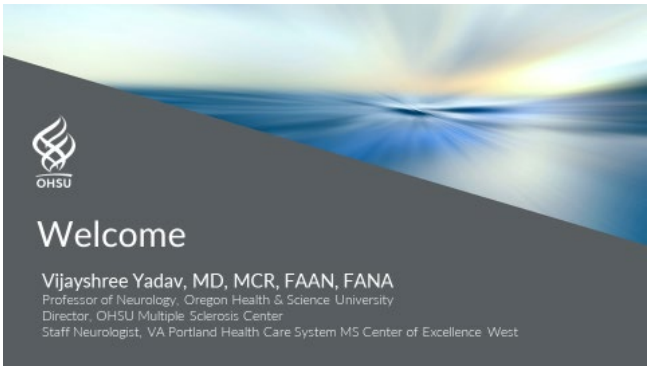

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3:00 p.m.	Adjourn

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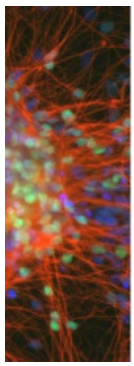

OHSU MS Center

A leader in multiple sclerosis care and research

- Founded in 1983
- Number of people followed in clinics > 1500
- Affiliated with: VA, U.S. Department of Veterans Affairs, Veterans Health Administration, Multiple Sclerosis Centers of Excellence
- Member of: CMSC, RACE TO ERASE MS, MS Center for Comprehensive MS Care

Race to Erase MS Center Without Walls is a network of the nation's top MS institutions including Harvard, UC San Francisco, Yale, USC, UCLA and Johns Hopkins

OHSU

OHSU MS Center Faculty

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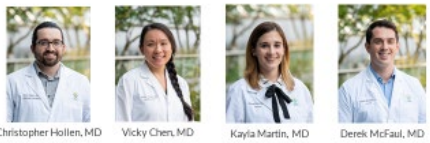
MS/Neuroimmunology Fellows

Training the next generation of MS clinical scientists



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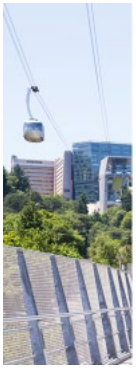


MS Center Education

Provider Education

- MS Fellowships
- MS Wellness Research Symposium
- MS & CNS Neuroimmunology Symposium

Patient Education

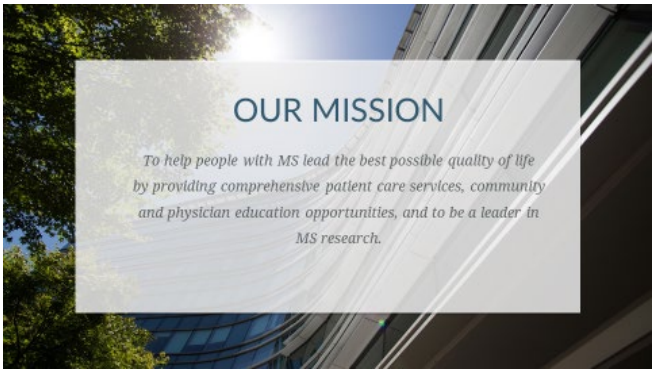
- At the Frontier & Beyond Annual MS Center conference
- MS Brown Bag Lunch Series
- COVID-19 education

Clinical Research by MS faculty

- **Collaborative MS Wellness Research Center (NMSS) -** 2015-2021
- **Lipoic Acid research, Thyroid hormone and MS** - Dennis Bourdette, MD, FAAN , FANA
- **Vascular diseases and MS, Diet and MS, anti-oxidants such as Lipoic acid, MitoQ for fatigue, and Stem cell transplant for MS** - Vijayshree Yadav, MD, MCR , FAAN
- **Lipoic acid in SPMS, use of treatments by people with MS** - Rebecca Spain, MD, MSPH
- **Aerobic exercise and remyelination** - Lindsey Wooliscroft, MD
- **Novel ways of visual assessments in MS** - Elizabeth Silbermann, MD
- **Fall prevention and assistive devices in MS** - Michelle Cameron, MD, PT, M

Basic Scientists in Research

- **Studying genes that control myelination** - Ben Emery, PhD
- **Researching genes that turn myelin formation on and off** - Kelly Monk, PhD
- **RTL 1000** - Arthur Vandenbark, PhD
- **Advanced MRI and MS** - William Rooney, PhD
- **Gait and Balance in MS** - Fay Horak, PhD
- **Thyroid hormone like drug to stimulate remyelination** - Thomas Scanlan, PhD
- **Studying virus that causes MS like disease** - Scott Wong, PhD



Amyotrophic Lateral Sclerosis: Update on Diagnostic Criteria, Guidelines and Therapies

Wendy Johnston, MD, FRCPC
Department of Medicine/Division of Neurology, University of Alberta

Disease Modifying Therapy Update for Multiple Sclerosis

Elizabeth Silbermann, MD
VA Portland Healthcare System
Oregon Health & Science University

Disclosures

- **Grant support:**
  - Department of Veterans Affairs
- **Foundation support:**
  - Mr. & Mrs. Anne & Will Foster

How do we frame our question?

Objectives

- Frame for conceptualizing disease modifying therapies
- Introduction to new medications
- Considerations in the era of COVID

Outline

01 **Framework for MS**
- Relapsing vs progressive
- Induction vs escalation
- Prognostic factors

02 **New medications**
- S1P inhibitor explosion
- B-cell therapies
- Fumarates

03 **COVID**
- Morbidity and mortality
- Vaccines

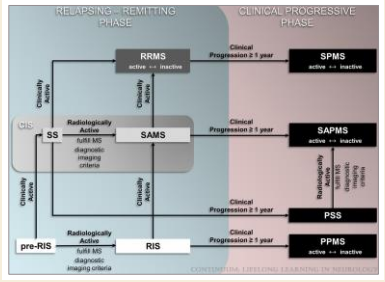
04 **Take home points**

Frameworks

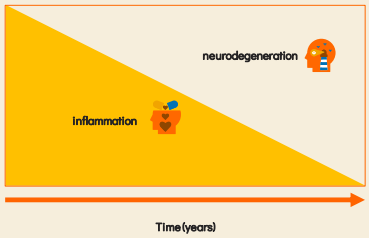
85% at onset

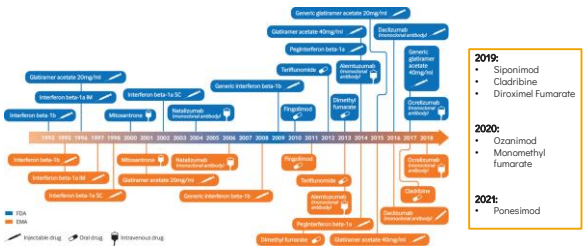
50% in 10 years

15-20% at onset



Kantarci, Orhun H. CONTINUUM: Lifelong Learning in Neurology25(3):636-654, June 2019. doi: 10.1212/CON.0000000000000737





De Angelis, Floriana, Nevin A. John, and Wallace J. Brownlee. "Disease-modifying therapies for multiple sclerosis." *bmj*363 (2018).

Induction vs Escalation

Hauser, Stephen L., Jonah R. Chan, and Jorge R. Oksenberg. "Multiple sclerosis: prospects and promise." *Annals of neurology* 74.3 (2013): 317-327.

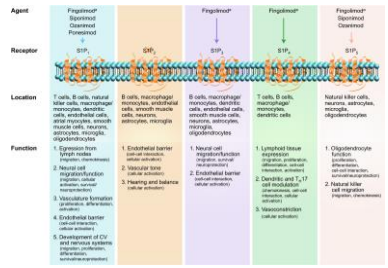
Prognostic Factors

	✔	✖
Demographics	caucasian	non-white males
Onset	monofocal	multifocal
Disease Activity	↓ relapse rate ↓ MRI lesion load	↑ relapse rate ↑ MRI lesion load
Disability @ 5 yrs	↓	↑
Other factors		Vascular comorbidities +OCB + high WBC

02

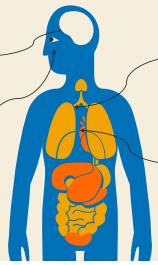
New Medications

S1P Receptor Modulators



Chun, Jerold, Gavin Giovannoni, and Samuel F. Hunter. "Sphingosine 1-phosphate receptor modulator therapy for multiple sclerosis: differential downstream receptor signalling and clinical profile effects." *Drugs*81.2 (2021): 207-231.

Examen Physique



CNS

Anti-inflammatory, neuro-protective, ?remyelination

Lungs

S1P1/4 vasoconstriction
bronchospasm

Eyes

Endothelial abnormalities

Early macular edema

Cardiac

S1P1/3 transient agonism

Bradycardia, ?mild htn

Clinical Efficacy

Fingolimod (Gilenya)

- ARR 0.18 vs 0.4 (placebo)

Ponesimod (Ponvory)

- ARR 0.20 vs 0.29 (teriflunomide)

Siponimod (Mayzent)

- ARR 0.16 vs 0.45 (placebo)

Ozanimod (Zeposia)

- ARR 0.17 vs 0.28 (IFN β)

Kappos, Ludwig, et al. "Long-term effects of fingolimod in multiple sclerosis: the randomized FREEDOMS extension trial." *Neurology* 84.15 (2015): 1582-1591.
Kappos, Ludwig, et al. "Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study." *The Lancet* 391.10127 (2018): 1263-1273.
Kappos, Ludwig, et al. "Ponesimod compared with teriflunomide in patients with relapsing multiple sclerosis in the active-comparator phase 3 OPTIMUM study: a Randomized clinical trial." *JAMA neurology* 78.5 (2021): 558-567.
Cohen, Jeffrey A., et al. "Safety and efficacy of the selective sphingosine 1-phosphate receptor modulator ozanimod in relapsing multiple sclerosis (RADIANCE): a randomised, placebo-controlled, phase 2 trial." *The Lancet Neurology* 15.4 (2016): 373-381.

Brain Atrophy

26 %

↓Brain Volume Loss

Ozanimod vs IFN β

38 %

↓Brain Volume Loss

Fingolimod vs placebo

Kappos, Ludwig, et al. "Long-term effects of fingolimod in multiple sclerosis: the randomized FREEDOMS extension trial." *Neurology* 84.15 (2015): 1582-1591.
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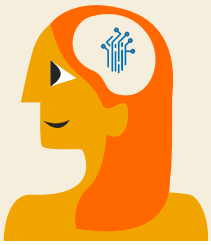
	Fingolimod	Ozanimod	Ponesimod	Siponimod
Before you Start	EKG CBC, LFTs, VZV Vaccines OCT	EKG CBC, LFTs, VZV Vaccines OCT	EKG CBC, LFTs, VZV Vaccines OCT	EKG CBC, LFTs, VZV Vaccines OCT **CYP2C9 g.**
Half-Life	6-9 d	21 hrs	33 hrs	30 hrs
Time to Count Recovery	30-60 d	2-3 d	7 d	1-5 d
Drug interactions	↑QT Rx Ketoconazole ↓HR	↑QT Rx Anti-arrhythmics ↓HR **MAO inhibitors** **Adrenergic/serotonergic drugs** **Caution with tyraminesl** CYP2C8 inhibitors/inducers	↑QT Rx ↓HR CYP3A4 + UGT1A1 inducers	↑QT Rx ↓HR CYP2C9/CYP3A4 inhibitors/inducers

	Fingolimod	Ozanimod	Ponesimod	Siponimod
Longer data?	✓	✗	✗	✗
Interested in pregnancy?	✗	✗	✗	✗
Complicated Meds?	✓	✗	✓	✓
Home titration?	✗	✓	✓	✓

02

New Medications

Fumarates



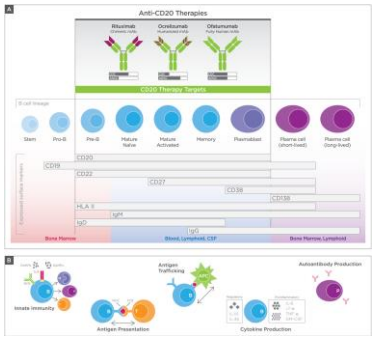
Fumarates

Dimethyl Fumarate (Tecfidera)	Monomethyl Fumarate (Bafiertam)	Diroximel Fumarate (Vumerity)
WITH or WITHOUT food	WITH or WITHOUT food	Take WITH food Better side effect profile (?)

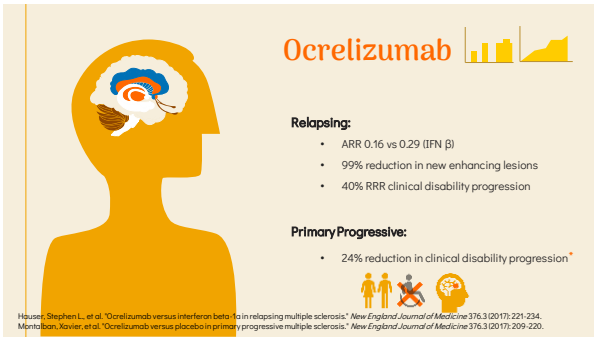
02

New Medications

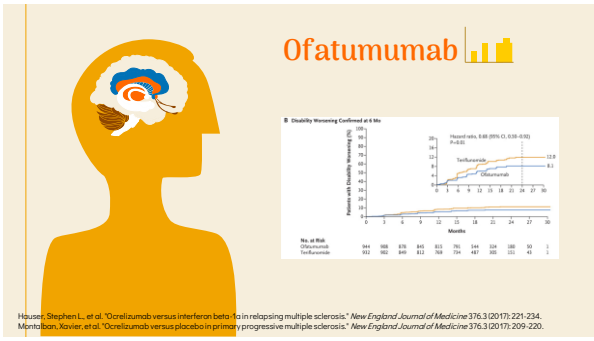
B cell therapies



Greenfield, Ariele L., and Stephen L. Hauser. "B-cell therapy for multiple sclerosis: entering an era." *Annals of neurology* 83.1 (2018): 13-26.



Hauser, Stephen L., et al. "Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis." *New England Journal of Medicine* 376.3 (2017): 221-234.
Montalban, Xavier, et al. "Ocrelizumab versus placebo in primary progressive multiple sclerosis." *New England Journal of Medicine* 376.3 (2017): 209-220.



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	Ocrelizumab	Ofatumumab
Indication	CIS, RRMS, active SPMS, PPMS	CIS, RRMS, active SPMS
Administration	Infusion q6 months	Subcutaneous q1 month
Immunoglobulins	↓IgG: 1.5% ↓IgA: 2.4% ↓ IgM 16.5%	↓IgM 14.3% 3.4% discontinued treatment due to low IgM
B cell recovery	72 weeks	40 weeks
Vaccines	4 weeks prior for live vaccines, 2 weeks prior for inactivated vaccines	

COVID?

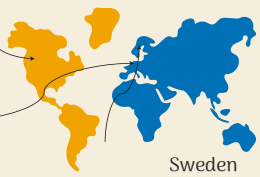
COVID and MS Globally

United States

↑ age, CV comorbidities, Black race, recent steroids, walking aids = ↑severity

France and Italy

↑age, ↑EDSS, CV comorbidities, male sex = ↑ severity

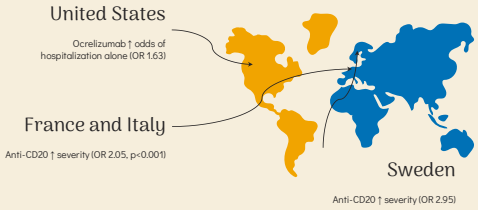


Sweden

↑age, ↑EDSS, male sex = ↑ severity

Salter et al Salter, Amber, et al. "Outcomes and risk factors associated with SARS-CoV-2 infection in a North American registry of patients with multiple sclerosis." *JAMA neurology* 78.6 (2021): 699-708.
Spelman, Tim, et al. "Increased rate of hospitalisation for COVID-19 among rituximab-treated multiple sclerosis patients: A study of the Swedish multiple sclerosis registry." *Multiple Sclerosis Journal* (2021): 13524585211026272.

COVID and MS Globally



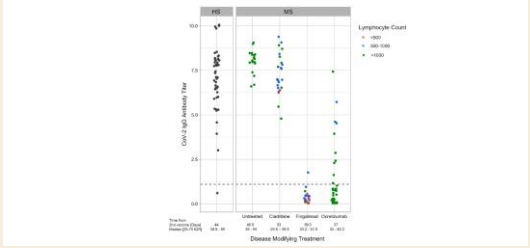
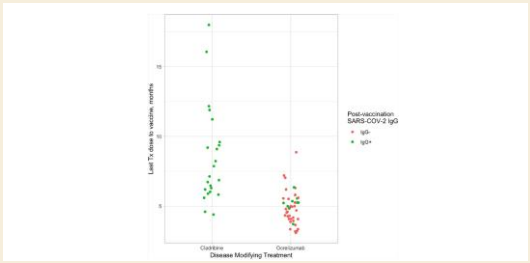


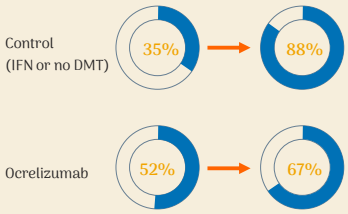
Figure 1. Post-vaccination SARS-CoV-2 IgG antibody titer by disease-modifying treatment in relation to absolute lymphocyte count presented as grading >1000 cells/mm3 (green circles), between 500 and 1000/cells mm3 (red), and <500 cells/mm3 (blue).



Positive post-vaccination SARS-CoV-2 IgG antibody titer is presented by a green circle; negative post-vaccination SARS-CoV-2 IgG antibody titer is presented by a red circle.

VEOLOCE Study

Proportion of patients with seroprotection after influenza vaccination



Amit Bar-Or et al. Neurology 2020;95:e1999-e2008

People with MS using the following DMTs may benefit from an additional dose (booster):

- S1P receptor modulators (Gilenya, Mayzent, Zeposia, Ponvory),
- alemtuzumab (Lemtrada) and
- anti-CD20 monoclonal antibodies (Ocrevus, Kesimpta, Rituxan and biosimilars)

Talk to your MS healthcare provider to determine what is best for you.

-NMSS

Next steps?

- Medications LOOK more complicated, but lots of redundancy
- Now, more than ever, counsel carefully
- We still need:
  - Better guidance on antibody testing
  - Better data on vaccine timing

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Thank you!

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Questions?

silberme@ohsu.edu

Icon Pack: Psychology | Flat

mRehab – Technology Innovation to Support MS Rehabilitation

Mike Jones, PhD, FACRM
Virginia C. Crawford Research Institute
Shepherd Center

RehabRERC

LiveWell App Factory

4th Annual MS/CNS Neuroimmunology Symposium

Presentation Overview

1. Drivers of innovation adoption in rehabilitation
2. Trends driving change in the delivery of rehabilitation services … to outpatient and home-based therapy
3. Our work in development of information and communication technologies (ICT) to support "mHealth" and "mRehab"
   - Mobile app development
   - "Big Data" analytics in mRehab

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Information and Communication Technologies?

"Devices, networks, applications and systems used to interact with the digital world."

Convergence of audio/visual, computer, and tele-communication networks.

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Andrew C. Carlos MS Institute

Ben Thrower, MD, Medical Director
Debbie Backus, PT, PhD, Director of MS Research

Rehab and Wellness	Medical Clinic	Research
• Day Program • PT, OT, SLP, EP • Outpatient rehab visits • Wellness Program	• MDs, APPs • RNs, Mas • CM, CMAs • IV Rooms • Clinic visits	• Outcomes • Clinical Trials • Rehabilitation Research / Translational Research

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STEP for MS Project

- Five-year multi-site study of the benefits of exercise in MS, comparing:
  - Facility-based exercise with coaching provided in person
  - Home-based exercise with coaching provided by centralized staff using telerehabilitation methods
- 16-week exercise intervention, with 12-mo follow-up assessment of walking/mobility, quality of life, and exercise self-efficacy outcomes.

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Motl RW, Backus D, Neal WN, Cutter G, Palmer L, McBurney R, Schmidt H, Bethoux F, Hebert J, Ng A, McCully K. Rationale and design of the STEP for MS Trial: Comparative effectiveness of Supervised versus Telerehabilitation Exercise Programs for Multiple Sclerosis. *Contemporary Clinical Trials*. 2019 Apr 22.

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What leads to technology adoption in rehabilitation?

1. **Compelling Problem** – problems/challenges that lend themselves to technology solution.
2. **Workable Solution** – technology that is sufficiently mature, robust, and readily applicable to the problem.
3. **Motivation for Change/Adoption** – Usually monetary but also necessity, altruism, greater effectiveness/efficiency.

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What leads to technology adoption in rehabilitation?

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Trends driving change in medical rehabilitation … to outpatient and home-based venues

1. **Compelling Problem** – The widening gap between supply and demand for rehabilitation services
2. **Potential Solution** – Use of ICT to optimize outpatient & home-based therapy
3. **Motivation for Change/Adoption** – Changes in reimbursement … and necessity (Covid-19)

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Trends driving change in medical rehabilitation

1. **Widening gap between supply and demand –**

Demand – *5-6% annual growth through 2028*

- More people with disability living longer
- Aging Boomers are the "Silver Tsunami"

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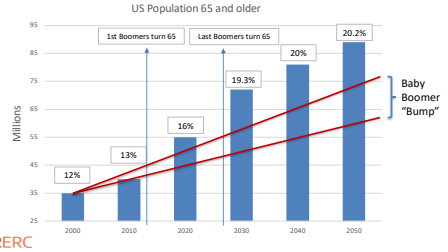
The Baby Boomer "Silver Tsunami"



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Trends driving change in medical rehabilitation

1. Widening gap between supply and demand –

Demand – ***5-6% annual growth through 2028***

- More people with disability living longer
- Aging Boomers are the "Silver Tsunami"

Supply –***17-27% shortfall in personnel*** across all disciplines by 2028

- PTs 22%
- OTs 18%
- SLPs 27%
- Physiatrists 17%
- Rehab Nurses 19%

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Trends driving change in medical rehabilitation

2. Advances in ICT

- **The Internet –**the rise of "Big Data" analytics … 1.2 billion gigabytes stored by Google, Amazon, Microsoft and Facebook alone!
- **Mobile Computing** – more power in your pocket than Apollo 11 … 100,000x more
- **Mobile Apps** – growth of Digital Health … 2 million apps in the Apple store; >400,000 mHealth apps and counting
- **Internet of Things** – sensors everywhere tracking everything … 26 billion devices in 2020
- **Machine Learning and Artificial Intelligence … (M2M)** the machines are running the machines

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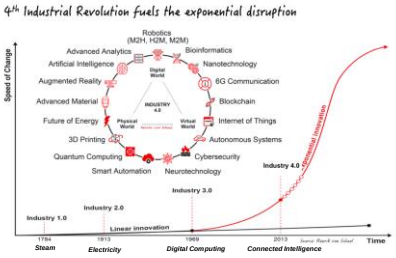
The 4th Industrial Revolution (Henrik von Scheel)

Combining emerging, connected, "smart" technologies to digitally transform industry

… including healthcare.



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Trends driving change in medical rehabilitation

3. **Changes in Reimbursement** – *fewer resources but also new opportunities*
   - **ACA** (2010) – rehabilitation included as an essential (but finite) benefit
   - **IMPACT Act** (2014) – Mandates site-neutral payment for post-acute care (PAC) starting in 2021(?)
   - **CMS** (2020) – payment for "remote physiologic monitoring" (RPM codes)
     - (2021) – proposed payment codes for remote *therapeutic* monitoring (RTM)
   - **CONNECT Act (S.1512)** would make Covid-19 changes in telehealth reimbursement permanent

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There's an app for that …

Mobile apps for health management in MS

- Symptom tracking
- Education
- Communication with care providers
- Comprehensive self-management

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The App Factory project

Advent of *application programming interface* (APIs) for mobile operating systems ("mobile apps")

How can we use this "ecosystem" for rapid development of specialized AT solutions?

Objectives:

- Fund commercial developers to build apps that address needs of disabled users via "pay for performance" model.
- Establish a "curation" site to assist users in locating apps that meet their needs.

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The App Factory – Results (2011-2020)

- 3-5 app projects a year
- Budgets: $5,000-$90,000/app
- 80/20 split between private-sector vs. academia-based developers
- 44 projects funded (6 still in development); 30 published apps = 79% success rate
- $632,823 in funding (~$21,000/app)
- Over 815,000 downloads (78 cents/user)
- $2.2M grant in 2020 to fund mHealth/mRehab app development

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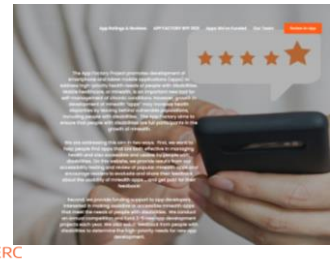
https://www.theappfactory.org



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LiveWell App Factory

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RERC on ICT Access for Mobile Rehabilitation (mRehab RERC)

Mission *– Develop, validate and promote adoption of new models of care using ICT to optimize outpatient and home-based rehabilitation.*

Shepherd Center · DukeHealth · UCI · MRRI · Pt Pal · FlintRehab Tools to spark recovery

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How can we optimize outpatient rehabilitation?

Challenges with the traditional outpatient model

- Transportation and logistical barriers
- Adherence and engagement with home-based therapeutic activities
- Gauging progress (capacity in clinic vs function at home)
- Providing feedback and updating exercises between visits

Can we create new models of care using ICT?

- Therapy management platforms
- Sensor-enhanced activity monitoring (SEAM)
- Algorithms drawn from "big data" to manage therapy progression

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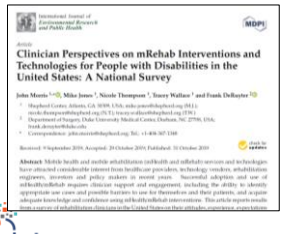
Acceptance of mRehab approaches by providers



Clinician Perspectives on mRehab Interventions and Technologies for People with Disabilities in the United States: A National Survey

- Comfort with technology
- Incorporation into clinical workflow
- Reimbursement concerns
- Evidence of effectiveness and ROI
- 73% report patients need additional therapy post-DC
- 54% report patients need home therapy between visits
- 95% think mRehab could be effective
- 48% are comfortable about integrating mRehab into their practice
- 21% feel knowledgeable about how to use ICT to support home therapy
- 12.5% already use online management tools for home therapy

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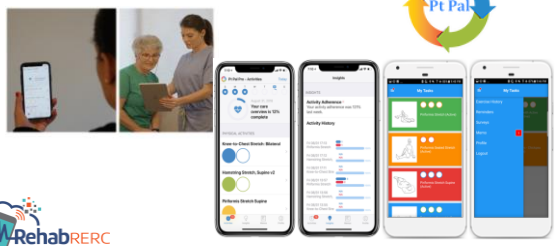
Pt Pal Therapy Management Platform



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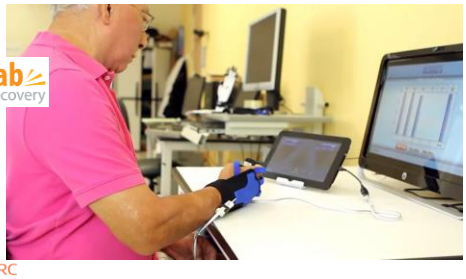

FlintRehab
Tools to spark recovery

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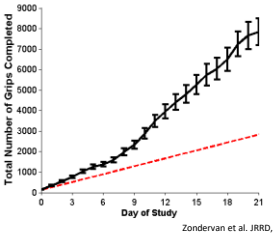
FlintRehab instrumented therapy devices

MusicGlove – Cumulative practice "reps"



Zondervan et al. JRRD, 2016

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Using AI to emulate clinician treatment algorithms

1. Create a "Big Data" lake from historic data (>500,000 patients representing >70 million practice "reps").
2. Identify behavioral profiles based on activity:
   - Nonadherent
   - Adherent but not progressing
   - On-track and making progress
   - Over-performing; likely to drop off
3. Define optimal clinical path and frequency/schedule of clinic visits
4. Adjust the path based on activity:
   - Vary the pace of progression (intensity or type of exercise; levels achieved in gamified exercises)
   - Build-in messaging from the therapist ("nudges")
   - Vary the frequency or timing of clinic visits
5. Adjust (semi-)autonomously based on performance

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25

Big Data analytics and sensor-enhanced activity management (SEAM)

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Some early results

... data from 2,583 patients over 3 years conducting over 602,000 exercise sessions

1. **In "gamified" exercise (FitMi), early success or failure predicts adherence (starting session) and engagement (completing session).**
   There is a "sweet spot" of initial difficulty, measured as successful progress of game levels.
2. **After one month of FitMi use, we can accurately predict who will "drop-out."**
   Predictors of perseverance include – impairment level, success in "leveling up", and consistent ("slow and steady") use over time.
3. **Over time users of the FitMi game play less often, but with the same intensity.**
   *If users start the game, they play with the same intensity as before. This suggest that we need to identify incentives for **starting** the game.*

Ramos, E., Swanson, V., Johnson, C., Anderson, R., Rabinowitz, A., Zondervan, D., Collier, G., Reinkensmeyer, D. , Using large-scale sensor data to identify factors related to perseverance with home exercise. *International Jour Environ Research and Public Health, 2021.*

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Big Data analytics and SEAM – Early Success

$$[Success\ Rate] = \frac{[Levels\ Completed]}{[Levels\ Attempted]} \times 100$$

***Example**: If I start **10** exercises and successfully complete **6**, then I have a **60%** success rate.*

"Can we level set the difficulty of exercise to improve adherence and performance?"

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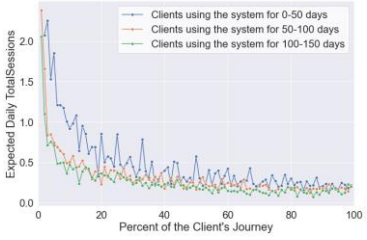
Common use patterns over time

Patterns of use and "extinction" are the same regardless of how long you use the system?.



Some conclusions

The data show that:

- Success in the first week has a large effect on the amount of practice in subsequent weeks
- Adherence (session initiation) decreases over time in a smooth fashion, regardless of the lifetime of use
- Yet, over time, in any session, users work as hard as before

This suggests that:

- We can modify the game to improve success in the first week and, therefore, reduce drop-outs
- The in-game reinforcers for playing are strong and support engagement once a session is initiated
- **The key to adherence is finding more powerful incentives for initiation** (virtual coaching; peer support)

In closing, we have a …

1. **Compelling Problem** – The gap between supply and demand requires adoption of new models and strategies.
2. **Workable Solution** – Is the technology sufficiently mature, robust, and applicable? – That's our challenge!
3. **Motivation for Adoption** – Covid-19 pandemic has opened the door to new sources of reimbursement.

What does the future hold?

1. Will advances in ICT change models of care in medical rehabilitation?
2. Will AI/ML lead to "commoditization" of rehabilitation?
3. Will it provide for greater autonomy and control by consumers?
4. Could it lead to denial of claims for poor adherence?
5. Does it bring us closer to payment for outcomes?

Join our mRehab journey…

- Provider Advisory Network
- Clinical collaborators
- Big Data contributors

https://www.mrehabrerc.org/mrehab-news

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Autoimmune-Associated Epilepsy: Diagnosis and Management

Marissa Kellogg, MD, MPH

OHSU 4th Annual MS and CNS Neuroimmunology Symposium

September 18, 2021

Autoimmune-Associated Epilepsy – Lecture Outline

- Case Introduction
- Definitions / Concepts
- Diagnosis
  - How do we diagnose autoimmune encephalitis (AE)?
  - How do we diagnose autoimmune-associated epilepsy (AAE)?
  - Who should be evaluated for AAE?
- Management
- Case Wrap-up
- References

Case Introduction

- 18yo healthy woman presented with onset of convulsive seizures with LOC. Her first seizure was described as a "**choking spell**" by her boyfriend while she was sleeping. Within a week, she had two additional spells both characterized by **face contortion, drooling and then stiffening up**. She continued to have seizures and was seen by an outpatient neurologist and started on phenytoin. 4 weeks after onset of seizures, she was admitted to an OSH with **AMS, ataxia, worsening paranoia and memory issues**. EEG was notable for diffuse slowing and occasional **RIGHT temporal and rare LEFT temporal sharp waves**. She was continued on Keppra and Vimpat was added. She was transferred to OHSU and monitored on cEEG; she continued to have **bilateral fronto-temporal seizures despite ASDs**. She was **started on prednisone** 60mg PO on HD#5 which was increased to 100mg PO on HD#6. Seizures stopped on HD#7. There was concern for possible hashimoto's since her TPO was elevated. Neuroimmunology was contacted to weigh in on her case. She was treated with **3 days of 1g IV solumedrol** given that she was already on steroids for 2 weeks prior. She was discharged on prednisone 60mg qday and cellcept titration up to a goal of 1000mg BID with follow-up in OHSU neuroimmunology clinic.
- She suffered **recurrence of her limbic encephalitis 2 months after hospital discharge (confusion, disinhibition, auditory visual hallucinations, complex partial seizures on EEG) in the setting of tapering Prednisone** to 40mg (tapered by 10mg every 2 weeks) **and also tapering Vimpat** to 100mg BID (Keppra level came back at 4). She received 5 days of methylprednisolone 1g IV and prednisone was increased back to 60mg daily…

Definitions / Concepts

- Autoimmune epilepsy
  - Originally suggested as a concept in 2002
  - Unclear / imprecise term
    - implies active autoimmune process and/or sole autoimmune cause
    - may downplay other important neurological manifestations in these patients
    - some seizures due to autoimmune diseases resolve entirely with immunotherapy
- Conceptual definitions (2) proposed by the ILAE (International League Against Epilepsy) Autoimmunity and Inflammation Taskforce (2020):
  - **Acute symptomatic seizures secondary to autoimmune encephalitis** = seizures occurring in the setting of the active phase of immune-mediated encephalitis
  - **Autoimmune-associated epilepsy** = chronic seizures (i.e. epilepsy) determined to be secondary to autoimmune brain diseases
  - This distinction has clinical and therapeutic implications

Steriade, C. *et al.* Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: Conceptual definitions. *Epilepsia* **61**, 1341–1351 (2020).

Definitions / Concepts

	Acute symptomatic seizures secondary to autoimmune encephalitis (AE)	Autoimmune-associated epilepsy
Underlying antibodies or conditions	Antibodies against certain surface antigens (NMDAR, LGI1, CASPR2, GABAAR, GABABR, mGluR5, DPPX, AMPAR) and intracellular antigens (onconeural, GAD65)	Antibodies against intracellular antigens (onconeural, GAD65) Rasmussen encephalitis Persistent epilepsy after acute AE
Hypothesized patho-physiology	Antibody-mediated ictogenesis	Epileptogenesis due to structural postencephalitic pathology and/or ongoing T-cell mediated brain inflammation
Therapy	Immunotherapy Antiseizure medications (ASMs) (usually ineffective in isolation)	Antiseizure meds (ASMs) (often ineffective) Epilepsy surgery (usually incomplete response) Immunotherapy (usually poor response)
Outcome	Seizures usually terminate with remission of encephalitis Potential for ASM discontinuation Potential enduring cognitive deficits	Pharmacoresistant focal epilepsy common Potential enduring cognitive deficits

Steriade, C. *et al.* Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: Conceptual definitions. *Epilepsia* **61**, 1341–1351 (2020).

Diagnosis

- **How do we diagnose autoimmune encephalitis (AE)?**
  - What criteria do we use?
  - What testing is indicated?
- **How do we diagnose autoimmune-associated epilepsy (AAE)?**
  - Do all patients with AE develop AAE?
  - Can you have AAE and never previously have had encephalitis?
- **Who should we test for AAE?**
  - Who is at greatest risk for developing AAE?
  - What if antibody testing results are negative or variable?

Critical caveat: there are no strict operational time definitions for these disorders given the wide spectrum in clinical presentation, which can vary according to the particular associated antibody and timing of immune-targeted therapy.

Diagnosis: autoimmune encephalitis (AE)

- Diagnostic criteria by expert panel (lead by Graus & Dalmau) & evidence-based consensus (2016):
- Panel 1: **POSSIBLE autoimmune encephalitis** (all 3 criteria must be met):
  1. Subacute onset (rapid progression of less than 3 months) of working memory deficits, altered mental status, or psychiatric symptoms
  2. At least one of the following:
     - New focal CNS findings
     - Seizures not explained by a previously known seizure disorder *(caution here!)*
     - CSF pleocytosis (WBC >5 cells/mm3)
     - MRI features suggestive of encephalitis
  3. Reasonable exclusion of alternative causes (eg infections, sepsis, drug toxicity, neoplasm, etc)
- Panel 2: **DEFINITE autoimmune limbic encephalitis** (all 4 criteria must be met):
  1. Subacute onset (<3 months) of working memory deficits, seizures, or psychiatric symptoms (suggesting involvement of limbic system)
  2. Bilateral brain abnormalities on T2-weighted FLAIR MRI highly restricted to medial temporal lobes
  3. At least one of the following:
     - CSF pleocytosis (WBC >5 cells/mm3)
     - EEG with epileptic or slow-wave activity involving the temporal lobes
  4. Reasonable exclusion of alternative causes
- → **Antibody panel testing…**

Graus, F. *et al.* A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* **15**, 391–404 (2016).

Diagnosis: Encephalopathy-Autoimmune Eval

(Mayo Clinic Lab ENS2) - **Always performed** *(21):*

Test ID	Reporting Name
AEESI	Encephalopathy, Interpretation, S
AMPCS	AMPA-R Ab CBA, S
AMPHS	Amphiphysin Ab, S
AGN1S	Anti-Glial Nuclear Ab, Type 1
ANN1S	Anti-Neuronal Nuclear Ab, Type 1
ANN2S	Anti-Neuronal Nuclear Ab, Type 2
ANN3S	Anti-Neuronal Nuclear Ab, Type 3
CS2CS	CASPR2-IgG CBA, S
CRMS	CRMP-5-IgG, S
DPPIS	DPPX Ab IFA, S

Test ID	Reporting Name
GABCS	GABA-B-R Ab CBA, S
GD65S	GAD65 Ab Assay, S
GFAIS	GFAP IFA, S
IG5IS	IgLON5 IFA, S
LG1CS	LGI1 IgG CBA, S
GL1IS	mGluR1 Ab IFA, S
NIFIS	NIF IFA, S
NMDCS	NMDA-R Ab CBA, S
PCABP	Purkinje Cell Cytoplasmic Ab Type 1
PCAB2	Purkinje Cell Cytoplasmic Ab Type 2
PCATR	Purkinje Cell Cytoplasmic Ab Type Tr

https://www.mayocliniclabs.com/test-catalog/Overview/92116; link accessed 8/26/2021

Diagnosis: Encephalopathy-Autoimmune Eval

(Mayo Clinic Lab ENS2) - **Reflex Tests** *(23):*

Test ID	Reporting Name
ARBI	ACh Receptor (Muscle) Binding Ab
AGNBS	AGNA-1 Immunoblot, S
AINCS	Alpha Internexin CBA, S
AMPIS	AMPA-R Ab IF Titer Assay, S
AMIBS	Amphiphysin Immunoblot, S
AN1BS	ANNA-1 Immunoblot, S
AN2BS	ANNA-2 Immunoblot, S
CRMWS	CRMP-5-IgG Western Blot, S
DPPCS	DPPX Ab CBA, S
DPPTS	DPPX Ab IFA Titer, S
GABIS	GABA-B-R Ab IF Titer Assay, S
GFACS	GFAP CBA, S
GFATS	GFAP IFA Titer, S

IG5CS	IgLON5 CBA, S
IG5TS	IgLON5 IFA Titer, S
GL1CS	mGluR1 Ab CBA, S
GL1TS	mGluR1 Ab IFA Titer, S

Test ID	Reporting Name
NFHCS	NIF Heavy Chain CBA, S
NIFTS	NIF IFA Titer, S
NFLCS	NIF Light Chain CBA, S
NMDIS	NMDA-R Ab IF Titer Assay, S
PC1BS	PCA-1 Immunoblot, S
PCTBS	PCA-Tr Immunoblot, S

https://www.mayocliniclabs.com/test-catalog/Overview/92116; link accessed 8/26/2021

Diagnosis: Encephalopathy-Autoimmune Eval

(Mayo Clinic Lab ENS2) – **Methods and Cautions**

- **Methods**:
  - **Indirect Immunofluorescence Assay (IFA):** AGN1S, AMPHS, AMPIS, ANN1S, ANN2S, ANN3S, CRMS, DPPIS, DPPTS, GABIS, GFAIS, GFATS, GL1IS, GL1TS, IG5IS, IG5TS, NIFIS, NIFTS, NMDIS, PCAB2, PCABP, PCATR
  - **Cell-Binding Assay (CBA):** AINCS, AMPCS, CS2CS, DPPCS, GABCS, GFACS, GL1CS, IG5CS, LG1CS, NFHCS, NFLCS, NMDCS
  - **Western Blot (WB):** CRMWS
  - **Immunoblot (IB):** AGNBS, AMIBS, AN1BS, AN2BS, PC1BS, PCTBS
  - **Radioimmunoassay (RIA):** ARBI, GD65S
- **Cautions:**
  - ***Negative results do not exclude autoimmune encephalopathy or cancer.***
  - This test does not detect Ma1 or Ma2 antibodies (alias MaTa) (sometimes associated with brainstem and limbic encephalitis in the context of testicular germ cell neoplasms). Scrotal ultrasound is advised for men who present with unexplained subacute encephalitis.
  - Intravenous immunoglobulin (IVIg) treatment prior to the serum collection may cause a false-positive result.

https://www.mayocliniclabs.com/test-catalog/Overview/92116

Diagnosis: Other autoimmune testing

- In most patients:
  - Thyroid antibody testing (i.e. TPO), TSH – r/o Hashimoto's, Grave's
  - Malignancy screen: testicular/ovarian ultrasound, CT Chest/Abd/pelvis, consider PET
- Low threshold to send:
  - ANA / ENA – r/o SLE, Sjogren's
  - Lupus anticoagulant & anti-cardiolipin - r/o Antiphospholipid antibody syndrome (APLA)
  - HbA1c – r/o Type I diabetes
- In select patients:
  - Rheumatology consultation
  - Screening for: rheumatoid arthritis (RA), Behcet's, celiac disease, inflammatory bowel disease (ulcerative colitis and Crohn's), myasthenia gravis

Diagnosis: autoimmune encephalitis (AE)

Differential diagnosis in patients with **POSSIBLE autoimmune encephalitis**:

- CNS infection, septic encephalopathy, metabolic encephalopathy, drug toxity, cerebrovascular disease, neoplastic disorders, Creutzfeldt-Jakob disease, epileptic disorders, rheumatologic disorders (eg lupus, sarcoidosis, Sjogren's, Kikuchi-Fujimoto, Behcet, X-linked lymphoproliferative disease, other), Kleine-Levin, Reye syndrome (children), mitochondrial diseases, inborn errors of metabolism (children)

Differential dx of **autoimmune limbic encephalitis** -> clues -> diagnostics:

- Herpes simplex virus encephalitis (HSE) -> fever, brain bleed -> dx: HSV DNA in CSF
- HHV-6 encephalitis -> most common in immunosuppressed -> dx: HHV-6 DNA in CSF
- Glioma -> usually unilateral, no pleocytosis -> dx: biopsy
- Neurosyphilis -> sx & MRI lesions beyond medial temporal -> dx: CSF treponemal Ab
- Whipple -> systemic sx (polyarthralgia, diarrhea) -> dx: CSF *T whipplei* DNA
- HIV -> low CD4 count -> dx: positive HIV serology

Graus, F. *et al.* A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* **15**, 391–404 (2016).

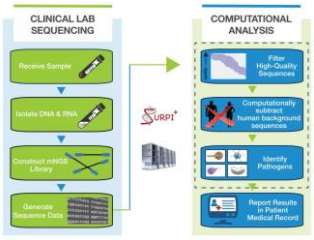
Diagnosis: autoimmune encephalitis (AE)

Metagenomic next-generation sequencing (mNGS) for CSF infections

UCSF Center for Next-Gen Precision Diagnostics

- can potentially diagnose all infectious agents (viruses, bacteria, fungi, and parasites) in a single test
- a shotgun sequencing approach in which all of the nucleic acid (DNA and RNA) in a clinical sample is sequenced at a very high depth, 10-20 million sequences per sample

https://nextgendiagnostics.ucsf.edu/providers/



Post-infectious vs autoimmune encephalitis?

Case Reports > BMJ Case Rep. 2021 May 26;14(5):e241136. doi: 10.1136/bcr-2020-241136.

Acute HSV and anti-NMDA encephalitis occurring as a neurosurgical complication

Jaime Toro [1], Juan Sebastian Rivera [2], Habib Moutran-Barroso [2], Natalia Valencia-Enciso [3]

Affiliations + expand

PMID: 34039543 PMCID: PMC8160154 (available on 2023-05-26) DOI: 10.1136/bcr-2020-241136

Case Reports > J Clin Virol. 2016 Oct;83:26-8. doi: 10.1016/j.jcv.2016.08.292. Epub 2016 Aug 11.

Anti-NMDA Receptor antibody encephalitis with concomitant detection of Varicella zoster virus

Natalia Solis [1], Lucrecia Salazar [2], Rodrigo Hasbun [3]

Affiliations + expand

PMID: 27529098 DOI: 10.1016/j.jcv.2016.08.292

Abstract

The typical presentation of anti-NMDA (N-Methyl-d-Aspartate) receptor encephalitis involves young women with psychiatric, neurologic and autonomic symptoms; it is often associated with mature ovarian teratomas. NMDA receptor encephalitis has been described following Herpes simplex virus (HSV) encephalitis. This case describes a classic presentation of anti-NMDA receptor encephalitis with the concomitant presence of Varicella zoster virus in the cerebrospinal fluid.

Case Reports > Front Neurol. 2020 Feb 18;11:38. doi: 10.3389/fneur.2020.00038. eCollection 2020.

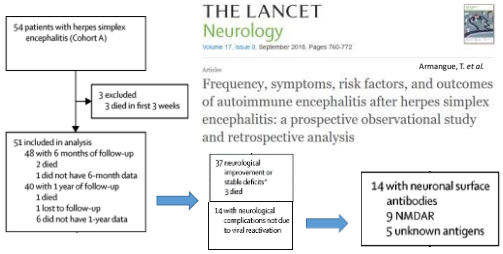
Two Cases of Late-Onset Anti-NMDAr Auto-Immune Encephalitis After Herpes Simplex Virus 1 Encephalitis

Guillaume Doort [1], Marie Benaiteau [1], Chloé Bost [2,3], Catherine Mengelle [4], Fabrice Bonneville [5,6], Guillaume Martin-Blondel [1,7], Jérémie Pariente [1,6]

Affiliations + expand

PMID: 32132963 PMCID: PMC7040193 DOI: 10.3389/fneur.2020.00038

Post-infectious vs autoimmune encephalitis?



THE LANCET Neurology

Volume 17, Issue 9, September 2018, Pages 760-772

Armangue, T. *et al.*

Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis

Diagnosis

- **How do we diagnose autoimmune encephalitis (AE)?**
  - What clinical criteria do we use? Graus & Dalmau expert consensus criteria (2016)
  - What testing is indicated? Autoimmune encephalopathy panel, r/o infections or other causes
- **How do we diagnose autoimmune-associated epilepsy (AAE)?**
  - Criteria? Testing?
  - Do all patients with AE develop AAE?
  - Can you have AAE and never previously have had encephalitis?
- **Who should we test for AAE?**
  - Who is at greatest risk for developing AAE?
  - What if antibody testing results are negative or variable?

Critical caveat: there are no strict operational time definitions for these disorders given the wide spectrum in clinical presentation, which can vary according to the particular associated antibody and timing of immune-targeted therapy.

Diagnosis

- **How do we diagnose autoimmune-associated epilepsy (AAE)?**
  - Criteria?
    - Definition: Chronic seizures determined to be secondary to autoimmune brain diseases
    - More likely if: history of AE, autoimmune disease, certain clinical features
    - Less likely if: generalized epilepsy, genetic syndrome, lesional MRI (*some exceptions*)
  - Testing?
    - Autoimmune encephalopathy panel + rule out other causes
    - ***SAME AS AE!!!*** *(though Mayo Clinic has an epilepsy panel, it's nearly identical to encephalopathy panel)*
  - Do all patients with AE develop AAE?
    - NO – depends on the antibody…
  - Can you have AAE and never previously have had encephalitis?
    - YES – depends on the antibody…

Diagnosis

- **How do we diagnose autoimmune encephalitis (AE)?**
  - What clinical criteria do we use? Graus & Dalmau expert consensus criteria (2016)
  - What testing is indicated? Autoimmune encephalopathy panel, r/o infections or other causes
- **How do we diagnose autoimmune-associated epilepsy (AAE)?**
  - Criteria? Chronic seizures. Testing? Same autoimmune evaluation as AE
  - Do all patients with AE develop AAE? NO
  - Can you have AAE and never previously have had encephalitis? YES
- **Who should we test for AAE?**
  - Who is at greatest risk for developing AAE?
  - What if antibody testing results are negative or variable?

Critical caveat: there are no strict operational time definitions for these disorders given the wide spectrum in clinical presentation, which can vary according to the particular associated antibody and timing of immune-targeted therapy.

JAMA Neurology | Original Investigation

Neurological Autoantibody Prevalence in Epilepsy of Unknown Etiology

Divyanshu Dubey, MD; Abdulradha Alqallaf, MD; Ryan Hays, MD; Matthew Freeman, MD; Kevin Chen, MD; Kan Ding, MD; Mark Agostini, MD; Steven Vernino, MD, PhD

IMPORTANCE Autoimmune epilepsy is an underrecognized condition, and its true incidence is unknown. Identifying patients with an underlying autoimmune origin is critical because these patients' condition may remain refractory to conventional antiseizure medications but may respond to immunotherapy.

OBJECTIVE To determine the prevalence of neurological autoantibodies (Abs) among adult patients with epilepsy of unknown etiology.

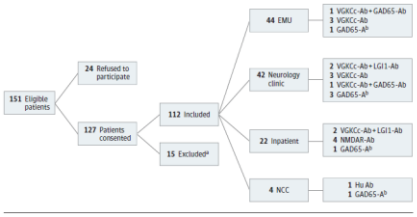
DESIGN, SETTING, AND PARTICIPANTS Consecutive patients presenting to neurology services with new-onset epilepsy or established epilepsy of unknown etiology were identified. Serum samples were tested for autoimmune encephalitis Abs as well as thyroperoxidase (TPO) and glutamic acid decarboxylase 65 (GAD65) Abs. An antibody prevalence in epilepsy (APE) score based on clinical characteristics was assigned prospectively. Data were collected from June 1, 2015, to June 1, 2016.

MAIN OUTCOMES AND MEASURES Presence of neurological Abs. A score based on clinical characteristics was assigned to estimate the probability of seropositivity prior to antibody test results. Good seizure outcome was estimated on the basis of significant reduction of seizure frequency at the first follow-up or seizure freedom.

Dubey, D. *et al. JAMA Neurology* **74**, 397–402 (2017).

APE Score = Antibody Prevalence in Epilepsy

Figure 1. Patient Selection, Enrollment, and Autoantibody-Positive Cases From Each Enrollment Location



EMU indicates epilepsy monitoring unit; GAD65-Ab, glutamic acid decarboxylase 65 antibody; LGI1-Ab, leucine-rich glioma-inactivated protein 1 antibody; NCC, neurocritical care unit; NMDAR-Ab, *N*-methyl-D-aspartate receptor antibody; TPO-Ab, thyroperoxidase antibody; and VGKCc-Ab, voltage-gated potassium channel complex antibody.

[a] No neurological autoantibodies detected in excluded cases.

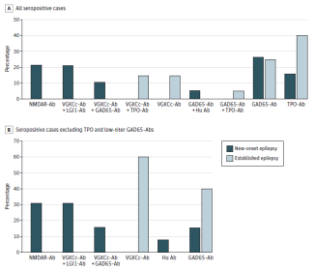
[b] GAD65-Ab level was >20 nmol/L (no precise or validated conversion from nanomoles per liter to units per liter for GAD65-Ab is available).

Dubey, D. *et al. JAMA Neurology* **74**, 397–402 (2017).

Neurological Autoantibody Prevalence in Epilepsy of Unknown Etiology

- There was a **higher prevalence of Abs in patients with new onset epilepsy** than in patients with established epilepsy (13 of 35 [37.1%] vs 10 of 77 [13.0%]; odds ratio [OR], 3.4; 95%CI, 1.5-7.8; *P* = .004).
- Among the 13 patients who were seropositive and had **new-onset epilepsy**, **predominant neurological Abs found were NMDAR, LGI1, and high-titer GAD65** *(Figure 2A)*
- Among the 10 patients with **unexplained established epilepsy: GKCC-Ab (without LGI1-Ab) and high-titer GAD65-Ab were detected** *(Figure 2B)*

Figure 2. Distribution of Autoantibody Specificity by New-Onset Epilepsy and Established Epilepsy



Dubey, D. *et al. JAMA Neurology* **74**, 397–402 (2017).

Table 2. Comparison Between Antibody-Positive Cases and Antibody-Negative Cases

Variables	Antibody Cases, No. (%) Positive (n = 23)	Negative (n = 89)	P Value
Age, median (range), y[a]	46 (19-76)	38 (17-80)	.11
Female[b]	7 (30.4)	46 (51.7)	.10
APE score			
Median (range)[a]	5 (1-11)	2 (0-12)	<.001
≥4	19 (82.6)	17 (19.1)	<.001
New-onset seizures[b]	13 (56.5)	22 (24.7)	.004
Neuropsychiatric changes[b]	18 (78.3)	21 (23.6)	<.001
Autonomic dysfunction[b]	9 (39.1)	3 (3.4)	<.001
Viral prodrome[b]	7 (30.4)	3 (3.4)	.001
FBDS or facial dyskinesias[b]	4 (17.4)	3 (3.4)	.03
Refractory seizure[b]	12 (52.2)	62 (69.7)	.14
CSF findings consistent with inflammation[b]	5 (21.7)	8 (9.0)	.14
Medial temporal sclerosis FLAIR/T2 hyperintensity[b]	11 (47.8)	16 (18.0)	.002
Mesial temporal sclerosis[b]	8 (34.8)	15 (16.9)	.15
Malignancy[b]	1 (4.3)	0	.20
Good clinical outcome[b]	15 (65.2)	24 (27.0)	.002
Seizure freedom at first clinic visit[b]	9 (39.1)	16 (18.0)	.02
Temporal lobe onset seizures[b]	11 (47.8)	40 (44.9)	.22
Focal nonconvulsive status epilepticus[b]	4 (17.4)	7 (7.9)	.17
Refractory status epilepticus[b]	3 (13.0)	4 (4.5)	.09
Type of epilepsy[b]			
Generalized	0	5 (5.6)	.73
Focal	21 (91.3)	74 (83.1)	
Unspecified	2 (8.7)	10 (11.2)	
Location of enrollment[b]			
EMU	5 (21.7)	39 (43.8)	.10
Inpatient	7 (30.4)	15 (16.9)	
Neurology clinic	9 (39.1)	33 (37.1)	
NCC	2 (8.7)	2 (2.2)	

Dubey, D. *et al. JAMA Neurology* **74**, 397–402 (2017).

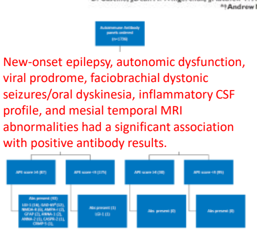
Neurological Autoantibody Prevalence in Epilepsy of Unknown Etiology

Demographic and clinical characteristics found more commonly in patients with positive serologic Ab findings than in patients with negative serologic findings *(Table 2):*

- **Viral prodrome** (7 [30.4%]vs 3 [3.4%];OR,12.5; *P* = .001)
- **Autonomic dysfunction** (9 [39.1%] vs 3 [3.4%]; OR, 18.2; *P* < .001)
- **Neuropsychiatric changes** (18 [78.3%]vs 21 [23.6%]; OR, 11.7; *P* < .001)
- **Faciobrachial dystonic spells or facial dyskinesias** (4 [17.4%] vs 3 [3.4%]; OR, 6.0; *P* = .03)
- **Mesial temporal MRI abnormality** (11 [47.8%] vs 16 [18.0%]; OR, 4.8; *P* = .002)

Predictive models in the diagnosis and treatment of autoimmune epilepsy

*Divyanshu Dubey, *Jaysingh Singh, *Jeffrey W. Britton, *†Sean J. Pittock, *†Eoin P. Flanagan, *†‡Vanda A. Lennon, *Jan-Mendelt Tillema, *Elaine Wirrell, *Cheolsu Shin, *Elson So, *Gregory D. Cascino, §Dean M. Wingerchuk, §Matthew T. Hoerth, ¶Jerry J. Shih, *Katherine C. Nickels, and *†Andrew McKeon



New-onset epilepsy, autonomic dysfunction, viral prodrome, faciobrachial dystonic seizures/oral dyskinesia, inflammatory CSF profile, and mesial temporal MRI abnormalities had a significant association with positive antibody results.

Table 2. Comparison of antibody-positive and antibody-negative cases

Variables	Antibody-positive cases (n = 44)	Antibody-negative cases (n = 343)	p-Value
Median age, years (range)[a]	53 (3-87)	44 (8.5-76)	NS
Female N (%)[b]	21 (47.7)	197 (57.4)	NS
Median APE score (range)[a]	6 (3-12)	3 (0-9)	<0.01
APE Score ≥ 4	43 (97.7)	46 (21.1)	<0.01
New-onset seizures (%)[b]	31 (72.1)	114 (33.1)	<0.01
Neuropsychiatric changes[f] (%)[b]	32 (72.7)	88 (25.7)	<0.01
Autonomic dysfunction[c] (%)[b]	8 (18.2)	5 (1.5)	<0.01
Viral prodrome[d] (%)[b]	9 (20.5)	9 (2.6)	<0.01
Faciobrachial dystonic seizures or Facial dyskinesias (%)[b]	13 (29.5)	2 (0.6)	<0.01
Refractory seizure (%)[b]	35 (79.5)	173 (50.5)	<0.01
CSF protein >50 mg/dl (%)[b]	15 (40.5)	31 (16.4)	<0.01
CSF cell count >5 cells/dl (%)[b]	13 (35.1)	9 (10.3)	<0.01
Specific oligoclonal bands in CSF >4 (%)	5 (14.3)	7 (4.2)	<0.05
Medial temporal FLAIR/T2 hyperintensity (%)[b]	14 (31.8)	58 (16.9)	<0.05
Systemic malignancy detected (%)[b]	6 (13.6)	34 (9.9)	NS
Temporal lobe-onset seizures[e] (%)[b]	25 (67.9)	20 (47.6)	NS
Cognitive dysfunction (%)[b]	31 (81.6)	122 (38.6)	<0.01
Fatigue (%)[b]	3 (8.3)	23 (7.4)	NS
Hypersomnolence (%)[b]	3 (8.6)	13 (4.3)	NS
Headache (%)[b]	8 (22.2)	68 (22.5)	NS
Other Autoimmune conditions[a] (%)[b]	6 (15.8)	39 (12.1)	NS
Piloerection (%)[b]	2 (5.2%)	0	<0.01
Mesial temporal sclerosis (%)[b]	3 (7.7)	21 (9.1)	NS
Type of epilepsy (%)[b]	0	74 (21.5)	<0.01
Generalized	0	74 (21.5)	<0.01
Focal	44 (100)	247 (72.1)	
Unspecified	0	22 (6.4)	

[a]Mann-Whitney U-test; [b]chi-square or Fisher's exact test. NS, nonsignificant. [c]sustained sinus tachycardia or bradycardia, orthostatic hypotension (≥20 mm Hg fall in systolic pressure or ≥10 mm Hg fall in diastolic pressure within 3 min of standing), hyperhidrosis, persistently labile blood pressure, ventricular tachycardia, or cardiac asystole. [d]rhinorrhea, sore throat, low-grade fever. [e]localization of seizure determined based on ictal or interictal findings on electroencephalography (EEG). [f]agitation, aggressiveness, emotional lability.

Dubey, D. *et al.* Predictive models in the diagnosis and treatment of autoimmune epilepsy. *Epilepsia* **58**, 1181–1189 (2017).

Diagnosis: APE2 score
(Antibody Prevalence in Epilepsy and Encephalopathy)

APE2 score:

- A validated model to predict seropositivity of neural-specific antibodies and favorable response to an immunotherapy trial among patients with epilepsy
- Purpose: to optimize selection of cases for autoimmune epilepsy evaluation and management
- Modification (2019 – *Mayo Clinic*) from the original APE score (2017 – *UTSW*) to improve accuracy

Diagnostic criteria for AAE (proposed by authors Dubey et al):

1. **APE2 score**
2. Neural-specific antibody serum status (presence or absence of Abs)
3. Response to a trial of immunotherapy (favorable vs un-favorable)

Dubey, D., Pittock, S. J. & McKeon, A. Antibody Prevalence in Epilepsy and Encephalopathy score: Increased specificity and applicability. *Epilepsia* **60**, 367–369 (2019).

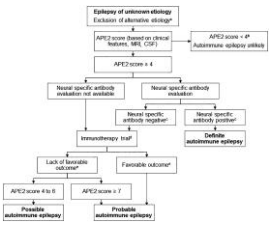
Diagnosis: **APE2 score** (max 18 points)
(Antibody Prevalence in Epilepsy and Encephalopathy)

- **New onset, rapidly progressive mental status changes** that developed over 1-6 weeks or **new-onset seizure** activity (within 1 year of evaluation) **(+1)**
- **Neuropsychiatric changes**; agitation, aggressiveness, emotional lability **(+1)**
- **Autonomic dysfunction** (sustained atrial tachycardia or bradycardia, orthostatic hypotension), hyperhidrosis, persistently labile BP, vtach, cardiac asystole, *or gastric dysmotility* **(+1)**
- **Viral prodrome** (rhinorrhea, sore throat, low-grade fever) to be scored in absence of underlying systemic malignancy *within 5 years of symptom onset* **(+2)**
- **Faciobrachial dystonic *seizures*** *(FBDS)* **(+3)**
- ***Facial dyskinesias*** *(to be scored in absence of FBDS)* **(+2)**
- **Seizures refractory** to at least 2 antiseizure meds **(+2)**
- **CSF findings c/w inflammation** (CSF protein >50, pleocytosis >5) **(+2)**
- **Brain MRI** showing signal changes c/w limbic encephalitis (medial temporal T2/FLAIR signal changes, *or multifocal grey matter, white matter, or both compatible with demyelination or inflammation*) **(+2)**
- **Systemic cancer** diagnosed within 5 years of neurological symptom onset (excluding cutaneous squamous or basal cell Ca, *brain tumor, cancer with brain metastasis*) **(+2)**

Dubey, D. *et al.* Predictive models in the diagnosis and treatment of autoimmune epilepsy. *Epilepsia* **58**, 1181–1189 (2017).
Dubey, D., Pittock, S. J. & McKeon, A. Antibody Prevalence in Epilepsy and Encephalopathy score: Increased specificity and applicability. *Epilepsia* **60**, 367–369 (2019). ***Note: Items in italics are new additions / modifications (Dubey et al 2019) from original APE Score (Dubey et al 2017).***

Diagnosis: **APE2 score** (max 18 points)
(Antibody Prevalence in Epilepsy and Encephalopathy)

- **APE2 score ≥ 4** among patients with epilepsy of unknown etiology:
  - ***Send antibody testing!!!***
  - 98% sensitivity and 85% specificity for an autoimmune etiology (*79% with APE*)
- **APE2 score ≥7** = 100% specificity for an autoimmune etiology of epilepsy
- *If neural-specific antibody testing is:*
  - **POSITIVE** -> "definite AAE"
  - **NEGATIVE** -> follow algorithm *(figure)*



Dubey, D., Pittock, S. J. & McKeon, A. Antibody Prevalence in Epilepsy and Encephalopathy score: Increased specificity and applicability. *Epilepsia* **60**, 367–369 (2019).

Prognosis: RITE2 score (max 22 points)
Response to Immunotherapy in Epilepsy and Encephalopathy score

- APE2 score plus:
- **Immunotherapy initiated within 6 months of symptom onset (+2)**
- **Neural plasma membrane autoantibody detected (NMDAR, $GABA_AR$, AMPAR, DPPX, mGluR1, LGI1, CASPR2, neurexin-3α, MOG) (+2)**

(AMPAR: amino-3-hydroxy-5-methyl-4-isoxazolepropionic, ANNA-1 : Anti-neuronal nuclear antibody-1, ANNA-2: Anti-neuronal nuclear antibody-2, ANNA-3 : Anti-neuronal nuclear antibody-3, CASPR-2: Contactin Associated Protein 2, DPPX: dipeptidyl-peptidase-like protein 6, FLAIR: fluid attenuated inversion recovery, $GABA_AR$: γ-aminobutyric acid-A receptor, $GABA_BR$: γ-aminobutyric acid-B receptor, GFAP α: Glial fibrillary acidic protein, LGI1: leucine-rich glioma-inactivated protein-1, MOG: myelin oligodendrocyte glycoprotein, mGluR1: metabotropic glutamate receptor 1, mGluR5: metabotropic glutamate receptor 5, NMDAR: N-methyl D-Aspartate Receptor)

Dubey, D. *et al.* Predictive models in the diagnosis and treatment of autoimmune epilepsy. *Epilepsia* **58**, 1181–1189 (2017).

Predictive models in the diagnosis and treatment of autoimmune epilepsy

*Divyanshu Dubey, *Jaysingh Singh, *Jeffrey W. Britton, *†Sean J. Pittock, *†Eoin P. Flanagan, *†‡Vanda A. Lennon, *Jan-Mendelt Tillema, *Elaine Wirrell, *Cheolsu Shin, *Elson So, *Gregory D. Cascino, §Dean M. Wingerchuk, §Matthew T. Hoerth, ¶Jerry J. Shih, *Katherine C. Nickels, and *†Andrew McKeon

Table 3. Comparison of responders and nonresponders following a trial of immunotherapy

Variables	Responders (N = 40)	Nonresponders (N = 37)	p-Value
Median age, years (range)[a]	44 (3–87)	45 (2–89)	NS
Female N (%)[b]	19 (47.5)	27 (73)	<0.05
Neural autoantibody detected (%)[b]	29 (72.5)	10 (27)	<0.01
Neural antibody of plasma membrane specificity (%)[b]	23 (57.5)	1 (2.7)	<0.01
Neural antibody of intracellular specificity (%)[b]	6 (15)	9 (24.3)	NS
Median APE score (range)[a]	6 (1–12)	4 (0–8)	<0.01
APE score ≥4 (%)[b]	37 (92.5)	20 (54.1)	<0.01
Median RITE score (range)[a]	9 (1–16)	4 (0–12)	<0.01
RITE score ≥7 (%)[b]	35 (87.5)	6 (16.2)	<0.01
New-onset seizures (%)[b]	36 (90.0)	10 (27)	<0.01
Neuropsychiatric changes (%)[b]	28 (70)	14 (37.8)	<0.01
Autonomic dysfunction (%)[b]	8 (20)	0	<0.01
Viral prodrome (%)[b]	6 (15)	3 (8.1)	NS
Faciobrachial dystonic seizures or facial dyskinesias (%)[b]	14 (35)	2 (5.4)	<0.01
Refractory seizures prior to immunotherapy trial (%)[b]	30 (75)	31 (83.8)	NS
CSF protein >50 mg/dl (%)[b]	14 (42.4)	11 (30.6)	NS
CSF cell count >5 cells/dl (%)[b]	10 (30.3)	6 (17.6)	NS
Specific oligoclonal bands in CSF >4 (%)	4 (13.8)	5 (15.6)	NS
Medial temporal FLAIR/T2 changes (%)[b]	9 (22.5)	6 (16.2)	NS
Mesial temporal sclerosis	2 (5.6)	4 (11.1)	NS
Systemic malignancy detected (%)[b]	4 (10)	3 (8.1)	NS
Symptom onset to immunotherapy, days (range)[a]	72 (10–535)	415 (30–4184)	<0.01
Interval of symptom onset to immunotherapy <6 months (%)[b]	33 (82.5)	6 (16.2)	<0.01
IVMP (%)[b]	33 (89.2)	25 (67.6)	<0.05
IVIG (%)[b]	22 (56.4)	21 (60)	NS
PLEX (%)[b]	4 (10.8)	3 (8.6)	NS
Second-line agent[c] (%)[b]	21 (52.5)	11 (29.7)	<0.05

[a]Mann-Whitney U-test; [b]chi-square or Fisher's exact test, NS – not significant; [c]use of rituximab or cyclophosphamide.

Factors associated with favorable seizure outcome
In pts who received immunotherapy (N = 77) *(Table 3):*

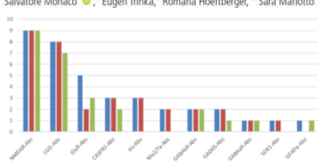
- **neural Ab positivity** (72.5% vs. 27%, p < 0.01)
- **plasma membrane protein Ab positivity** (57.5% vs. 2.7%, p < 0.01)
- **new-onset epilepsy** (90.0% vs. 27%, p < 0.01)
- **autonomic dysfunction** (20% vs. 0%, p < 0.05)
- **FBDS or oral dyskinesias** (35% vs. 5.4%, p < 0.01)
- **Initiation of immunotherapy within 6 months of symptom onset** *(82.5% vs. 16.2%, p < 0.01)*

A significantly higher proportion of patients with an APE score ≥4 responded to immunotherapy (ie 50% reduction in seizure frequency on first follow-up visit after completion of immunotherapy trial; 92.5% vs. 54.1%, p < 0.01)

Dubey, D. *et al.* Predictive models in the diagnosis and treatment of autoimmune epilepsy. *Epilepsia* **58**, 1181–1189 (2017).

Epileptic seizures of suspected autoimmune origin: a multicentre retrospective study

Silvia Bozzetti,[1] Fabio Rossini,[2] Sergio Ferrari,[1] Rachele Delogu,[3] Gaetano Cantalupo,[4] Fabio Marchioretto,[5] Giampietro Zanette,[6] Tiziano Zanoni,[7] Marco Turatti,[1] Giuseppina Vitale,[8] Morena Cadaldini,[9] Francesca Rossi,[10] Luca Di Tizio,[11] Carmela Zuco,[12] Giorgia Teresa Maniscalco,[13] Fabio Soldani,[14] Salvatore Monaco,[1] Eugen Trinka,[2] Romana Hoeftberger,[15] Sara Mariotto[1]



Objective: To analyze autoantibody status in a well-defined European multicentre cohort of patients with epilepsy of unknown aetiology and to validate the APE2 and RITE2 scores.

Methods: Retrospectively collected clinical data of 92 patients referred to the Neurology Units of Verona and Salzburg between January 2014 and July 2019 with new-onset epilepsy, status epilepticus or chronic epilepsy of unknown etiology.

Bozzetti, S. *et al. J Neurol Neurosurg Psychiatry* **91**, 1145–1153 (2020).

Epileptic seizures of suspected autoimmune origin: a multicentre retrospective study - Results:

- Autoantibodies were detected in 29/92 patients (31.5%), with multiple positivity observed in 6/29
- APE2 score (median 5, range 1–15) significantly correlated with antibody positivity (p=0.014), especially for the presence of:
  - neuropsychiatric symptoms (p<0.01)
  - movement disorders (p<0.01)
  - dysautonomia (p=0.03)
  - faciobrachial dyskinesias (p=0.03)
  - cancer history (p<0.01).
- Status epilepticus was significantly more frequent in antibody-negative patients (p<0.01).
- Among the items of the RITE2 score, early initiation of immunotherapy correlated with a good treatment response (p=0.001), whereas a cancer history was significantly more common among non-responders (p<0.01).
- Persistence of neuropsychiatric symptoms and seizures correlated with antiepileptic maintenance after at least 1 year.

Bozzetti, S. *et al. J Neurol Neurosurg Psychiatry* **91**, 1145–1153 (2020).

Research Article | Open Access

Antibodies Contributing to Focal Epilepsy Signs and Symptoms Score

Marienke A. A. M. de Bruijn MD, Anna E. M. Bastiaansen MD, Hana Mojzisova MD, Agnes van Sonderen MD, PhD, Roland D. Thijs MD, PhD, Marian J. M. Majoie MD, PhD, ... See all authors

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ACES SCORE

	Point
Cognitive symptoms	1
Behavioral changes	1
Autonomic symptoms	1
Speech problems	1
Autoimmune diseases	1
Temporal MRI hyperintensities	1

ACES Score

- To preselect patients for Ab testing
- Determined by multivariate logistic regression in a prospective multicenter European cohort of 582 patients
- ACES score ≥ 2 indicates need for Ab testing

Cutoff[a]	n (%)[b]	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
≥1 point	305 (53%)	6.5 (2.8–13.1)	100 (81.4–100)	100 (81.4–100)	48.2 (36.5–63.6)
≥2 point	103 (18%)	19.4 (12.2–29.7)	100 (81.4–100)	100 (81.4–100)	84.9 (67.9–100)
≥3 point	22 (4%)	54.5 (41.4–70.5)	98.5 (80.5–100)	60 (45.8–77.2)	98.2 (80.5–100)
≥4 point	1 (0.2%)	100 (81.4–100)	96.7 (78.7–100)	5 (1.6–11.7)	100 (81.4–100)

Bruijn, M. A. A. M. de *et al.* Antibodies Contributing to Focal Epilepsy Signs and Symptoms Score. *Annals of Neurology* **89**, 698–710 (2021).

Definitions / Concepts

Management

	Acute symptomatic seizures secondary to autoimmune encephalitis (AE)	Autoimmune-associated epilepsy
Underlying antibodies or conditions	Antibodies against certain surface antigens (NMDAR, LGI1, CASPR2, GABAAR, GABABR, mGluR5, DPPX, AMPAR) and intracellular antigens (onconeural, GAD65)	Antibodies against intracellular antigens (onconeural, GAD65) Rasmussen encephalitis Persistent epilepsy after acute AE
Hypothesized patho-physiology	Antibody-mediated ictogenesis	Epileptogenesis due to structural postencephalitic pathology and/or ongoing T-cell mediated brain inflammation
Therapy	Immunotherapy Antiseizure medications (ASMs) (usually ineffective in isolation)	Antiseizure meds (ASMs) (often ineffective) Epilepsy surgery (usually incomplete response) Immunotherapy (usually poor response)
Outcome	Seizures usually terminate with remission of encephalitis Potential for ASM discontinuation Potential enduring cognitive deficits	Pharmacoresistant focal epilepsy common Potential enduring cognitive deficits

Steriade, C. *et al.* Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: Conceptual definitions. *Epilepsia* **61**, 1341–1351 (2020).

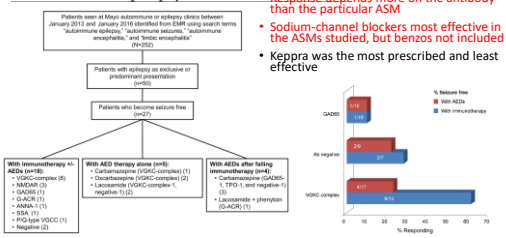
Management: Antiseizure medications (ASMs)

- Systematic Review (2018) of ASMs for AE
  - 6 retrospective observational studies met criteria for:
    - Including patients exclusively treated with ASMs (not immunotherapy/surgery)
    - level of evidence between 2+ and 3 -> SIGN B recommendation
    - N = 139 (total number of patients) exclusively treated with ASMs
  - Results highlights
    - 10.7% = estimated seizure-freedom rate with exclusive ASD treatment in AE
    - AE subtype responders (ie seizure freedom or >50% reduction in seizure frequency):
      - 18% of seronegative patients
      - 11% in VGKC+ patients (LGI1, CASPR2)
      - 8% in GAD65+ patients
    - 73% of responders were in treatment with Na+ channel blockers in monotherapy or in combination

Cabezudo-García, P., Mena-Vázquez, N., Villagrán-García, M. & Serrano-Castro, P. J. Efficacy of antiepileptic drugs in autoimmune epilepsy: A systematic review. *Seizure* **59**, 72–76 (2018).

Antiepileptic drug therapy in patients with autoimmune epilepsy

- Response depends more on the antibody than the particular ASM
- Sodium-channel blockers most effective in the ASMs studied, but benzos not included
- Keppra was the most prescribed and least effective



Feyissa, A. M., Chiriboga, A. S. L & Britton, J. W. *Neurology: Neuroimmunology and NeuroInflammation* **4**, (2017).

Management: Antiseizure medications (ASMs)

- Summary / Recommendations:
  - ASMs are often ineffective, but occasionally work (Specific Ab has prognostic value)
  - ASMs with sodium channel blocking properties may be more effective *(Feyissa et al 2017 [NB: benzos not included in study]; systematic review)*
  - Anecdotal / experiential suggestion that benzos may be more effective in AE, particularly in preventing GTCs and status epilepticus *(Mayo expert opinion + speaker's personal experience)*
- Prospective studies are needed

Management: Epilepsy surgery

- Usually incomplete response
- Resective surgery: seizures may recur from alternative (e.g. contralateral foci)
- Neurostimulation increasingly utilized with mixed (but some promising) results, especially RNS
  - Feyissa, A. M. *et al*. Brain-responsive neurostimulation treatment in patients with GAD65 antibody–associated autoimmune mesial temporal lobe epilepsy. *Epilepsia Open* **5**, 307–313 (2020).

Caveat: Data on the topic of epilepsy surgery in patients with AE is limited to case reports, case series, and expert consensus. Additionally, RNS/DBS therapies are relatively new (FDA approved in the last 2-8 years).

Management: Epilepsy Surgery – **APES score**

New-onset status epilepticus or flurry of seizures OR progressive altered mental status (≤3 months)	+1	Refractory to at least 2 ASMs (e.g. **Refractory to anti-psychotics**	+2
Triad: (a) episodic symptoms onset +unusual neuropsychiatric changes +MRI/PET changes	+1	**PET** b/hat hypo/hypermetabolism	+1
Autonomic dysfunctions (ictal tachycardia/bradycardia, labile BP/HR, persistent tachycardia, postural hypotension) or autonomic seizures	+1	MRI: unilateral/bilateral mesial temporal sclerosis, inflammatory changes (ie, medial temporal T2/FLAIR hyperintensities)	+2
Viral prodrome, meningitis/encephalitis of unclear etiology	+1	Underlying malignancy	+2
Facial dyskinesias or faciobrachial dystonic seizures (FBDS)	+2	**PMH or FHx autoimmunity:** APLAS, lupus, DM type 1, myasthenia gravis, Sjogren's, RA, maternal RA, Crohn's, celiac, UC, Hashimoto's, Graves, psoriasis	+1
New focal CNS findings[b]: speech changes, cerebellar signs,[c] myoclonus, hyperkplexia, mutism, catatonia	+1	Systemic: weight loss ≥10 pounds, hyponatremia <130 mmol/L, sleep disorder/excluding obstructive sleep apnea, neurosyncopsis, peripheral nerve hyperexcitability	+1
		Total Score	/6

Bolded components are modified upon previously validated Dubey's APES[a] score for epilepsy with unknown etiology.

APES score ≥4 has high sensitivity for predicting the occurrence of CNS-specific Abs in patients with focal DRE, especially in those with valid PET results.

- **33.72% of patients with focal drug-resident epilepsy (DRE) are serum Ab+** (most Abs are nonspecific)
- **8.14% of patients with focal DRE undergoing pre-surgical epilepsy evaluation are CNS–specific Ab+**

Li, Y., Tymchuk, S., Barry, J., Muppidi, S. & Le, S. Antibody Prevalence in Epilepsy before Surgery (APES) in drug-resistant focal epilepsy. *Epilepsia* **62**, 720–728 (2021).

Management: Immunotherapy

- Usually poor response… *(but worth a try in the speaker's opinion)*
- No RCT or high-quality clinical data exists
- Recommend:
  - Mayo Clinic neuro-immunology consultation by phone (complementary when autoimmune panel is processed at Mayo Lab)
  - Often start with high-dose steroids +/- IV Ig
  - Often requires complex team-based care:
    - Always: Neuro-Immunology + epilepsy
    - Sometimes: rheumatology, hematology, oncology, psychiatry/psychology, physical/occupational therapy, neuro-psych, etc.

Case Wrap-up

- 18yo healthy woman presented with onset of convulsive seizures with LOC. Her first seizure was described as a "**choking spell**" by her boyfriend while she was sleeping. Within a week, she had two additional spells both characterized by **face contortion, drooling and then stiffening up**. She continued to have seizures and was seen by an outpatient neurologist and started on phenytoin. 4 weeks after onset of seizures, she was admitted to an OSH with **AMS, ataxia, worsening paranoia and memory issues**. EEG was notable for diffuse slowing and occasional **RIGHT temporal and rare LEFT temporal sharp waves**. She was continued on Keppra and Vimpat was added. She was transferred to OHSU and monitored on cEEG; she continued to have **bilateral fronto-temporal seizures despite ASDs**. She was **started on prednisone** 60mg PO on HD#5 which was increased to 100mg PO on HD#6. Seizures stopped on HD#7. There was concern for possible hashimoto's since her TPO was elevated. Neuroimmunology was contacted to weigh in on her case. She was treated with **3 days of 1g IV solumedrol** given that she was already on steroids for 2 weeks prior. She was discharged on prednisone 60mg qday and cellcept titration up to a goal of 1000mg BID with follow-up in OHSU neuroimmunology clinic.
- She suffered **recurrence of her limbic encephalitis 2 months after hospital discharge (confusion, disinhibition, auditory visual hallucinations, complex partial seizures on EEG) in the setting of tapering Prednisone** to 40mg (tapered by 10mg every 2 weeks) **and also tapering Vimpat** to 100mg BID (Keppra level came back at 4). She received 5 days of methylprednisolone 1g IV and prednisone was increased back to 60mg daily…

Case Wrap-up

Summary: Definitions / Concepts

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Steriade, C. *et al.* Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: Conceptual definitions. *Epilepsia* **61**, 1341–1351 (2020).

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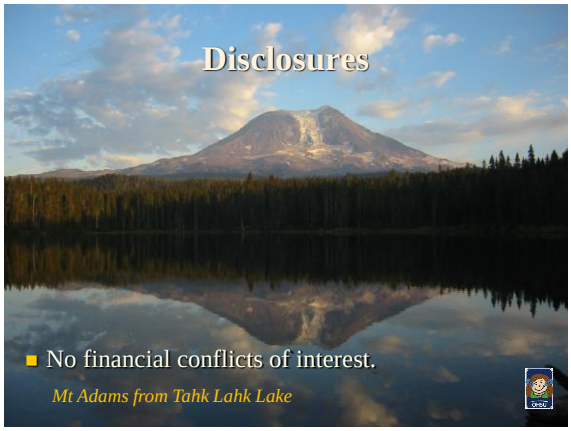
- Mayo Clinic autoimmune encephalopathy testing: https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/92116
- UCSF mNGS testing: https://nextgendiagnostics.ucsf.edu/providers/



Why not "Transverse Myelitis"?

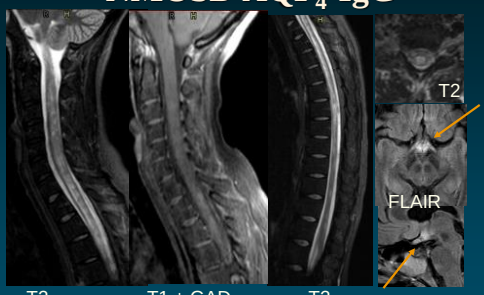
- Many times it is not "transverse" clinically or radiographically on MRI
  - "partial transverse myelitis"
- Many times it is not an inflammatory "-itis"
  - The differential diagnosis is broad
    - Autoimmune/Inflammatory
    - Infectious
    - Neoplastic
    - Metabolic/Genetic
    - Vascular
    - Hydrodynamic
    - Complications

Autoimmune/Inflammatory causes of LETM

- Neuromyelitis optica (NMOSD, AQP_4-IgG)
- Myelin Oligodendrocyte Glycoprotein IgG (MOG-IgG)
- Autoimmune GFAP Astrocytopathy (GFAP-IgG)
- Multiple Sclerosis (confluent)
- Acute Disseminated Encephalo-Myelitis
- Neuro-Behçets
- NeuroSarcoidosis
- Systemic Lupus Erythematosus (SLE)
- Sjögren's Syndrome
- Antiphospholipid Syndrome

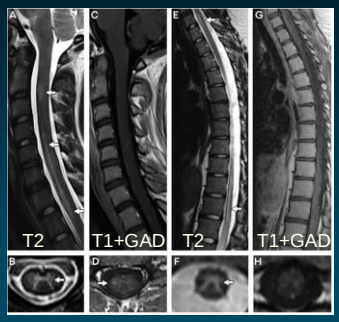
} ?AQP_4-IgG

NMOSD AQP_4-IgG



KEY: Optic nerve/chiasm/3rdV Minimal WM lesions

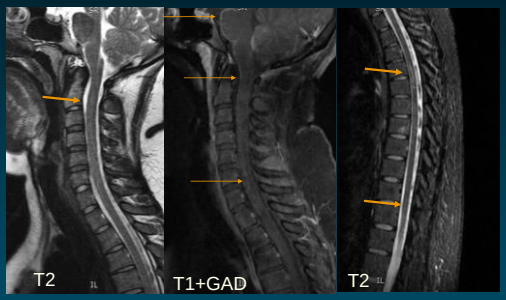
MOG-IgG



KEY: Involvement of only the cord grey matter and minimal to no enhancement

Lopez Chiriboga, Flanagan, Myelitis…, CONTINUUM 2021

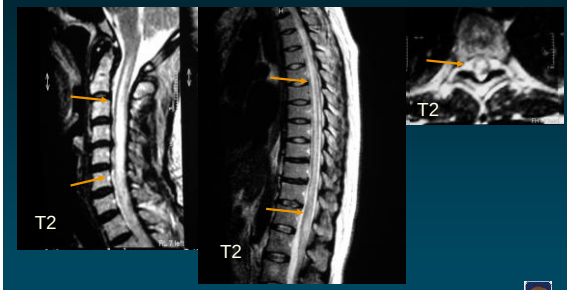
GFAP-IgG Astrocytopathy



KEY: Thin Leptomeningeal enhancement

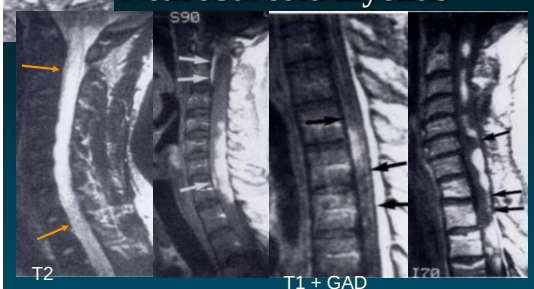
Case. Courtesy of Lindsey Wooliscroft, MD

Lupus myelitis



KEY: History and laboratory analysis +/- AQP_4 –IgG+

NeuroSarcoid myelitis



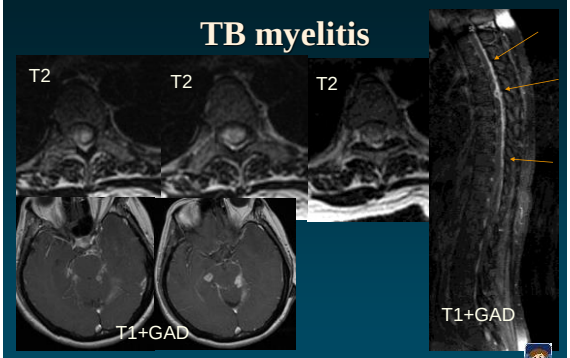
KEY: Thick nodular leptomeningeal enhancement

Nesbit GM et al, Spinal Cord Sarcoidosis…, Radiology, 1989

Infectious causes of LETM

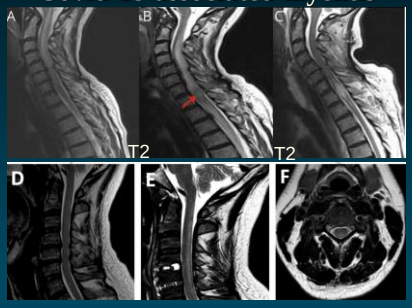
- Parainfectious
- EBV,CMV,HSV,VSV,mycopl.,Hep,Lyme, Covid-19?
- Syphilis, HIV
- Brainstem/diencephalon involvement
- Tuberculosis
- Nodular leptomeningeal and peripheral lesions
- Schistosomiasis,*Toxacara canis*, *Ascaris suum*
- Leptomeningeal enhancement Brain involvement

TB myelitis



KEY: Thick nodular leptomeningeal enhancement

Covid-19 associated myelitis



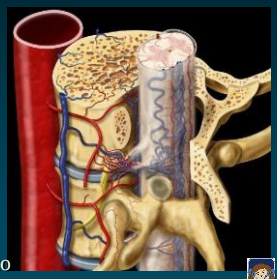
Kim, Abdullayev, Neuneier, et al Neurological Research and Practice, 2021
Sotoca , Rodríguez-Álvarez Neurol Neuroimunol Neuroinflamm, 2020

Vascular causes of LETM

- Arteriovenous Fistula/Malformations
  - Type I: Dural Arterio-Venous Fistula (surface)
  - Type IV: Intradural Perimedullary AVF (surface)
  - Type II/III: Intramedullary/Juvenile-type AVM (cord)
  - Dilated vessels (flow voids or enhancing)
- Spinal Cord Infarct
  - Thoraco-Lumbar Surgery/aortic disease
  - Fibro-cartilagenous embolus – minor trauma
  - Surfer's myelopathy
  - Transforaminal epidural steroid injection

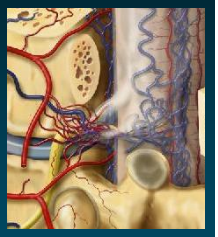
Spinal Dural Arteriovenous Fistula (Type 1 DAVF)

- Spinal arteriovenous fistula within dura, with intra-dural distended draining veins
- Lesions are acquired AVFs, not true AVMs
- Supplied by small dural arteries and no intervening nidus
- Fistula drains directly into radiculo-medullary vein



Spinal Dural Arteriovenous Fistula
Etiology

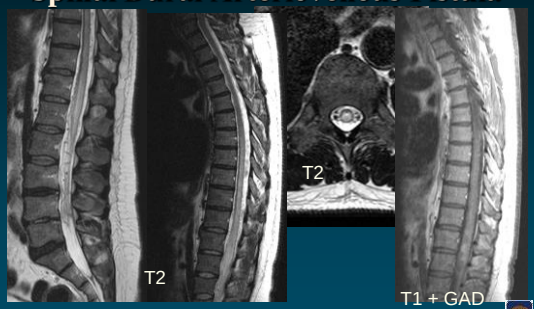
- Venous drainage from the DAVF results in venous hypertension in spinal cord veins
- Venous hypertension increases interstitial water (edema) ultimately causing reduced tissue perfusion & cord ischemia
- Thought to be due to thrombosis of extra-dural venous system, or from minor trauma



Spinal Dural Arteriovenous Fistula
Clinical Features

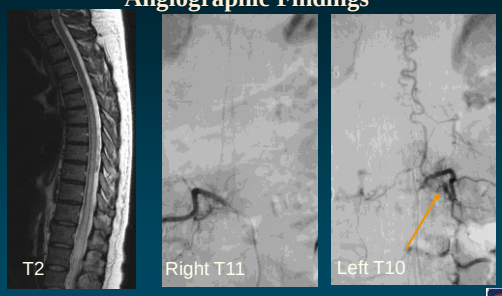
- Subacute necrotizing myelopathy
  - Gradual onset, progressive myelopathy and back pain
  - Time from symptom onset to diagnosis often delayed
  - Slowly progressive clinical course
  - Rarely presents with subarachnoid/cord hemorrhage or acute myelopathy, probably due to progressive thrombosis
- Usually male, > 50y.o.
- No correlation between location of AV shunt, clinical level of spinal dysfunction, or location of cord edema
- From the skull base to the sacrum

Spinal Dural Arteriovenous Fistula



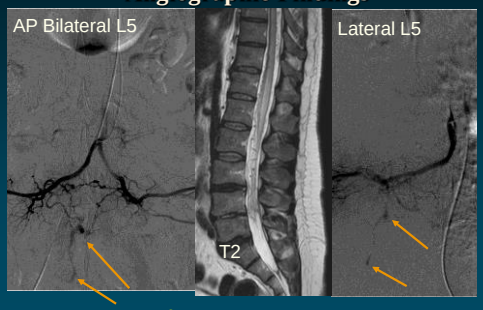
KEY: enlarged tortuous vessel flow voids/enhancement

Spinal Dural Arteriovenous Fistula
Angiographic Findings



KEY: ASA normal, delayed/absent venous phase

Spinal Dural Arteriovenous Fistula
Angiographic Findings



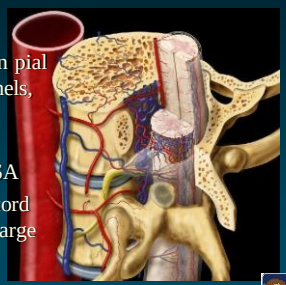
KEY: must evaluate from skull base to sacrum

Spinal Dural Arteriovenous Fistula
Treatment results

- 40-60% improve following obliteration of fistula, treatment earlier in the course results in more improvement
- Significant bowel/bladder dysfunction & impotence rarely improve, even after successful obliteration of fistula
- T2 cord edema decreases over 1-4 months following successful embolization
- Improved cord appearance on MR following treatment does not necessarily correlate with improved symptoms

Perimedullary AV Fistula
(Type IV Pial AVM)

- Congenital direct communication between pial arterial & venous channels, without intervening capillary bed
- Supplied by ASA or PSA
- Venous hypertension, cord edema and sometimes large varix

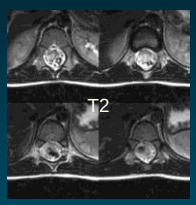


Perimedullary AV Fistula
Clinical Features

- Two clinical courses
  - Gradual progressive conus/cauda equina syndrome very similar to Dural AVF due to venous hypertension
  - More rapid or acute course from cord compression from venous varices, SAH
- Presents younger childhood to young adult
- Associated with Hereditary Hemorrhagic Telangiectasia, RASA1, syndromes

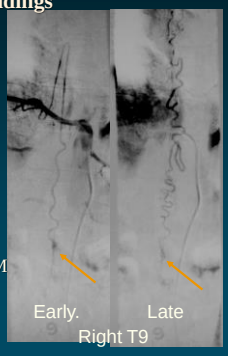
Perimedullary AV Fistula
Imaging Findings

- Can look identical to DAVF in MRI +/- gadolinium
- Enlarged draining veins on dorsal or ventral surface of cord
- Can have larger varices and flow voids may distort/displace cord
- Hyperintense T2 cord: LETM
- Enhancing pial vessels, +/- patchy enhancement within cord



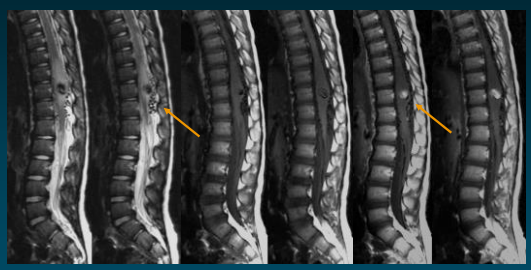
Perimedullary AV Fistula
Angiographic Findings

- Supply will be from ASA and PSA
- Fistula connects directly with spinal vein/varix (no nidus)
- Venous drainage variable
  - May be extensive and look like DAVF
  - May be tortuous and variceal and look like a Juvenile complex AVM



Perimedullary AV Fistula

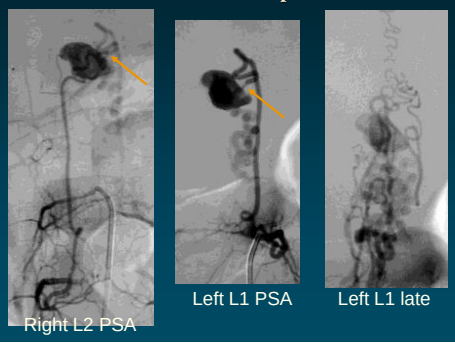
5 y.o. Progressive myelopathy HHT



T2 T1 T1 + GAD

Perimedullary AV Fistula

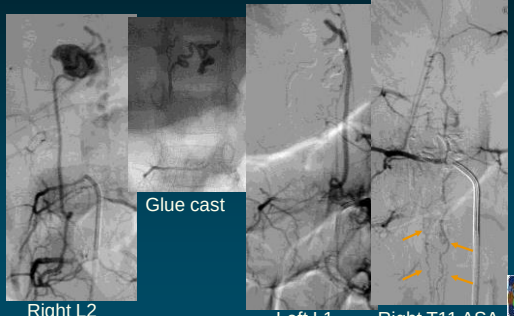
More complex



Right L2 PSA Left L1 PSA Left L1 late

Perimedullary AV Fistula

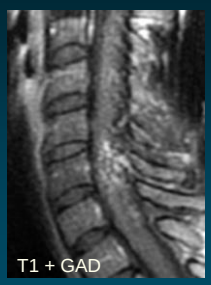
Treatment

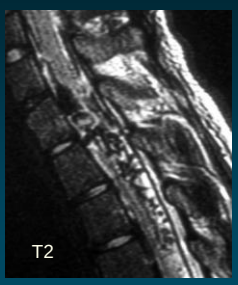


Right L2 Left L1 Right T11 ASA

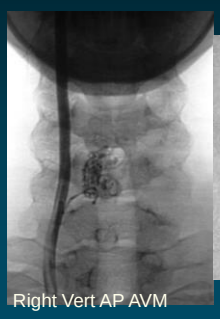
Intramedullary/Juvenile Complex AVM
Intramedullary vessels and beyond

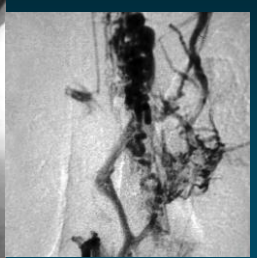

Intramedullary AVM/Juvenile Complex AVM
Imaging findings


T1 + GAD

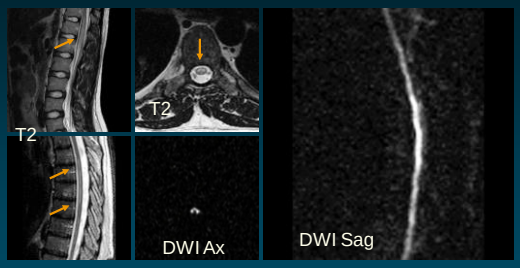

T2

Intramedullary AVM/Juvenile Complex AVM
Angiographic findings


Right Vert AP AVM

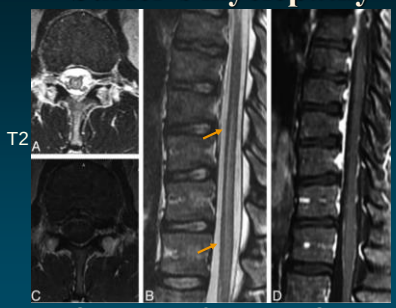

Left Vert Lat JC AVM

Spinal cord infarct



KEY: Acute symptom onset, ask for a DWI of the spinal cord

Surfer's myelopathy

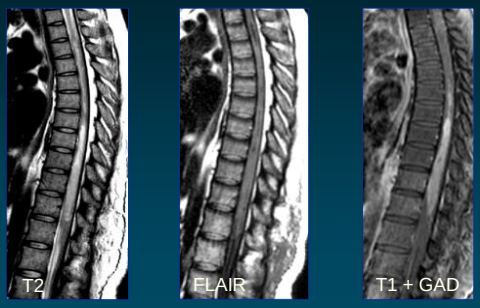


Nakamoto ,et al AJNR Am J Neuroradiol. 2013 Dec; 34(12): 2393–2398.

Neoplastic causes of LETM

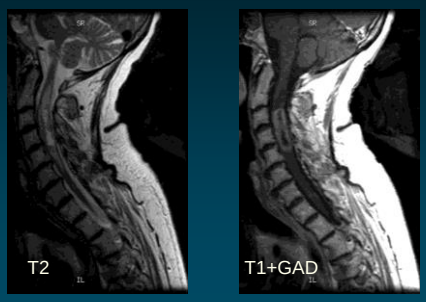
- Paraneoplastic
  - CRMP-5, anti-Neuronal, amphiphysin antibodies
  - Symmetric Lateral Column involvement
- Intramedullary primary tumor
  - Astrocytoma, ependymoma, Lymphoma
- Intramedullary metastasis
- The MRI is much more impressive than the symptoms, unlike in inflammatory/autoimmune

Ependymoma



KEY: Minimal LE symptoms

Small cell CA mets

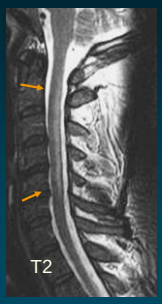


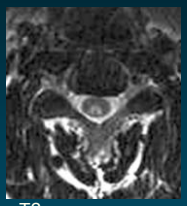
Metabolic/Toxic causes of LETM

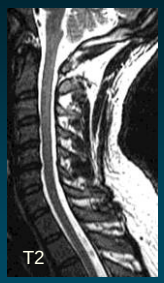
- Cyanocobalamin (B12) deficiency
- Copper (Wilson's)
- Vitamin E deficiency
- Cerebral folate deficiency
- Biotinidase (B7) deficiency
- Mitochondrial encephalomyelopathy
- Intrathecal Methotrexate
- Heroine

} Dorsal columns

B 12 deficiency

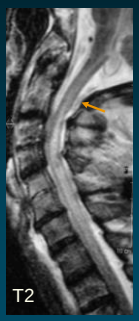


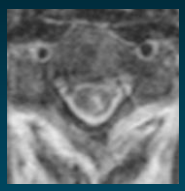




KEY: exclusive involvement of dorsal columns

Intrathecal MTX given at C1-2



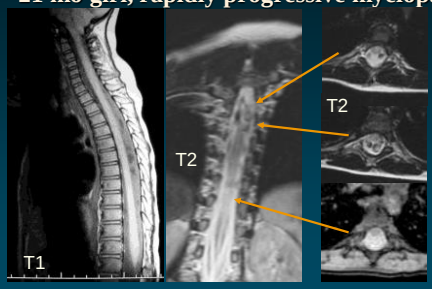


Hydrodynamic causes of LETM

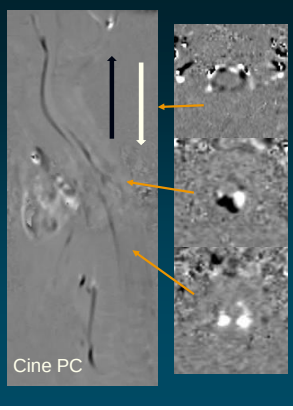
- Arachnoid web: Disturbed pulsation artifacts (DPA)
- Arachnoid cyst: DPA and "mass effect" upon the spinal cord
- Arachnoiditis: DPA and history of surgery, meningitis, IT chemo, may just see obliteration the CSF w/o compression
- Spinal cord herniation: Extension of spinal cord through a dural defect
- Spondylotic Myelopathy: Spinal canal stenosis with a focal area of enhancement

Arachnoid Web

21 mo girl, rapidly progressive myelopathy



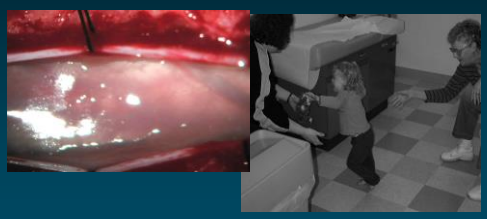
KEY: Abnormal pulsation artifacts in the spinal CSF



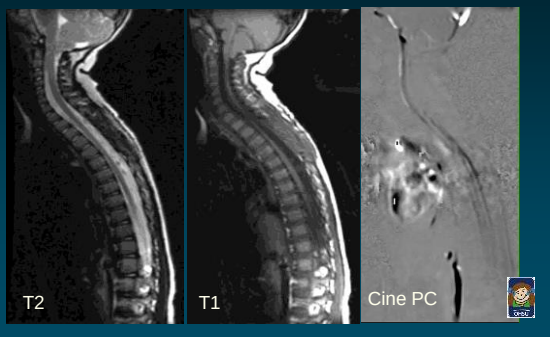
- Cine phase contrast CSF Flow analysis
- Caudal: White
- Cranial: Black

Kizziar R, **Nesbit GM**. The Quantitative Evaluation of Cerebral Spinal Fluid Flow. Seminars in Ultrasound, CT, and MRI. 21(6):452-461, Dec 2000.

Laminectomy T3-T6, lysis of arachnoid adhesions

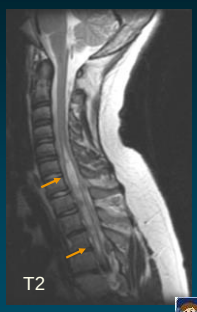


Follow up spine MRI

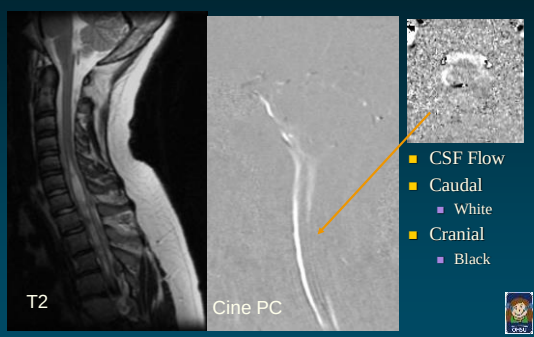


Chiari 0 Malformation

- Idiopathic cervical syringomyelia
  - No tonsillar ectopia
  - CSF Flow anomaly at the foramen magnum or elsewhere in C spine
- Pre-syrinx state
  - The cord signal may not be cystic and may look like LETM

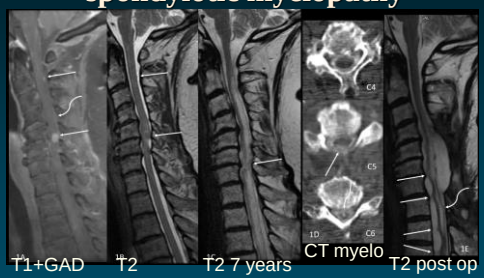


Chiari 0 Malformation



- CSF Flow
- Caudal
  - White
- Cranial
  - Black

Adhesive Arachnoiditis & possible spondylotic myelopathy



KEY: Modest stenosis, history of spinal surgery and meningitis, obliteration of CSF space, focal enhancement

Clark, et al Cervical Adhesive arachnoiditis: a case report, M S Relat Disord, 2020

Imaging Myelopathy

- Acute onset: Get Spine MRI +/- Gad and DWI
- Subacute onset: Get Brain and Spine MRI +/-
  - NMOSD: Optic chiasm, 3rdV, minimal WM hits
  - MOG-IgG: Cord Grey matter, min enhancement
  - GFAP-IgG: Thin leptomeningeal enhancement
  - Sarcoid/TB: Thick nodular enhancement
  - DAVF/Pial AVM: Abnormal spinal vessels
  - B_{12}, CU, Vit D: Dorsal columns
- If history, imaging, lab, path, etc fails…
  - Consider hydrodynamic: Cine CSF flow analysis or myelography

Myelitis and Other Autoimmune Myelopathies
Sebastian Lopez Chiriboga, MD; Eoin P. Flanagan, MBBCh
CONTINUUM 2021;27: 62–92.

nesbitg@ohsu.edu

Three Fingered Jack from Lake Duffy

Stimulating Remyelination for the Treatment of MS

Dennis Bourdette, MD, FAAN, FANA
OHSU Department of Neurology

Closing Remarks

Vijayshree Yadav, MD, MCR, FAAN, FANA
OHSU Department of Neurology