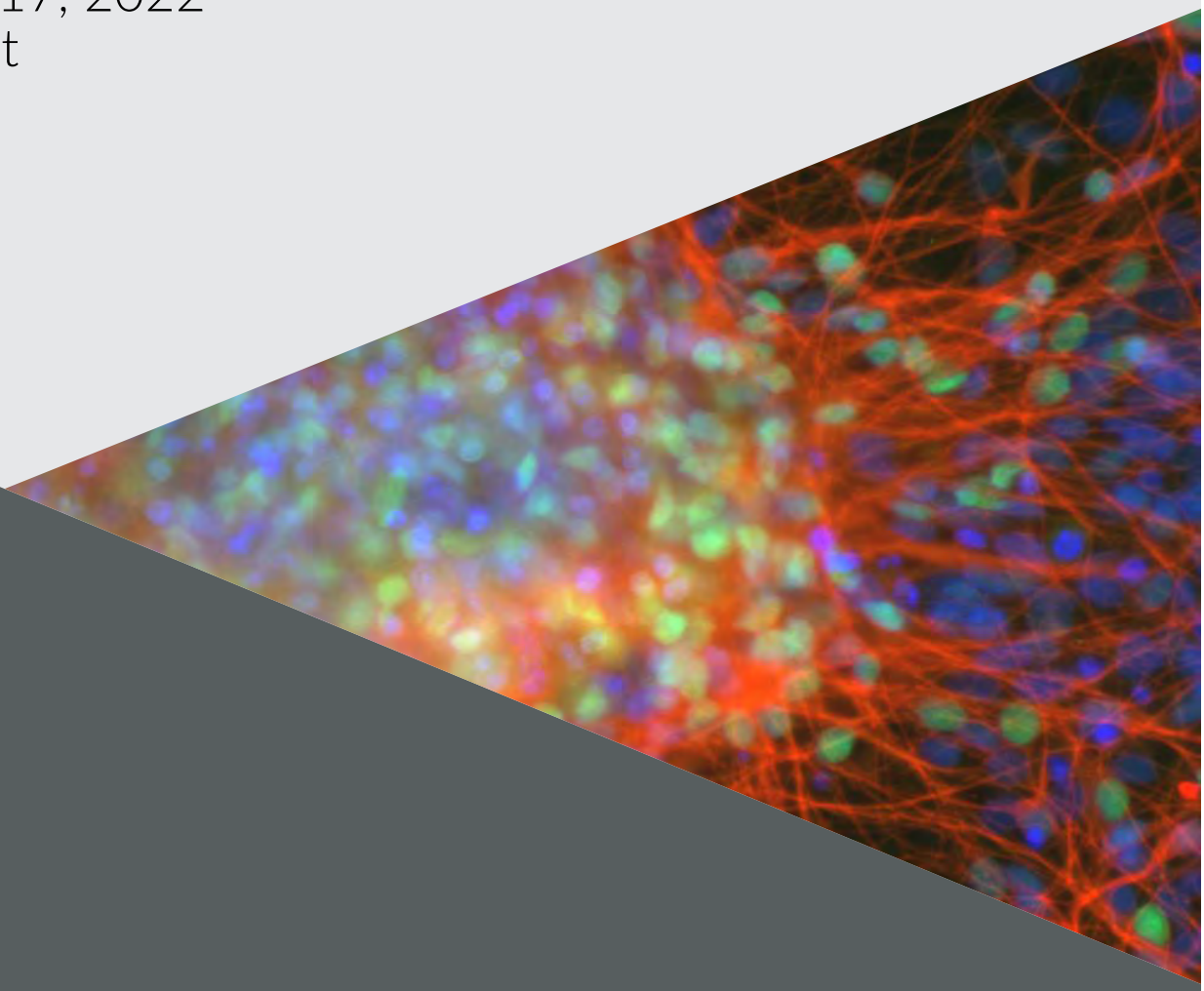
MULITPLE SCLEROSIS CENTER

5TH ANNUAL

MS and CNS Neuroimmunology Symposium: Advances and Updates

September 17, 2022
virtual event



Oregon Health & Science University
Multiple Sclerosis Center
Portland, OR

www.ohsu.edu/ms

OHSU

TABLE OF CONTENTS

AGENDA

8:30 a.m.	**Opening remarks** Vijayshree Yadav, MD, MCR, FANA, FAAN *Department of Neurology, OHSU and VA Portland Health Care System*
8:45 a.m.	**COVID-19 and the Care of People with MS and Related Diseases** Anne H. Cross, MD *Neuroimmunology Section, Dept. of Neurology, Washington University School of Medicine*
9:35 a.m.	**Treatment Updates in Multiple Sclerosis** Lindsey Wooliscroft, MD, MSc *Department of Neurology, OHSU and VA Portland Health Care System*
10:25 a.m.	**Break/Exhibit Hall** (20 minutes)
10:45 a.m.	**Autoimmune Neurology: Clinical and Diagnostic Update** Divyanshu Dubey, MD *Dept. of Neurology and Laboratory Medicine & Pathology, Mayo Clinic*
11:35 a.m.	**Pediatric MOG Antibody Disease: Case-Based Presentation** Kayla Martin, MD *Department of Neurology, OHSU and VA Portland Health Care System*
12:25 p.m.	**Lunch break/Exhibit Hall** (40 minutes)
1:05 p.m.	**CNS Vasculitis: Case-Based Presentation** Vicky Chen, MD *Department of Neurology, OHSU and VA Portland Health Care System*
1:55 p.m.	**Closing remarks** Vijayshree Yadav, MD, MCR, FANA, FAAN *Department of Neurology, OHSU and VA Portland Health Care System*
2:10 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

Vicky Chen, MD	Nothing to disclose
Anne H. Cross, MD	A consultant for Biogen receiving honoraria. On scientific advisory board for EMD Serono, Novartis, and Genentech receiving consulting fees. A consultant for Horizon Therapeutics receiving consulting fees and travel. Consultant for Greenwich Biosciences receiving consulting fees.
Divyanshu Dubey, MD	On scientific advisory board for UCB receiving consulting fees. A consultant for Arialys, Argenx, and Astellas receiving consulting fees.
Kayla Martin, MD	Nothing to disclose
Lindsey Wooliscroft, MD, MSc	Nothing to disclose
Vijayshree Yadav, MD, MCR, FANA, FAAN	Nothing to disclose

ACKNOWLEDGEMENTS

GRANT SUPPORT

Portland VA Health Care System MS Center of Excellence West

EXHIBITORS

Biogen

Bristol Myers Squibb

Genentech

Johnson & Johnson/Janssen

Novartis

CREDIT STATEMENT

Accreditation

OHSU 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 4.25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

SPEAKER BIOGRAPHIES

Vicky Chen, MD, is a second year Neuroimmunology and Multiple Sclerosis Fellow at Oregon Health & Science University (OHSU) and the Portland VA Medical Center. She grew up in the San Francisco Bay Area and attended Tufts University School of Medicine in Boston. She moved to the Pacific Northwest to complete her neurology residency at OHSU where she discovered her passion for the field of neuroimmunology and multiple sclerosis. She is excited about caring for those with neuroimmunologic conditions and multiple sclerosis because the field is rapidly growing with new and highly effective immunotherapies. Her research focus is on the symptoms of multiple sclerosis such as gait impairment and fatigue. She is currently the PI for a study to validate a self-reported gait index that can be used by clinicians and physical therapists providing care remotely to people with MS with gait impairment.

Dr. Anne H. Cross, MD, is a professor of Neurology at Washington University in St. Louis, where she is Head of the Neuroimmunology/ Multiple Sclerosis Section in the Neurology Department since 2001. She holds the Manny & Rosalyn Rosenthal – Dr. John L. Trotter MS Center Chair in Neuroimmunology. Dr. Cross was raised in Alabama and attended the University of Alabama School of Medicine. After training in adult neurology at the George Washington University in Washington DC, she did fellowship training in neuroimmunology at the National Institute of Health with Drs. Dale McFarlin and Henry McFarland and subsequently did a fellowship in neuropathology at Albert Einstein College of Medicine with Dr. Cedric Raine. She received the Harry Weaver Neuroscience Scholar award of the National Multiple Sclerosis Society in 1990. Dr. Cross joined the Washington University Department of Neurology in 1991. Her research has received funding by the National MS Society USA, the NIH and the US Department of Defense. In 2002, she began one of the first studies of B cell depletion in MS patients, in an “add-on” study of rituximab in 30 MS patients funded by the National MS Society. In 2019, she received the John Jay Dystel Prize of the National MS Society and the American Academy of Neurology. Together with several colleagues from around North America, she helped to initiate the COViMS Registry for North American MS patients who got COVID-19, to help understand the impacts of the disease and drugs used to treat it on COVID-19 outcomes.

Divyanshu Dubey, MD, is an Associate Professor of Neurology and Laboratory Medicine & Pathology at Mayo Clinic, Rochester, MN. His research focus is central and peripheral autoimmune neurological conditions. This includes search for novel biomarkers and analysis of

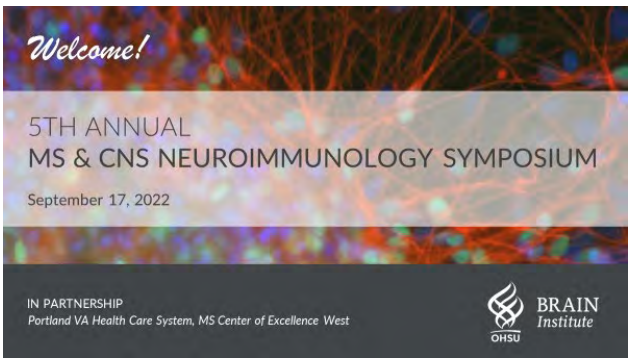
clinical and radiological features of autoimmune neurological disorders. He has played a crucial role in the discovery of multiple neural specific antibody biomarkers of autoimmune neurological disorders including KLHL11 IgG, LUZP4 IgG and Cavin-4 IgG. He has authored more than 120 peer reviewed articles in various high impact factor journals such as NEJM, JAMA Neurology, Brain, Annals of Neurology and Neurology. He has been an invited speaker at multiple national and international conferences.

Kayla Martin, MD, is a second year clinical and research fellow at Oregon Health & Science University (OHSU) and VA Portland Medical Center in Portland, OR. She completed her residency at the University of Michigan in Ann Arbor, MI and her medical degree from Wayne State University in Detroit, MI. She is pursuing a graduate certificate in Human Investigations through the Oregon Clinical and Translational Research Institute. She is applying these skills in developing the center's first comprehensive clinical database on the population of patients with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) at OHSU. She will utilize this to identify factors that may be associated with relapsing disease and evaluate the efficacies of commonly used immunotherapies to prevent relapses. She was awarded the Tartar Trust Fellowship for her work on this project. After she completes her fellowship, she plans to stay in academia with a position that includes clinical practice focused on multiple sclerosis and other neuroimmunological conditions, clinical research, and teaching.

Lindsey Wooliscroft, MD, MS, is an Assistant Professor of Neurology at Oregon Health & Science University (OHSU) and Associate Director of Research for the VA Multiple Sclerosis (MS) Center of Excellence-West. She received her medical degree from Texas Tech University HSC in Lubbock, TX. She completed her neurology residency at Washington University in St. Louis and her fellowship in Neuroimmunology at OHSU and the Portland VA. She receives research funding from the NIH NCMRR, VA, EMD Serono, Myelin Repair Foundation, Oregon Medical Research Foundation, and OHSU Foundation and her research interests include rehabilitative approaches to myelin repair in people with MS.

Vijayshree Yadav, MD, MCR, FANA, FAAN, is Professor of Neurology with endowed Professorship in MS Wellness Research from Tykeson Foundation and serves as the Director of the MS Center at Oregon Health & Science University (OHSU). She is a board-certified neurologist who is fellowship trained in MS and Neuro-immunology and honored with a Masters degree in Clinical Research. She also serves as a Staff Neurologist and a Merit-Awarded Researcher at the Portland VA Medical Center (PVAMC) and has been the MS and Neuroimmunology Fellowship Director at OHSU and PVAMC since 2017. Her research

interests include improving health in people with MS using complementary therapies such as dietary modification and supplements and she has pioneered MS research evaluating effects of diet intervention and antioxidants such as lipoic acid and MitoQ. Her current research has been funded by the Department of Veterans Affairs, National Institute of Health, National MS Society, Tykeson Foundation and OHSU Foundation. Dr Yadav is well-published and regular presenter at local and national meetings.



Acknowledgment

Grant support

Portland VA Health Care System, MSCoE West
Anonymous philanthropy through OHSU foundation

Exhibits

Biogen
Bristol Myers Squibb
Genentech
Johnson & Johnson/Janssen
Novartis

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2:10 p.m. Adjourn

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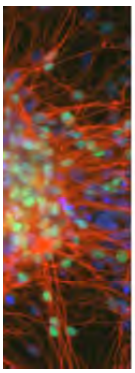


OHSU MS Center

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 The Consortium of Multiple Sclerosis Centers

RACE TO ERASE MS — *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*

MS Center for Comprehensive MS Care

OHSU

OHSU MS Center Faculty

MS/Neuroimmunology Fellows

Training the next generation of MS clinical scientists

Incoming fellows 2022-2023:

Cole Crowson, MD; William "Bill" Chapman, DO, PharmD; Carolina Garcia, DO

OHSU

MS Center Education

Provider Education

- MS and Neuroimmunology Fellowship Training Program - Training 3-5 Neurologists each year to specialize in MS and Neuroimmunology.
  - ACTRIMS Didactic Webinar Series - National education for fellowship trainees since September 2020.
- MS & CNS Neuroimmunology Symposium -Annual Symposium for healthcare professionals.

Patient Education

- At the Frontier & Beyond - Annual MS Center conference
- COVID-19 education - MS specific COVID education webinars
  - Latest COVID Update webinar program on 4/22/22 is available on www.ohsu.edu/ms
- Research and annual MS Center newsletters

2021 Neuroimmunology Symposium stats

90% Attendees learned new info or strategies they can apply to their work or practice.

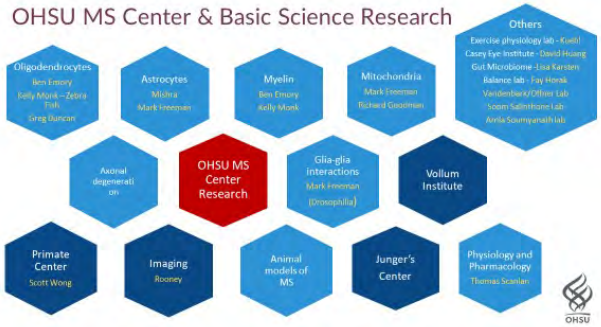
Over 120 views Registered attendees accessed recording

30% Attendees from out of state and/or country

50% Attendees were VA employees across the country

OHSU MS Center Clinical Research

OHSU MS Center & Basic Science Research



"COVID-19 and the Care of People with MS and Related Diseases"

Anne H Cross MD
Professor of Neurology
Washington University in St. Louis

Disclosures

- A. H. Cross has performed paid consulting in past two years for:
- Biogen, Bristol Myers Squibb, EMD Serono/Merck, Genentech/Roche, Horizon, Janssen, Jazz Pharmaceuticals, Novartis, TG Therapeutics

Learning Objectives:

- To be able to discuss how specific Disease-Modifying Therapies DMTs affect the course of COVID-19 in people with MS and related diseases.
- To know how specific DMT for MS may alter responses to vaccinations against COVID-19, and what to do about it

MS & COVID-19

- At the pandemic beginning, the MS community recognized a gap in information on COVID-19 infections in MS patients
- Physician-based registries (COViMS, MUSC, French, Dutch) and patient-based (UK) registries were initiated to gather information
- Eventually, data from these were combined to provide more powerful conclusions.

PubMed search of "COVID + Multiple Sclerosis"
April 10, 2021 found 367 papers
Aug 26, 2022 found 1,032 papers

COViMS Registry *www.COVIMS.org*

- Developed to focus on North America.
- Data entry by health care providers (HCPs)
- Designed to answer **2 key questions**:
  1. **How do MS patients fare with COVID-19?**
  2. **How do individual disease modifying therapies affect outcomes?**
- Began April 1, 2020, Data to be presented as of August 26, 2022

NMO=Neuromyelitis Optica, MOG=Myelin oligodendrocyte

Supported by:
Consortium of MS Centers
MS Society of Canada
National MS Society

Dr. Amber Salter
Assistant Professor of Biostatistics at University of Texas-Southwestern

Leadership Team

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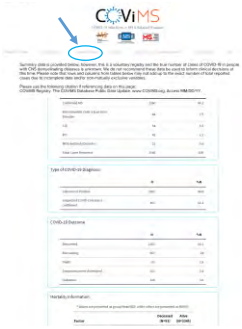
Pam Kanellis, MS Canada



Data Collection

- Healthcare professionals asked to enter patients with confirmed or suspected COVID-19 infection
- Report after a minimum of 7 days and sufficient time had passed to observe the disease course through resolution of acute illness or death
- Summary level information available in real-time www.COViMS.org/currentdata
- Entered into a secure HIPAA compliant REDCap database housed at Washington University in St Louis, as a survey available publically at www.COViMS.org
- Closed for new entries Sept, 2022

Possible Risk Factors

- **Demographics** (sex, race, age, cigarette use)
- **Comorbidities**
  - Cardiovascular disease,
  - Cerebrovascular disease,
  - Chronic kidney disease,
  - Chronic lung disease,
  - Diabetes,
  - Hypertension,
  - Morbid obesity
- **Clinical characteristics**
  - MS clinical course (CIS/RR/SP/PP)
  - Impairment/Disability: Ambulation status
- **Disease modifying therapy use**

Vaccination status (questions added April 27, 2021)

COVID-19 Outcome

- Levels of Clinical Severity:
  - Not hospitalized
  - Hospitalization only
  - Admitted to the Intensive Care Unit (ICU) and/or required ventilation
  - Death

COViMS Registry MS cases as of Aug 26, 2022

n = 8075 total entries (4424 non-missing state/province), 124 deaths (84 non-missing state/province)

U.S. By Census region

1. Northeast 962 (23.4%)
2. South 1484 (36.1%)
3. Midwest 1207 (29.3 %)
4. West 461 (11.2%)

Puerto Rico (n=8)

Canada: 310
Ontario (n=184); Saskatchewan (n=40); Quebec (n=13);
British Columbia (n=3), Alberta (n=4); Nova Scotia (n=6); MB (n=1), NB (n=50)
Mexico: 2

Results

Total Entries as of 08/26/22 (n=8,075)

Female	75.5%
Age	47.5 ± 12.9
Race	
Non-Hispanic White	75.8%
Black or African American	15.4%
Hispanic or Latino	4.6%
Other/Unknown	4.2%
Disease Duration	14.1 ± 9.9
MS Clinical Course	
RRMS/CIS	5283 (79.2%)
Progressive	1390 (20.8%)
Ambulatory Status	
Fully ambulatory	4429 (60.1%)
Walk with Assistance	2392 (32.5%)
Non-ambulatory	544 (7.4%)

Age and Male sex increase risk of COVID severity in People with MS

	Outcome	Odds Ratio	P-Value
For every 10 years of age	Death	**1.803**	<0.0001
For every 10 years of age	Hosp plus **ICU &/or vent**	**1.432**	0.0003
For every 10 years of age	Hospitalization only	1.311	< 0.0001
Male vs Female	**Death**	**1.941**	0.0154
Male vs Female	Hosp plus **ICU &/or vent**	1.199	0.4119

Every 10 years of age increased risk of death by 80.3%
Male gender increases risk of death by 1.94 times

These data were updated on August 26, 2022

Race influence on Risk of COVID severity in People with MS

	Outcome	Odds Ratio	P-Value
Black/AA vs non-Hisp white	Death	1.439	0.28
Black/AA vs non-Hisp white	**Hosp plus ICU &/or vent**	**1.982**	0.005
Black/AA vs non-Hisp white	Hospitalization only	**1.515**	0.005
Hispanic/Latino vs non-Hisp White	Death, Hosp plus ICU &/or vent, Hospitalization only	0.645, 1.582, 1.035	0.58 0.25 0.89

Being Black increases risk of Hosp/ICU/Ventilator by 1.98 times

Data are current as of August 26, 2022

Higher proportions of those with ambulation problems were hospitalized, in ICU &/or vent and died

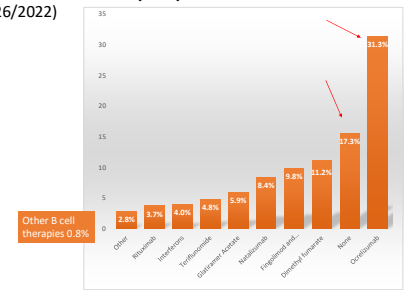
	Not hospitalized	Hospitalized	ICU/Vent	Death
Fully ambulatory	**92.7%**	5.4%	1.6%	0.4%
Walk with Assistance	91.6%	5.9%	1.6%	0.9%
Non-ambulatory	71.5%	15.6%	5.0%	**7.9%**

P < 0.001

These data are current as of August 26, 2022

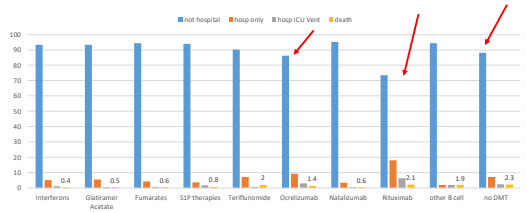
COViMS patient DMT proportion

(accessed 08/26/2022)



COViMS Outcomes based on DMT:

(Proportion of not hospitalized vs. hospitalized only vs. Hosp/ICU/Vent vs. Deaths for each DMT)

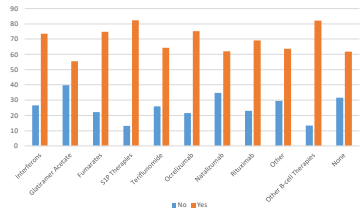


Percent taking each DMT who died is provided atop gold bars

Vaccinated proportions on DMTs for MS

COVID-19 in 2021, between April 27, 2021 and July 15, 2022
(after the question on vaccination was added)

N= 365 – NO Vaccination (24.8%)
N= 1050 – YES Vaccination (70.7%)
N= 66 – Unknown (4.5%)
N = 1481 total



Did COVID vaccination lead to reduced severity?

Current DMT	Vaccination: No (n=365)		Vaccination: Yes (n=1050)	
	Not hosp	Hosp/ICU/Vent or Death	Not hosp	Hosp/ICU/Vent or Death
IFNs	6	3	24	1
Glat A	30	3 (9%)	46	0 (0%)
Fumarates	21	1 (4.5%)	70	4 (5.4%)
S1P Therapies	19	1 (5%)	120	6 (4.8%)
Teriflunomide	19	2	48	4
Ocrelizumab	105 (85%)	19 (15%)	366 (85%)	65 (15%)
Natalizumab	40	2 (4.8%)	74	1 (1.3%)
Rituximab	4	5	23	4
Other B-cell depleters	6	0	35	2
No DMT	58	8 (12.1%)	119	10 (7.8%)

12 Deaths in Vaccinated MS patients as of Aug 26, 2022 – COViMS Registry

Sex	Age range	race	ethnicity	vaccine	Time vaccine to COVID	DMT	Comorbidities
Female	65-70	B	Non-Hispanic	Moderna	<2weeks	Teriflunomide	yes
Female	50-55	W	Hispanic	Pfizer	2wk -6 mo	Ublituximab	no
Female	30-35	B	Non-Hispanic	Pfizer	<2weeks	Ocrelizumab	no
Female	55-60	W	Non-Hispanic	Pfizer	unknown	Siponimod	yes
Male	55-60	W	Non-Hispanic	Pfizer	2wk -6 mo	Ocrelizumab	yes
Female	55-60	W	Non-Hispanic	Pfizer	2wk -6 mo	Fingolimod	yes
Female	60-65	W	Non-Hispanic	J&J	2wk –6 mo	Ocrelizumab	yes
Male	60-65	W	Non-Hispanic	Pfizer	2wk -6 mo	Ocrelizumab	yes
Female	60-65	W	Non-Hispanic	J&J	2wk -6 mo	Ocrelizumab	yes
Female	30-35	B	Non-Hispanic	Pfizer	>6 mo	Ocrelizumab	yes
Male	55-60	W	Non- Hispanic	J&J	>6 mo	Ocrelizumab	yes
Female	55-60	W	Non-Hispanic	Moderna	>6 Mo	Ocrelizumab	yes

All deaths from United States
Comorbidities: hypertension, morbid obesity, chronic kidney disease, chronic neurological disease

COVID outcomes not worse in pregnant or postpartum MS patients:

Outcomes in Women with MS who were pregnant/postpartum compared to Propensity Score Matched cohort	Pregnant/ Postpartum* (N=31)	Comparator Cohort (N=62)	p-value
Symptoms: Fever	14(45.2)	20(32.3)	0.18[b]
Symptoms: Dry cough	13(41.9)	20(32.3)	0.41[b]
Symptoms: Fatigue	11(35.5)	28(45.2)	0.34[b]
Symptoms: Pain (joint, bone, muscle)	10(32.3)	16(25.8)	0.58[b]
Symptoms: Shortness of breath	7(22.6)	15(24.2)	0.99[b]
Symptoms: Ageusia (loss of taste)	8(25.8)	20(32.3)	0.58[b]
Symptoms: Anosmia (loss of smell)	12(38.7)	23(37.1)	0.99[b]
Pneumonia	1(3.2)	1(1.6)	
Clinical Severity Outcome			0.99[a]
Not hospitalized	29(93.5)	58(93.5)	
Hospitalization only	1(3.2)	2(3.2)	
Hospitalization and/or ICU/Ventilation	1(3.2)	1(1.6)	
Death	0(0.0)	1(1.6)	
Clinical Severity Outcome (Dichotomized)			0.99[b]
Not hospitalized	29(93.5)	58(93.5)	
Hospitalization, ICU/Ventilation and/or Death	2(6.5)	4(6.5)	

*Five pregnant/postpartum cases could not be propensity score matched. Values presented as N (column %). p-values: a=Wilcoxon sign rank test, b=McNemar's test. Salter A, Cross AH, Cutter GR et al. Mult Scler Relat Disord. 2022 Jul 5;65:104028

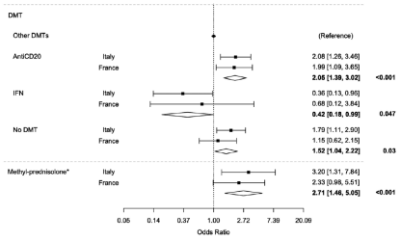
Information from other Databases

Italian MS Registry early report (n=844)

- Retrospective, suspected or confirmed COVID-19
- **Anti-CD20 associated with severe course** (OR 2.37, p=0.015)
- **Recent use of methylprednisolone associated with worse outcome** (OR 5.2, p=0.001)

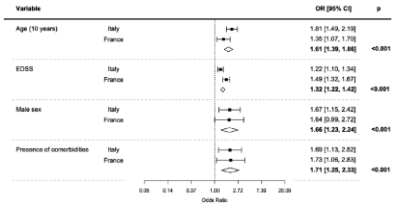
Sormani MP et al Ann Neurol 2021;89:780–789

DMTs and COVID-19 Severity in MS. Pooled analysis from Italy and France



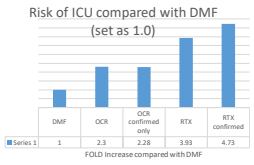
Sormani MP, Salvetti M, et al Ann Clin Transl Neurol 2021; 8:1738-1744.

COVID-19 Severity in MS. Pooled analysis from Italy and France



Sormani MP, Salvetti M, et al Ann Clin Transl Neurol 2021; 8:1738-1744.

International group (combining registries)



- 2,340* patients, of whom 1,683(71.9%) had confirmed COVID-19.
- 20.9% hospitalized, 5.4% admitted to ICU, 4.1% required artificial ventilation, and 3.2% died.
- No DMTs showed statistically significant associations with death

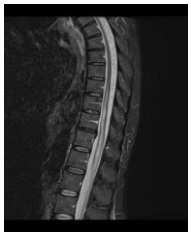
Simpson-Yap S, De Brouwer E. et al. Neurology. 2021 Nov 9; 97(19):e1870-e1885.
*1,161 (49.6%) of the subjects derived from COViMS Registry

International cross-sectional registry study (2020–2022) of 5,568 MS patients with COVID-19 *did not* confirm lower COVID-19 severity for Interferon-β treatment

- No evidence for difference in COVID-19 severity for those on interferon-β compared to pooled other DMTs with ***B-cell depleting agents excluded***.
- Interferon-β-treated patients had lower risks of hospitalizations, ICU admission/requiring artificial ventilation, and death rates compared to *untreated MS patients*.

Simpson-Yap S et al. Multiple Sclerosis and Related Disorders 66 (2022) 104072

COVID-19 and Neuromyelitis Optica Spectrum Disease (NMOSD)



Newsome SD, Cross AH et al. COVID-19 in Patients With Neuromyelitis Optica Spectrum Disorders and Myelin Oligodendrocyte Glycoprotein Antibody Disease in North America. Neurol Neuroimmunol Neuroinflamm. 2021 Aug 24;8:e1057

Neuromyelitis Optica Spectrum Disease (NMOSD) in COViMS

- 103 NMOSD patients reported in the COViMS Registry (63.6% were anti-AQP4 IgG+)
- Most NMOSD patients were taking rituximab at time of COVID-19.

- 38.8% hospitalized
- 8.7% were admitted to the ICU and/or ventilated
- 10.7% died.

Data collection April 1, 2020 though April 8, 2022
Newsome SD, Cross AH et al. COVID-19 in Patients With Neuromyelitis Optica Spectrum Disorders and Myelin Oligodendrocyte Glycoprotein Antibody Disease in North America. Neurol Neuroimmunol Neuroinflamm. 2021 Aug 24;8:e1057

Myelin Oligodendrocyte Glycoprotein Antibody Disorder

- 25 MOGAD patients reported in the COViMS Registry.
- 24/25 MOGAD patients were laboratory positive for SARS-CoV-2
- 50% taking rituximab
- 6 were hospitalized and one of these died
- No factors were different between those not hospitalized versus those hospitalized, admitted to the ICU, or ventilated (small number).

Data as of April 8, 2022

11 Deaths among 103 NMO (10.7%) and 1 death among 25 MOGAD (4%) patients as of April 7, 2022 – COViMS Registry*

Sex	Age range	race	Year of COVID	DMT	Vaccinated?	Ambulatory?	Comorbidities?
F	71-75	W	2020	None	-	Assist	yes
F	26-30	B	2020	Rituximab	-	Fully	yes
F	51-55	unk	2020	Rituximab	-	Assist	yes
F	36-40	B	2020	Rituximab + Leflunomide, Prednisone	-	Non-amb	yes
F	26-30	B	2020	Rituximab	-	Fully	yes
M	76-80	W	2020	Rituximab	-	Non-amb	yes
F	46-50	W	2021	Rituximab	-	Fully	yes
F	51-55	B	2021	Rituximab	-	Fully	yes
F	56-60	W	2021	Rituximab	No	Fully	yes
F	51-55	W	2021	Rituximab	No	Assist	yes
F	**26-30**	**W**	**2021**	Rituximab	yes	Fully	no
F	66-70 **MOGAD**	unk	2022	Rituximab + steroids in prior month	**Yes**	Assist	yes

*Limitations of registry data appl

Comorbidities: hypertension, morbid obesity, chronic kidney disease

Limitations of Registry data

- Registry – Patients voluntarily submitted - Ascertainment bias
- No denominators
- Behavior of the populations uncontrolled for
- Behavior of population different over time and geography
- Alterations in treatments of COVID-19 as the pandemic has proceeded
- Virus variations over time

Does COVID-19 alter the course of MS?

- NYC study of **474 early cases** (2/2020→12/2020), 49 patients (10.3%) had pseudo-exacerbation of existing neuro symptoms. Two (0.4%) developed true disease activity with new-onset sensory myelitis 1 & 3 weeks post-resolution of mild COVID-19.[1]
- **One case** from Vienna, Austria of RRMS exacerbation 2 weeks after mild COVID-19. MRI revealed an enhancing lesion over two segments in the thoracic spine. [2]
- **Meta-analysis of 26 studies** of Neurological Illnesses and COVID 19. 13 MS patients reported: 0/13 worsening, No exacerbations.[3]
- Iranian **retrospective cohort study of 56 RRMS patients** with COVID and 69 non-COVID-19 RRMS (approximately) matched to those with COVID showed no excess relapses (lower ARR in COVID patients, but the COVID+ tended to be on stronger DMTs). No signif. ARR difference comparing prior 6 mons pre-COVID to 6 mon after COVID in the 56 RRMS pts.[4]

1. Klineova S et al. MSARD https://doi.org/10.1016/j.msard.2021.103153;
2. Finsterer J. . Clin Neurol Neurosurg. 2022 Apr;215:107210. doi: 10.1016/j.clineuro.2022.107210
3. Kubota T and Kuroda N. Clin Neurol Neurosurg. https://doi.org/10.1016/j.clineuro.2020.106349.
4. Etemadifar M et al. MSARD 2021

Does COVID-19 alter the course of MS?

- Retrospective, observational study from Czech nationwide registry compared proportion of patients with relapse in the 90 days following infection to the 90-day intervals during the year before. 495 unvaccinated MS patients who had COVID-19 identified **slight increase (~1%) in MS exacerbations** soon after COVID-19. [1]
- **Retrospective analysis of charts of 400 MS patients** in Argentina found 41 patients with COVID-19. 61% (n = 25) reported neurological worsening, 9.7% (n = 4) were relapses. [2]

1. Garjani A. et al. Mult Scler Rel. Disord 2021
2. Michelena G, Casas M, et al. Mult Scler Relat Disord. 2022;57:103368.

Does COVID-19 Vaccination alter or initiate MS?

- 7 cases reported from 3 large New Engl medical centers had worsening of symptoms compatible with exacerbation soon after mRNA vaccinations. Four were known cases of MS with new exacerbations, two were new onset MS, and one was new onset +AQP4 Ab NMOSD. All recovered with steroids. [1]
- Retrospective, observational study from Czech nationwide registry compared proportion of patients with relapse in the 90 days following vaccination to the same 90-day interval the year before. 1661 vaccinated (90.11% BNT162b2) MS patients without history of COVID-19- just vaccination- slight increase (~1%) in MS relapses soon after vaccination. [2]
- mRNA BNT162b2 COVID-19 vaccines did not increase the short-term risk of clinical relapses in a prospective study at 25 Italian MS centers. Compared relapses 2 months prior and 2 months after vaccination. Relapses in 6/324 before and 7/324 after[3]

1. Khayat-Khoei M et al. J Neurol (2022) 269:1093–1106.
2. Stastna D, et al. Mult Scler Relat Disord . 2022;65:104014. doi: 10.1016/j.msard.2022.104014.
3. Di Filippo M, et al. J Neurol Neurosurg Psychiatry. 2022;93

Recent systematic review

- Identified 32 cases reported in literature: 17 after mRNA, 10 after viral vector vaccine, and 5 after inactivated vaccine
- Transverse myelitis (n=12), ADEM (n=5), MS-like (n=12, 6 with prior known MS), NMOSD (n=3, n=2/3 AQP4 Ab +).

Ismail II, Salama S. A systematic review of cases of CNS demyelination following COVID-19 vaccination. J. Neuroimmunol 2022; 362: 577765

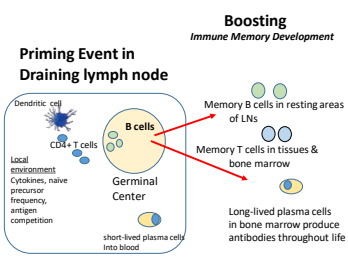
COVID-19 Prevention and Treatment

- Responses to vaccination in people with MS on different DMTs
- Passive vaccination against severe COVID-19 (tixagevimab + cilgavimab) for those who may not respond well to vaccination.
- Treatment of high risk MS outpatients who get COVID-19

Immune Response to Vaccination

- Antigen from vaccine is processed by APCs (newer vaccines involve additional steps)
- APCs migrate to lymphatic tissue where they induce proliferation and differentiation of naïve antigen-specific CD4+ T cells into effector T-helper cells of multiple subtypes
- Interaction with T cells leads to B cell activation
- B cells differentiate into plasma cells, which produces antibodies
- Memory T and B cells reactivate upon booster immunization or encounter with specific pathogen

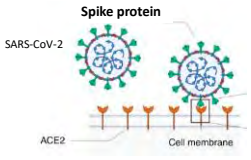
Clem AS. *J Glob Infect Dis.* 2011;3:73-78



Long-term, effective immune response is the goal

COVID-19 Vaccines Authorized for Use in the US

Coronavirus spike protein is the target



Spike proteins are involved in binding to the ACE2 receptor on host cells as the first step in viral invasion

Name (Manufacturer)	Vaccine Profile	Number of Doses (IM)
mRNA-1273 (Moderna)	Nucleoside-modified mRNA; encodes the spike glycoprotein in lipid nanoparticles	2 (28 days apart)
BNT162b2 (Pfizer-BioNTech)[a]		2 (21 days apart)
Ad26.COV2.S (Janssen/ Johnson & Johnson)	Recombinant, replication-defective human adenovirus serotype-26 vector; encodes the stabilized spike protein	1
Novavax[a]	protein subunit	2 (21 days apart)

[a]*Full FDA approval granted August 23, 2021*

SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; ACE2=angiotensin converting enzyme; IM, intramuscular. Kelly H et al. *J Neuroimmunol.* 2021;356:577599; Yoo JH. *J Korean Med Sci.* 2021;36:e54; Figure adapted from Yang J et al. *Nat Commun.* 2020;11:4541, under a Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/).

Novavax® Protein Subunit Vaccine: for 12yr +

- May be more acceptable to some people who declined the mRNA vaccines
- Number of Shots: 2 doses in the primary series, given **3**–8 weeks apart.
- 90.4% effective in preventing PCR-confirmed symptomatic mild, moderate, or severe COVID-19 occurring at least 7 days after Dose 2
- People who are moderately or severely immunocompromised should also receive 2 doses, given 3 weeks apart (a 3rd primary dose is not currently authorized).
- Novavax COVID-19 vaccine is not authorized for use as a booster.

DMT Class	Vaccine Response?	COVID-19 Vaccine Serological Responses in People With MS
Beta interferons	+	Data show normal humoral responses
Glatiramer acetate	+	Data show normal humoral responses
Teriflunomide	+	Data show normal humoral response; all pwMS had full responses in Italian and UK studies
Fumarates (DMF)	+	Data show normal humoral responses
Natalizumab	+	Data show normal humoral responses
Alemtuzumab	+	Italian study→normal humoral response in 15/15 pwMS; UK study→ 24 /28 (86%) seroconverted
Cladribine (oral)	+	Normal humoral responses **to BNT162b2 mRNA vaccine** in Israeli (n=23) and Italian (n=25) studies; 16 of 20 (80%) seroconverted in UK study
S1P receptor modulators (FGD)	–	**Reduced rates of response to BNT162b2-mRNA and mRNA-1273vaccines (rates ranging from 0 to over 50%, depending on study Israeli and Italian studies); 12 of 36 (33%) seroconverted in Tallantyre study**
Anti-CD20 (no data on ofatumumab)	–	**Ocrelizumab and rituximab → greatly reduced responses, including to BNT162b2-mRNA and mRNA-1273 vaccines)**

Achiron A et al. *Ther Adv Neurol Disord.* 2021;14:1-8;; Tallantyre EC et al Ann Neurol 2022 Jan; 91: 89-100; Brill L et al JAMA Neurol 2021; Pitzalis M Front Immunol 2021; Ali A, Dwyer D, Wu Q, et al. Vaccine. 2021;39(41):6111-6116; Brill L et al. Ann Neurol 2022

Little effect of BNT162b2-mRNA (Pfizer) Booster in pwMS taking Ocrelizumab

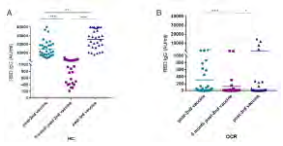
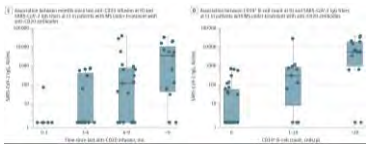


Figure taken from Brill L et al. Ann Neurol 2022

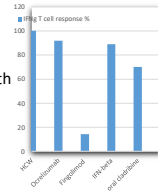
JAMA Network



DiSanto G. Et al. Association of Disease-Modifying Treatment and Anti-CD20 Infusion Timing With Humoral Response to 2 SARS-CoV-2 Vaccines in Patients With Multiple Sclerosis. JAMA Neurol. 2021 78: 1529-31.

T cell responses to vaccine in people with MS on DMTs

- 20 pwMS on anti-CD20 found T cell responses in all 20 (**100%**), but reduced. And Follicular T helper cells were especially reduced.[1]
- Another study: **97%** of the 33 on anti-CD20 who were studied showed detectable T cell responses[2]
- Prospective study in 108 MS on various DMTs and 78 health care workers (HCW) found T cell gamma IFN responses in 100% of HCW, **92% on Ocrelizumab** and 89% on IFNbeta, 70% on oral cladribine and **14.3% on fingolimod.**[3] -->



1. Apostolidis SA, Kakara M, Painter MM, et al. Nat Med. 2021;27(11):1990-2001.;
2. Gadani SP, Reyes-Mantilla M, Jank L, et al. EBioMedicine. 2021;73:103636. doi:10.1016/j.ebiom.2021.103636
3. Tortorella C, Aiello A, Gasperini C, et al. Neurology. 2021;doi:10.1212/wnl.0000000000013108

Passive Vaccination for Vaccine Non-Responders: EVUSHELD™ (tixagevimab co-packaged with cilgavimab)

- Neutralizing IgG1 mAbs that bind to non-overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV2.
- EUA for pre-exposure prophylaxis for those who may not mount an adequate immune response to COVID-19 vaccination.
- Two 300mg IM shots on same day to Adults and Pediatric patients 12 years of age and older weighing at least 40 kg. Every 6 months.

Additional information: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html

COVID-19 treatment for "High Risk" individuals: CDC Guidelines

- Oral Paxlovid po BID x 5 days. Initiate asap within 5 days of symptom onset. *Note: multiple complex drug interactions*. Nirmatrelvir packaged with Ritonavir. **PREFERRED**
- IV Remdesivir 200 mg IV on Day 1, then 100mg IV on days 2 and 3, within 7 days of symptom onset. **PREFERRED**
- Monoclonal anti-SARS-CoV-2: currently Bebtelovimab within 10 days of symptom onset, works for OMICRON BA.2.
- Oral molnupiravir 800mg BID po x 5 days. Initiate within 5 days of symptom onset (less effective –use only when none of the above options can be used). Do not use in pregnant women.

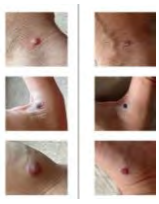
https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/
Accessed 4/6/22

Smallpox and Monkeypox Vaccine, Live, Non-Replicating Vaccine; Tradename: JYNNEOS

Smallpox/monkeypox vaccine (JYNNEOS™) is made using weakened live vaccinia virus and cannot cause smallpox, monkeypox, or any other infectious disease

Immunocompromised persons, including those receiving immunosuppressive therapy, may have a diminished immune response to JYNNEOS.

No contraindication for giving it to immunocompromised persons based on limited available data under this EUA.



AUGUST 26, 2022 https://www.fda.gov/media/160774/download

Summary

- Registry data:
  - Older, male, Black and more disabled people with MS have worse COVID-19.
  - B-cell depleting agents → worse COVID outcomes
  - Methylprednisolone treatment prior month assoc'd with worse COVID outcomes
  - No clear reduction in hospitalizations after vaccination in those on ocrelizumab.
- Reduced humoral responses to COVID-19 vaccines with anti-CD20 and S1PR modulators
- Prevention – EVUSHELD- and Treatments are available for those at risk.
- At this point in the pandemic, no compelling evidence of COVID-19 or vaccine →MS relapses, may cause pseudoexacerbations.

Acknowledgements

My wonderful group of coworkers at the John L. Trotter MS Center at Washington University & Barnes-Jewish Hospital, St. Louis Missouri

John L. Trotter MS Center pre-social distancing

B-2 (Stealth) over Barnes-Jewish Hospital, 2020

Treatment Updates in Multiple Sclerosis

Lindsey Wooliscroft, MD, MSc
OHSU and Portland VA Health Care System

Treatment Updates in Multiple Sclerosis

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OHSU and Portland VA Health Care System

MAYO CLINIC

Autoimmune Neurology: clinical and diagnostic update

Divyanshu Dubey, MD

Associate Professor
Department of Neurology,
Department of Pathology & Laboratory Medicine
Mayo Clinic, Rochester, MN

Disclosures

- Patents pending for KLHL11, LUZP4 and CAVIN4.
- Consulted for UCB, Astellas, Arialys, Argenx and Immunovant. All consulting fee paid directly
- Received funding from the DOD (CA210208) for germ cell tumor immunoprofiling.
- Discuss off label use of immunotherapy for autoimmune and paraneoplastic disorders.

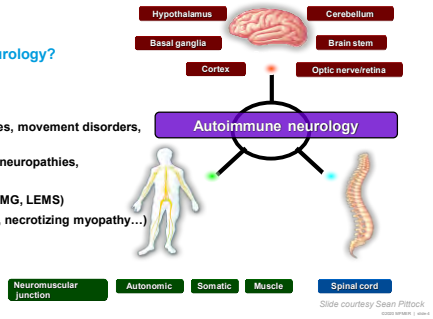
MAYO CLINIC

Outline

1. What is Autoimmune Neurology?
2. Are neural antibodies clinically helpful?
3. What is benefit of phenotype specific autoantibody evaluations?
4. How do we discover autoimmune/paraneoplastic neural specific antibodies?

MAYO CLINIC

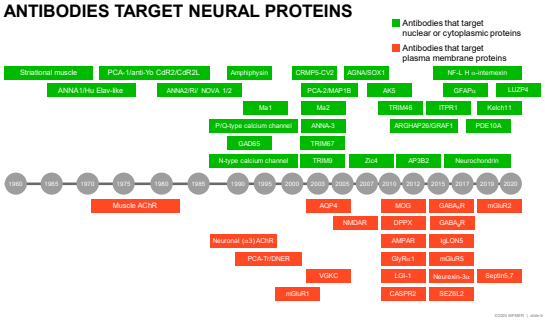
What is Autoimmune Neurology?



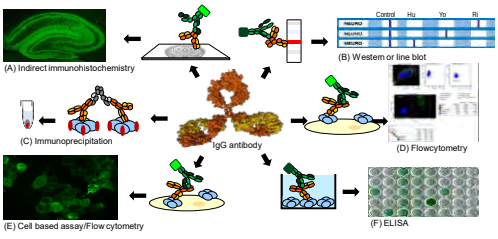
CNS (encephalitis, seizures, movement disorders, myelopathies…)
PNS and autonomic (polyneuropathies, GI dysmotility…)
Neuromuscular junction (MG, LEMS)
Muscle (dermatomyositis, necrotizing myopathy…)

Slide courtesy Sean Pittock

ANTIBODIES TARGET NEURAL PROTEINS

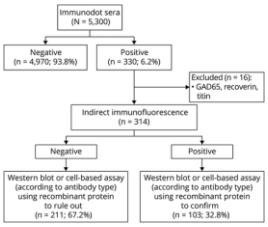


SIX TECHNIQUES FREQUENTLY USED TO DETECT ANTIBODIES IN AUTOIMMUNE NEUROLOGY



SENSITIVITY/ SPECIFICITY/PPV VARIES

Assay utilized



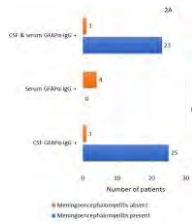
- Clinical data collected for:
  - 58 IFA positive immunodot + cases
  - 90 IFA negative immunodot + cases
- All patients with IFA confirmed presented clinical symptoms classically described with the identified antibody.
- *The clinical presentation of most* ***(84%)*** *of the IFA negative cases was incompatible with the antibody identified by immunodots.*

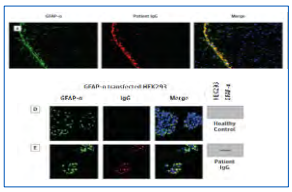
Déchelotte B, Et al. Neurol Neuroimmunol Neuroinflamm. 2020

SENSITIVITY/ SPECIFICITY/PPV VARIES

Antibody testing method and sample type

GFAP-IgG testing - CSF and + on 2 methods provides optimal testing methodology: >99% meningoencephalomyelitis





Fang & Mckeon et al. JAMA Neurol. 2016
Dubey et al. JNI. 2018

SENSITIVITY/ SPECIFICITY/PPV VARIES

Antibody titers

Ganglionic nicotinic acetylcholine receptor antibody

- Level above 0.40 nmol/L predicted severe autonomic failure with 92% specificity and 56% sensitivity.
- Level above 0.20 nmol/L had 80% specificity and 59% sensitivity for atleast moderate autonomic failure
- Levels below 0.20 nmol/L were not predictive of the presence or absence of autonomic dysfunction/failure.

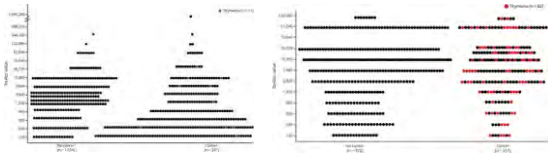
Cutsforth-Gregory et al. *Mayo Clinic proceedings.* 2018

SENSITIVITY/ SPECIFICITY/PPV VARIES

Antibodies with limited utility

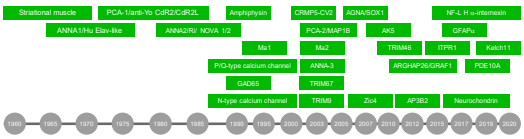
Striational testing *removed* from evaluations

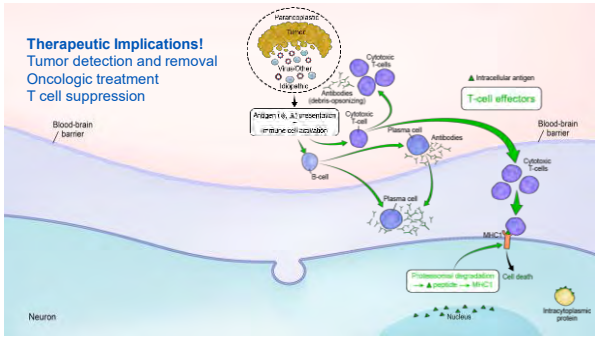
Striational antibody



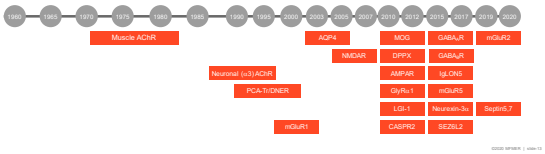
Paraneoplastic evaluation | MG evaluation

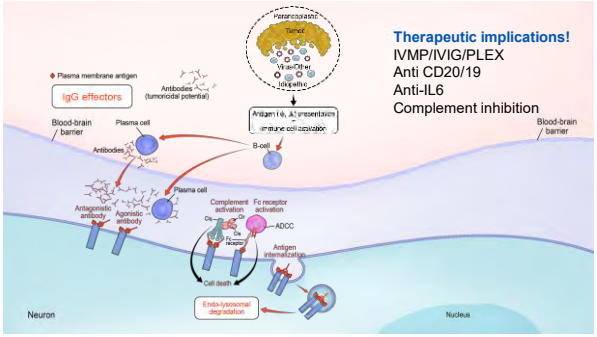
Antibodies that target nuclear or cytoplasmic neural proteins





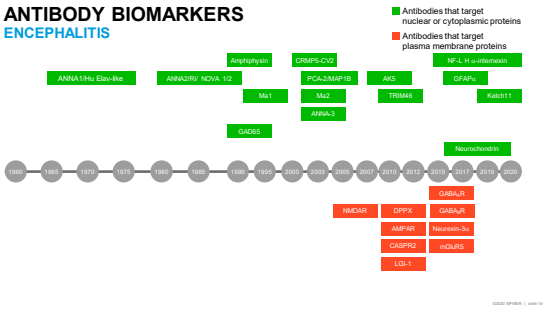
Antibodies that target plasma membrane neural proteins





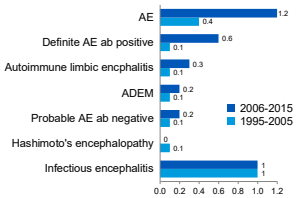
Therapeutic implications!
IVMP/IVIG/PLEX
Anti CD20/19
Anti-IL6
Complement inhibition

ANTIBODY BIOMARKERS
ENCEPHALITIS



Autoimmune Encephalitis Epidemiology

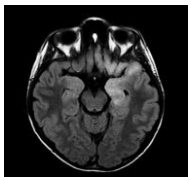
- The prevalence of autoimmune and infectious encephalitis was similar (13.7 vs 11.6/100,000)
- The incidence of autoimmune encephalitis is increasing over time
- Our study estimates:
  - 1 million worldwide have had autoimmune encephalitis
  - 90,000 per year develop autoimmune encephalitis



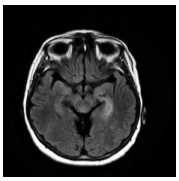
Dubey et al: Annals of Neurology, 2018

60-YEAR-OLD MALE WITH ENCEPHALOPATHY

ANNA1



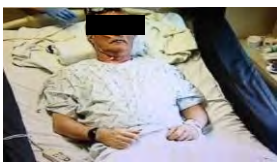
LG1-1



Similar clinical and radiological presentations

Neural Antibodies can inform clinical course and prognosis

LGI1 autoimmune encephalitis



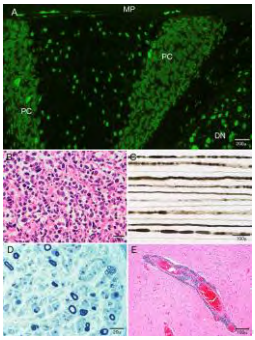
- He was initiated on intravenous methylprednisolone, 1 g for 5 days, followed by seven sessions of plasmapharesis.
- He had resolution of FBDS following completion of high dose corticosteroid and plasmapheresis treatment.
- He was discharged on oral prednisone taper and mycophenolate mofetil (1000 mg twice daily)
- **On follow-up visit in the clinic 4 months after the hospital discharge, the patient reported he was seizure free and cognitive dysfunction had resolved.**

Dubey et al: Neurol India, 2016

Neural Antibodies can inform clinical course and prognosis

A 60-year-old man ascending weakness and sensory loss, and confusion.

- CSF:
  - Protein: 326 mg/dl
  - Cell count: 3 cells/mm^3
- EMG: Severe axonal sensory-motor polyneuropathy
- Paraneoplastic panel: ANNA1 or anti-Hu
- Patient died



Clinical Tools to Improve Pretest Probability APE2 score

New onset, rapidly progressive mental status changes developed over 1-6 weeks or new onset seizure activity (within one year of evaluation)	(+1)
Neuropsychiatric changes; agitation, aggressiveness, emotional labiality	(+1)
Autonomic dysfunction	(+1)
Viral prodrome (rhinorrhea, sore throat, low grade fever) only to be scored in the absence of underlying malignancy within 5 years of neurological symptom onset	(+2)
Faciobrachial dystonic movements	(+3)
Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures	(+2)
Seizure refractory to at least to two anti-seizure medications	(+2)
CSF findings consistent with inflammation	(+2)
Brain MRI suggesting encephalitis (T2/FLAIR hyperintensity restricted to one or both medial temporal lobes, or multifocal in grey matter, white matter, or both compatible with demyelination or inflammation)[c]	(+2)
Systemic cancer diagnosed within 5 years of neurological symptom onset[c] (excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumor, cancer with brain metastasis)	(+2)
	Total (max: 19)

Dubey et al. Epilepsia. 2019

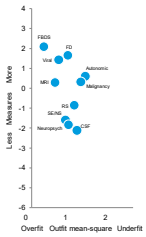
Antibody Prevalence in Epilepsy & Encephalopathy (APE2)

APE2 score ≥4 (encephalopathy)

- 99% sensitive
- 93% specific

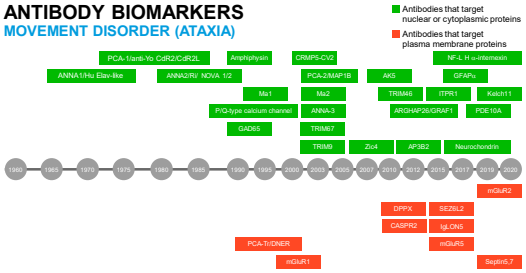
APE2 ≥4 (epilepsy)

- 98% sensitive
- 84% specific

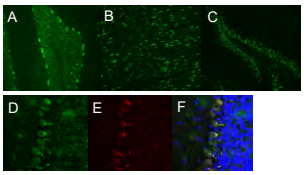


Dubey et al: J Neuroimmun, 2018
Dubey et al: Epilepsia, 2019

ANTIBODY BIOMARKERS
MOVEMENT DISORDER (ATAXIA)



Tadpoles



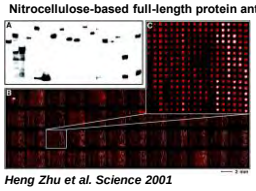
Patients
- 22 patients, 15 female (68%)
- Median age 67 years (range 25-87)

Clinical findings
- Subacute cerebellar syndrome (15, 68%)
- Limbic encephalitis (3)
- Myelopathy (2)
- Encephalopathy with/without seizures (2)

Oncological associations (Fig. 3)
- Cancer diagnosed in 18 patients (82%)
- Neuroendocrine carcinomas (n=9), adenocarcinomas (n=6; lung [2], ovarian [2], endometrial [1], breast [1]), sarcoma (n=2), and gastrointestinal tumor (n=1)
- 3 developed neurological symptoms after immune checkpoint inhibitor (ICI) therapy

Sanchez, Knight…Dubey. JNNP. 2021

Nitrocellulose-based full-length protein antibody-detection array



Heng Zhu et al. Science 2001

- Unclassified-IgG & CSF re-tested on tissue IFA
- Proteome microarray, test serum/CSF with identical patterns of tissue staining alongside controls.
- Microarrays contain 15,889 of 19,613 canonical human proteins (81%) in recombinant form (N-terminal GST and RGS-His6-tagged)
- Pre-printed in duplicate on nitrocellulose-coated glass slides.
- After blocking, 3mL of total specimen volume [serum [1:1000] dilution or CSF [1:2]) is added to the surface of the microarray.
- Overnight incubation at 4°C and washing, probing with goat-anti-human IgG secondary.
- After washing & drying, IgG evaluated using Genepix 4000B scanner

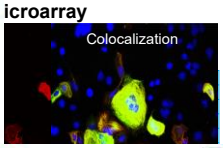
Neural IgG	Specimen tested	Protein	Neural protein rank (by Z score)	Overall protein rank (by Z score)
Amphiphysin	Serum	Amphiphysin	1	1
ANNA-1	Serum	ELAVL (Hu)	3	39
ANNA-1	CSF	ELAVL (Hu)	1	2
ANNA-2	Serum	NOVA (Ri)	1	1
CRMP5	Serum	DPYSL5 (CV2, CRMP5)	3	7
CRMP5	CSF	DPYSL5 (CV2, CRMP5)	2	3
GAD65	Serum	GAD2 (GAD65)	1	1
GAD65	CSF	GAD2 (GAD65)	1	1
GFAP	CSF	GFAP	1	24
Ma2	Serum	PNMA2	1	1
NCDN	Serum	NCDN	1	1
PCA1	Serum	CDR2L (Yo)	1	1
PCA1	CSF	CDR2L (Yo)	1	1

Slide by Andrew McKeon


Neuroscience Letters

A new paraneoplastic encephalomyelitis autoantibody reactive with the axon initial segment

icroarray



Neuron

TRIM46 Controls Neuronal Polarity and Axon Specification by Driving the Formation of Parallel Microtubule Arrays

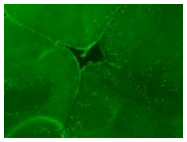
HuProt™ arrays: >20,000 full length proteins
After blocking, the serum samples were probed
overnight at 4°C in order to enhance potential b
washed and then probed with Alexa-647-anti-hu

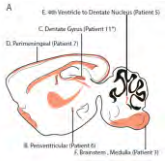
N Engl J Med 2019 July 04; 381(1): 47–54. doi:10.1056/NEJMoa1816721

Kelch-like Protein 11 Antibodies in Seminoma-Associated Paraneoplastic Encephalitis

Caleigh Mandel-Brehm, Ph.D.[#], Divyanshu Dubey, M.D.[#], Thomas J. Kryzer, A.S., Brian D. O'Donovan, Ph.D., Baouyen Tran, Ph.D., Sara E. Vazquez, B.S., Hannah A. Sample, B.S., Kelsey C. Zorn, M.H.S., Lillian M. Khan, B.S., Ian O. Bledsoe, M.D., Andrew McKeon, M.D., Samuel J. Pleasure, M.D., Ph.D., Vanda A. Lennon, M.D., Ph.D., Joseph L. DeRisi, Ph.D., Michael R. Wilson, M.D.[#], Sean J. Pittock, M.D.[#]

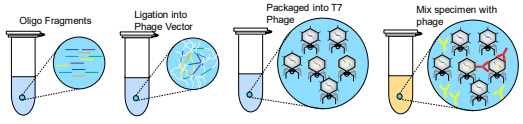
[#] These authors contributed equally to this work.



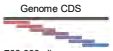


MAYO CLINIC

PHIP-SEQ EXPERIMENTAL APPROACH



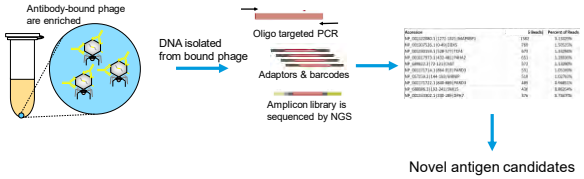
Genome CDS



700,000 oligos
Each coding 49 amino acids of human peptide

An aliquot is mixed with patient antibodies; some bind, most don't

PHIP-SEQ EXPERIMENTAL APPROACH



KLHL11 IgG (>60 patients)

Prevalence (males) : 2.8/100,000 population

Clinical presentation:

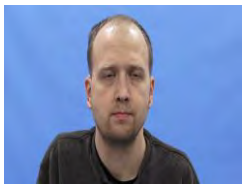
- Rhomboencephalitis (70%)
- Limbic encephalitis (15%)
- Both (15%)

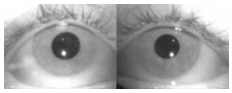
Hearing loss and tinnitus may precede other neurological presentations

Testicular cancer: >70% (commonly seminoma)

Mandel-Brehm & Dubey et al. NEJM. 2019
Dubey et al. JAMA Neurol. 2020

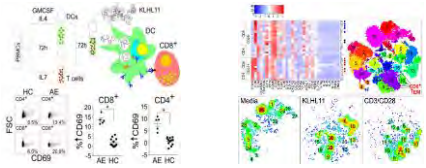
Rhombencephalitis





Dubey et al. JAMA Neurol. 2020

KLHL11 SPECIFIC T-CELL RESPONSE



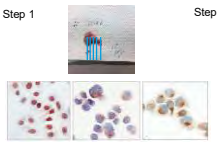
PBMC-derived Dendritic cell-T cell coculture assay (A). Flow cytometry at 72 hours post treatment demonstrated that KLHL11 antigen treated cells exhibited an increased frequency of CD69 expressing CD8+ and CD4+ T cells in KLHL11 seropositive patients but not healthy controls (B). CyTOF immunophenotyping demonstrated an increased frequency of CD25 expressing CD4+ and CD8+ (effector memory) T cells following antigen treatment (C).

Dubey et al. JAMA Neurol 2020

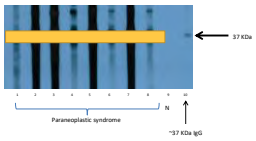
Tissue-immunoprecipitation (TIP)

Enriched antigen source: **specific areas of brain based on IFA or finding a cell lines expressing the putative antigen.**

Step 1



Step 2

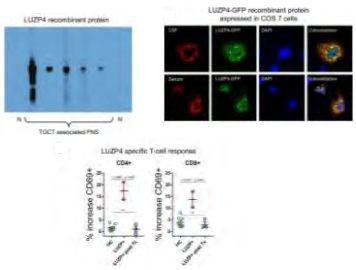


Step 3 **Immunoprecipitation Assay:**

1. Purified IgG mixed with the antigen
2. Magnetic bead with protein G to binds to patient IgG along with the antigen
3. Eluted proteins are separated by gel electrophoresis and visualized by staining with colloidal Coomassie blue
4. Antigen bands were prepared and analyzed with mass spectrometry

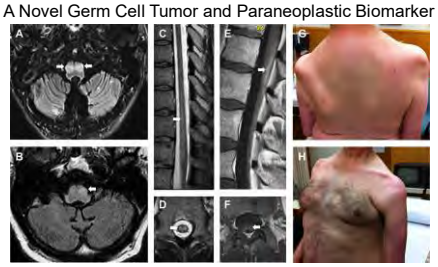
Schraf et al. Front Immunol 2018
Jong et al. Genes Chromosomes Cancer. 2008

Leucine Zipper 4 Autoantibody: A Novel Germ Cell Tumor and Paraneoplastic Biomarker



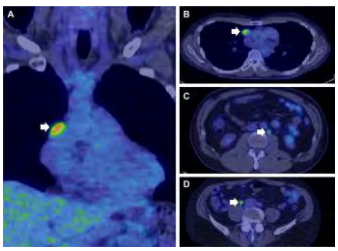
Dubey et al. Annals of Neurology, 2021, DOI: (10.1002/ana.26050)

Leucine Zipper 4 Autoantibody:
A Novel Germ Cell Tumor and Paraneoplastic Biomarker



Dubey et al. Annals of Neurology, 2021, DOI: (10.1002/ana.26050)

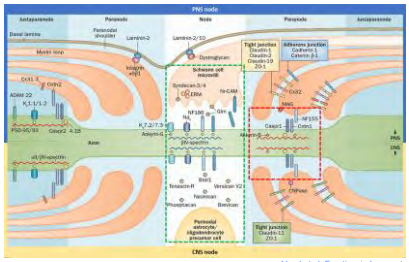
Extra-gonadal germ cell tumor



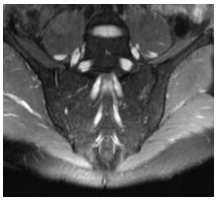
Autoimmune Cerebellar Ataxia

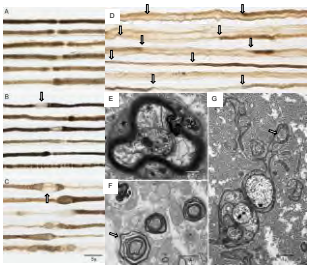
Antibody	Antibody
P/Q or N-type Calcium Channel	PCA-1 (anti-Yo)
LGI1	GAD65
DPPX	PCA-2 (MAP1B)
mGluR1	Ma1, Ma2 antibodies
CASPR2	Amphiphysin
PCA-Tr (DNER)	ANNA-1 (anti-Hu)
mGluR2	CRMP-5
Septin-5-IgG	ITPR1, ARGHAP26
	NIF-IgGs
	AP3B2-IgG
	Kelch-like 11/LUZP4
	TRIM46
	Neurochondrin

NODAL MOLECULAR TARGETS OF BIOMARKERS



Vural et al: Frontiers in Immunology, 2018





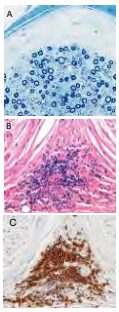
Shelly, Klein...Dubey. Neurology. 2021

NF155 IgG4 POSITIVE VS NEGATIVE CIDP CASES

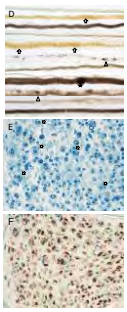
- Sensory ataxia (OR: 10.79, 95% CI: 5.24–22.22)
- Tremor (OR: 6.71, 95% CI: 3.37–13.39)
- Response to IVIg (OR: 0.09, 95% CI: 0.02–0.42)

Hu et al: Brain Behav, 2018
Ogata et al: Clinical and Experimental Neuroimmunology, 2018

NF155-IgG4 fascicular biopsy



NF155-IgG sural nerve biopsy



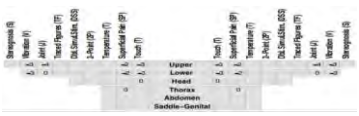
Shelly, Klein…Dubey. Neurology. 2021

Contactin-1 IgG+

19-YEAR-OLD MAN WITH NUMBNESS, TINGLING AND PAIN

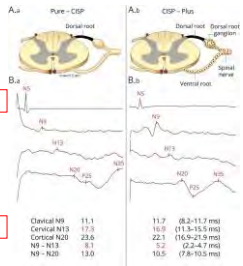
- 02/26 – Numbness [illegible] y
- 03/08 – Numbness [illegible] then involving the inner thighs and buttock area
- 03/22 – Gait instability
- **Exam** – Normal strength, absent DTRs

EMG and MRI spine normal

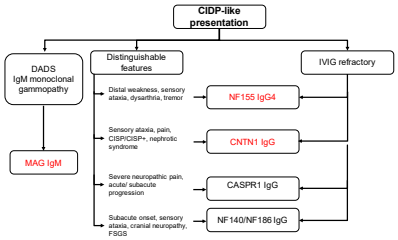


Median SSEP Pre and Post IVIG

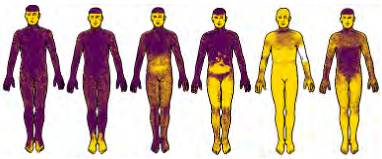
Cervical, N13	17.3	(11.3-15.5)
Clavicle, N9	11.1	(8.2-11.7)
Scalp, N20	23.6	(16.9-21.9)
N13-N20 interval	6.8	(4.7-6.6)
N9-N13 interval	8.1	(2.2-4.7)
N9-N20 interval	13.0	(7.8-10.5)
Cervical, N13	15.3	(11.3-15.5)
Clavicle, N9	10.78	(8.2-11.7)
Scalp, N20	20.6	(16.9-21.9)
N13-N20 interval	5.3	(4.7-6.6)
N9-N13 interval	4.6	(2.2-4.7)
N9-N20 interval	9.9	(7.8-10.5)

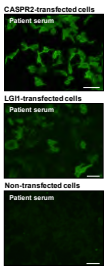


Dubey et al. Neurol Neuroimmunol Neuroinflamm 2020; Shahar et al. Neurology. 2021



PAIN AND SMALL FIBER NERVE INVOLVEMENTS

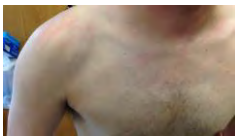




Klein et al. Neurology, 2012

Peripheral hyperexcitability

Nerve

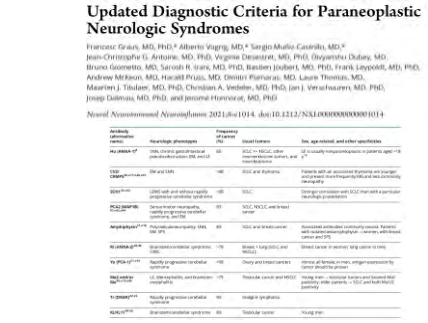


CASPR2 IgG

Muscle

Cavin-4 IgG

Dubey et al. JAMA Neurol. 2022

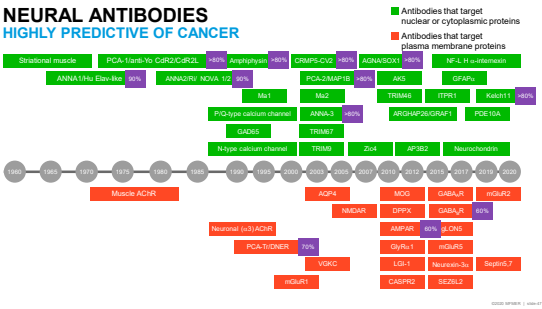


Updated Diagnostic Criteria for Paraneoplastic Neurologic Syndromes

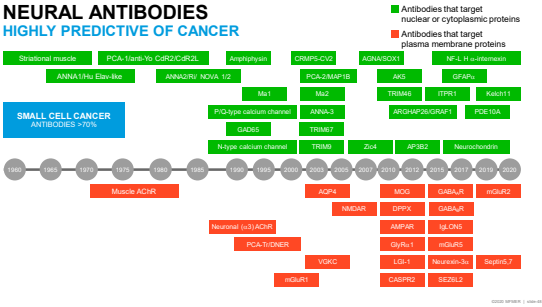
Francesc Graus, MD, PhD,* Alberto Vogrig, MD,* Sergio Muñiz-Castrillo, MD,* Jean-Christophe O. Antoine, MD, PhD, Virginie Desestret, MD, PhD, Divyanshu Dubey, MD, Bruno Giometto, MD, Sarosh R. Irani, MD, PhD, Bastien Joubert, MD, PhD, Frank Leypoldt, MD, PhD, Andrew Mirkovic, MD, Harald Prüss, MD, Dimitri Psimaras, MD, Laure Thomas, MD, Maarten J. Titulaer, MD, PhD, Christian A. Vedeler, MD, PhD, Jan J. Verschuuren, MD, PhD, Josep Dalmau, MD, PhD, and Jerome Honnorat, MD, PhD

Neurol Neuroimmunol Neuroinflamm 2021;8:e1014. doi:10.1212/NXI.0000000000001014

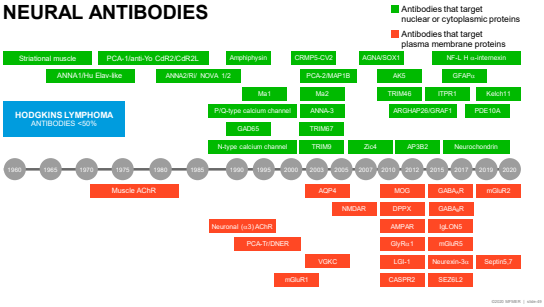
NEURAL ANTIBODIES
HIGHLY PREDICTIVE OF CANCER



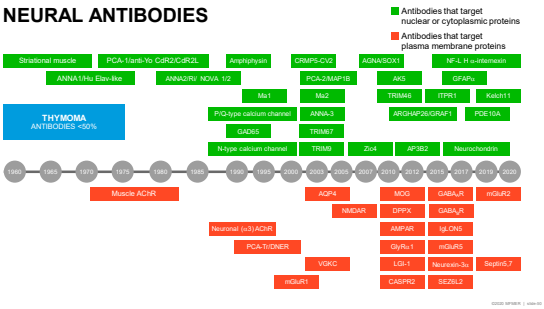
NEURAL ANTIBODIES
HIGHLY PREDICTIVE OF CANCER



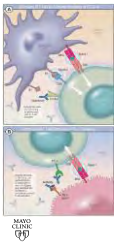
NEURAL ANTIBODIES



NEURAL ANTIBODIES



NEUROLOGICAL COMPLICATION OF IMMUNE CHECK POINT INHIBITORS



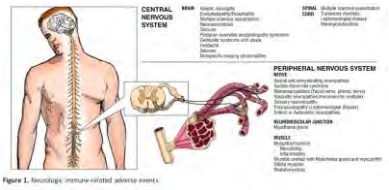
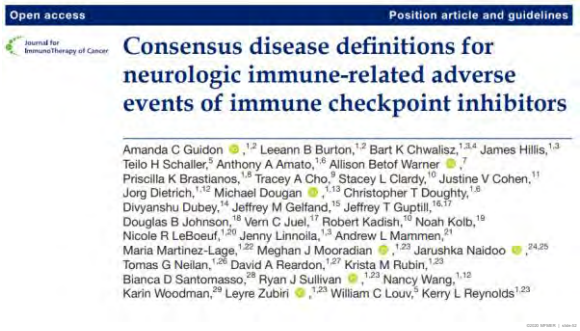


Figure 1. Neurologic immune-related adverse events.

Dubey et al: Annals of Neurology, 2020
Reynolds & Guidon. The Oncologist. 2018.



Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Consensus disease definitions for neurologic immune-related adverse events of immune checkpoint inhibitors

Amanda C Guidon ,[1,2] Leeann B Burton,[1,2] Bart K Chwalisz,[1,3,4] James Hillis,[1,3] Teilo H Schaller,[5] Anthony A Amato,[1,6] Allison Betof Warner ,[7] Priscilla K Brastianos,[1,8] Tracey A Cho,[9] Stacey L Clardy,[10] Justine V Cohen,[11] Jorg Dietrich,[1,12] Michael Dougan ,[1,13] Christopher T Doughty,[1,6] Divyanshu Dubey,[14] Jeffrey M Gelfand,[15] Jeffrey T Guptill,[16,17] Douglas B Johnson,[18] Vern C Juel,[17] Robert Kadish,[19] Noah Kolb,[19] Nicole R LeBoeuf,[1,20] Jenny Linnoila,[1,3] Andrew L Mammen,[21] Maria Martinez-Lage,[1,22] Meghan J Mooradian ,[1,23] Jarushka Naidoo ,[24,25] Tomas G Neilan,[1,26] David A Reardon,[1,27] Krista M Rubin,[1,23] Bianca D Santomasso,[28] Ryan J Sullivan ,[1,23] Nancy Wang,[1,12] Karin Woodman,[29] Leyre Zubiri ,[1,23] William C Louv,[3] Kerry L Reynolds[1,23]

Take home points

- Autoimmune neurological disorders can affect every level of the neuraxis
- Similar neurological presentations can be associated with multiple neural antibodies – highlighting utility of panels over individual antibodies
- New antibodies are being discovered nearly every few months
- Both serum and CSF should be tested for neural autoantibodies
- A negative antibody panel does not rule out an autoimmune diagnosis
- If clinical suspicion for neurological autoimmunity is high, immunotherapy should be initiated even before antibody results are available

MAYO CLINIC

THANK YOU!

QUESTIONS

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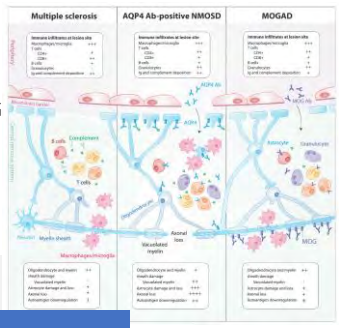
Pediatric MOG Antibody Disease: Case-Based Presentation

Kayla Martin, MD
Department of Neurology, OHSU and VA Portland Health Care System
9/17/2022

Objectives

- 1. Understand the clinical and radiologic characteristics of MOGAD in the pediatric population using a case-based approach.
- 2. Highlight factors that may predict relapse in pediatric MOGAD and how this compares to the adult population.
- 3. Discuss current and future treatment options for pediatric MOGAD.

What is MOG Antibody Disease (MOGAD)?



Lopez et al. 2021

Epidemiology of Pediatric MOGAD

- Higher prevalence in pediatric population compared to adults (0.31 compared to 0.13 per 100,000 in a Dutch study)
- Bimodal distribution including pediatric (35% of cases) and a second peak in young/mid adulthood
- MOG antibodies are present in one third of children with demyelinating syndromes
- Equal distribution of boys and girls (slight female predominance in older children)
- Mostly in white individuals but more systematic studies are needed

Bruijstens et al. 2020
De Mol et al. 2020
Longbrake 2022

MOGAD Diagnosis

1) Presence of MOG autoantibodies
   - Overall predictive value 72% (less with lower titer 1:20-1:40)
2) Congruent clinical phenotype (optic neuritis, ADEM, myelitis, or combination)

Irrespective of meeting McDonald Criteria or Wingerchuk criteria for seronegative NMOSD

Longbrake 2022

CSF Findings in MOGAD are similar in pediatric and adult patients

- WBC elevated in >50% and marked compared to MS or AQP4 NMO (median 40 WBC; range 6-256)
- Lymphocytic and neutrophilic pleocytosis detectable in half of specimens
- Unique oligoclonal bands absent in ~90% (and typically resolve after relapse if present)
- Less pronounced if presenting with isolated optic neuritis
- Some series have noted correlation of CSF abnormalities with attack severity

Jarius et al. 2020

Breakdown of MOGAD Phenotypes in Pediatric Population

- ADEM (46%) → Younger children
- Optic Neuritis (30%) → Older children
- Transverse myelitis (including LETM) (11%)
- NMOSD-like (combination of ON and TM) (4%)

*More common in adults

Bruijstens et al. 2020

MOGAD can be monophasic or relapsing. Serostatus and age have been associated with relapse in pediatric MOGAD.

- Likelihood of relapsing disease estimated to be between 37-95%
- 40% of patients will have second clinical event within two years

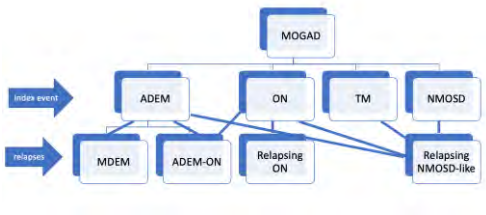
MOG titer

- 38% risk of relapse in pts remaining seropositive (compared to 13% converting to seronegative)

Age (older age at increased risk of relapse in peds)

Bruijstens et al. 2020
Longbrake 2022
Lui et al. 2021

MOGAD Phenotypes

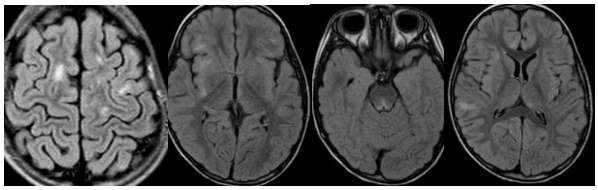


Derived from: Bruijstens et al. 2020

A 4 yo boy presents with 1 day of weakness of the lower extremities, refusal to bear weight, and irritability

- 4 days ago he had fever and viral URI symptoms
- Exam limited by cooperation but notable for mildly reduced strength in the lower extremities and diminished reflexes

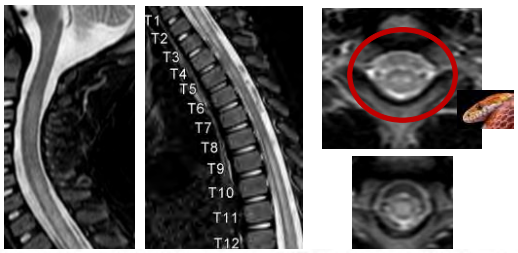
MRI Brain W/W/O



IMPRESSION:

Numerous nonenhancing T2/FLAIR hyperintense lesions in the juxtacortical white matter of the cerebral hemispheres with involvement of the left thalamus and brainstem. Acute disseminated encephalomyelitis is considered most likely. Other demyelinating etiologies and infectious encephalomyelitis are also possibilities.

MRI Total Spine W/W/O



Additional, longitudinally and cross-sectionally extensive enhancing T2/STIR hyperintensity in the cervical and thoracic spinal cord and conus medullaris. Given brain MRI findings, acute disseminated encephalomyelitis is considered most likely. Infectious encephalomyelitis and other demyelinating etiologies could also be considered.

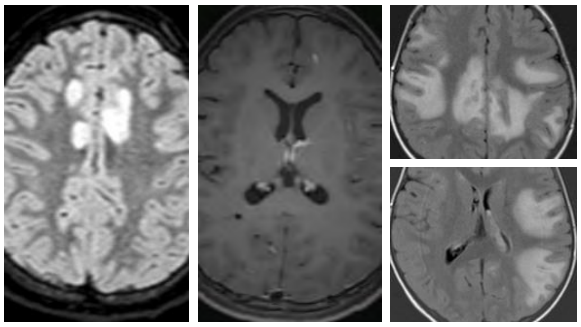
A 4 yo boy with imaging findings consistent with **acute disseminated encephalomyelitis** (ADEM)

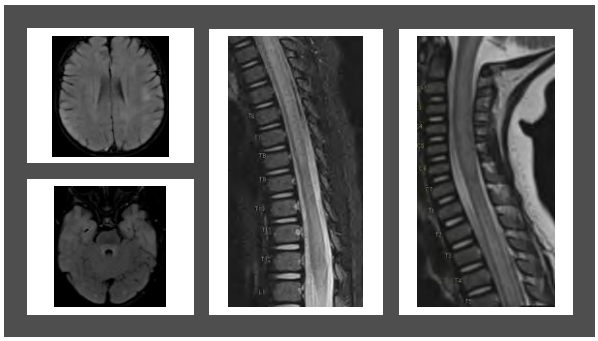
- Workup
  - CSF with elevated WBC 14 (no diff), RBC 597, normal protein and glucose, elevated IgG index (0.86), negative OCBs
  - NMO negative
- Treatment
  - IV Solumedrol for 5 days (30 mg/kg/day)
- Follow-up
  - Able to ambulate without assistance upon discharge
  - MOG returned positive (1:80)
  - Immunotherapy for relapse prevention not initiated and no reports of further attacks ~3 years later

Acute Disseminated Encephalomyelitis (ADEM)

- **Encephalopathy** and polyfocal neurologic deficits with characteristic imaging findings
  - Encephalopathy = altered consciousness or behavioral changes (not explained by fever)
- MRI with bilateral supratentorial lesions affecting white matter (subcortical and deep) and grey (basal ganglia and thalamus), large (> 2 cm), poorly demarcated, frequently resolve on follow-up imaging
- Flare up: Imaging findings can fluctuate during the acute phase for up to 3 months (not true relapse)
- About half of all pediatric ADEM cases are MOG positive
- Compared to MOG-negative ADEM cases, MOG positive ADEM:
  - Has a trend for higher CSF WBC
  - Higher risk of ongoing cognitive impairment and secondary epilepsy
  - Less likely to be monophasic

Krupp et al. 2013
Bruijstens et al. 2020





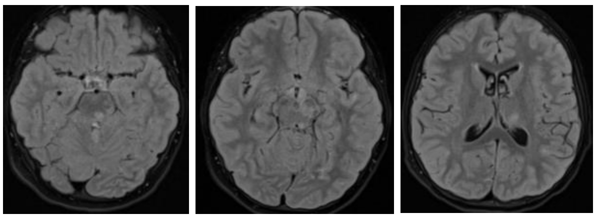
8 yo girl presents with headache and poor po intake ~1 week following 2nd dose of COVID vaccine

- Exam reported to be normal
- Positive rhinovirus
- CTH unremarkable
- CSF with 231 WBC (15% PMNs), RBC 6, glucose 61, protein 55, meningoencephalitis panel negative
- Diagnosed with aseptic meningitis following the vaccine and treated with dexamethasone for headache

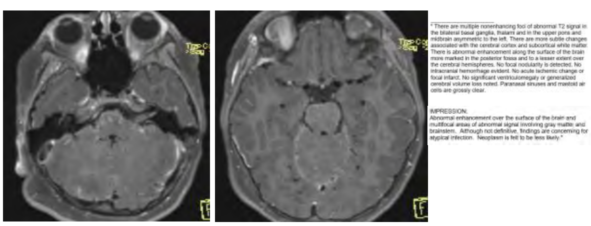
8 yo girl with headache and poor po intake re-admitted several days later with weakness, low-grade fevers, and mood swings

- Exam “normal strength, normal tone, brisk reflexes lower extremities”

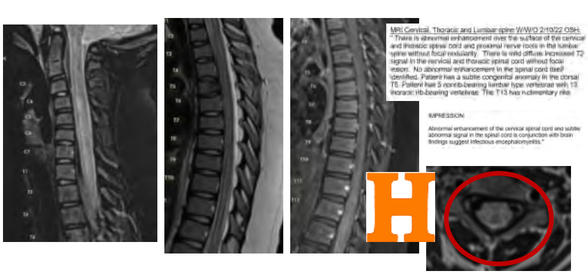
MRI Brain W/W/O



MRI Brain W/W/O



MRI Total Spine W/W/O



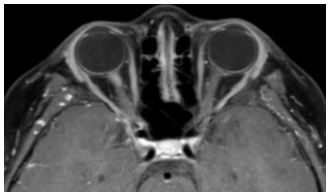
8 yo girl presents with headache, weakness, low-grade fevers, and mood swings, with imaging findings of **encephalomyelitis**

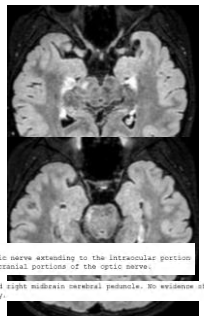
- Workup:
  - Repeat CSF with 752 WBC (45% PMNs and 46% lymph), negative OCBs, negative cytology. RBC and protein not documented.
- Treatment:
  - 5 days IV Solumedrol (500 mg bid)
  - IVIg (unknown dose)
- Follow-up:
  - Upon discharge minimal weight bearing and required assistance to transfer
  - PT/OT deferred as she moved out of state to be closer to family
  - MOG not checked and relapse prevention not initiated

8 yo girl with diagnosis of "autoimmune encephalomyelitis" presents ~3-4 weeks of vision loss in the left eye (now improving)

- Visual acuity 20/25 OD (-2) and 20/40 (-2) OS
- Color plates and visual fields normal
- Recent OCT found bilateral optic nerve atrophy with nasal and inferior thinning of the right eye (average thickness 76) and nasal, inferior, and temporal thinning of the left eye (average thickness 61)

MRI Brain W/W/O





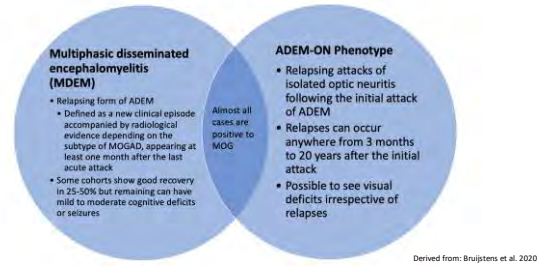
OPTIC NERVES:
* Abnormal short segment enhancement involving the distal intraorbital right optic nerve extending to the intraocular portion.
* Nonenhancing T2/FLAIR signal abnormality involving the left chiasmal and intracranial portions of the optic nerve.

BRAIN: Nonenhancing T2/FLAIR signal hyperintensity involving the right rostral pons and right midbrain cerebral peduncle. No evidence of hemorrhage, mass, or acute infarction. The ventricles are normal in size and morphology.

8 yo girl with diagnosis of "autoimmune encephalomyelitis" found to have **acute optic neuritis OD** and prior optic neuritis OS

Workup	Treatment	Follow-up
• MOG sent	• 1 g IV Solumedrol for 5 days • Discharged on prednisone 60 mg daily	• MOG returned positive (1:1000) • Maintenance IVIg (1 g/kg) initiated for relapse prevention and prednisone weaned

Relapsing syndromes of ADEM



Derived from: Bruijstens et al. 2020

MOGAD Following Infections and Vaccination

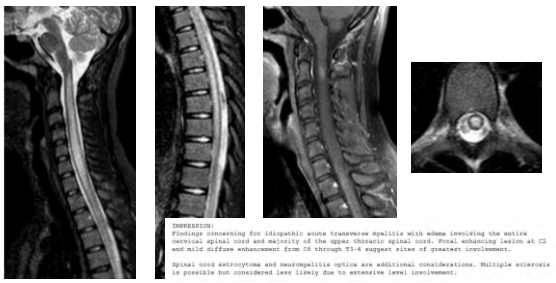
- More common after infection (rather than post-vaccine)
- Viral etiologies mainly (influenza, Epstein-Barr, herpes simplex, measles, Zika, SARS-CoV-2, HHV-6) but also bacteria such as Mycoplasma pneumoniae or Borrelia
- Mechanism suspected to be related to robust immune activation and disruption of the blood-brain barrier (rather than molecular mimicry)
- Unclear if postinfectious causes are more likely to follow a monophasic course

Longbrake 2022

12 yo girl presents with 2 days of bilateral lower extremity weakness, paresthesias, and urinary incontinence several weeks following gastroenteritis

- Motor: tone reduced in the lower extremities, mild weakness with hip flexion, otherwise strength 0/5 lower extremities
- Reflexes: 3+ upper extremities, trace at the patellae and ankles
- Sensation: absent pain sensation below T5, light touch impaired in the lower extremities, reduced vibration in the lower extremities

MRI Total Spine W/W/O



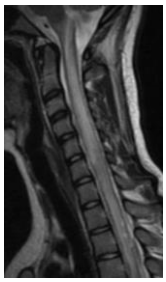
12 yo girl with **longitudinally extensive transverse myelitis**

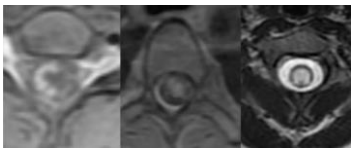
Workup:	Treatment:	Follow-up:
• CSF: 34 WBC (51% lymph, 8% PMNs), 7 RBC, protein 84, normal glucose, negative OCBs, IgG index normal (0.64) • NMO negative	• 1 g IV Solumedrol for 5 days • IVIg (2 g/kg over 3 days)	• Non-ambulatory and 2-person assist for transfers upon discharge to IPR • MOG antibody not tested and relapse prevention not initiated

12 yo girl with **longitudinally extensive transverse myelitis** presents with one day of weakness and sensory changes in the right hand (~28 days after onset of index event)

- Motor: new weakness in RUE (deltoid and biceps 4/5, triceps 4-/5, finger extensors 3/5, finger flexors 4/5). Paraplegia.
- Reflexes: 3+ upper extremities, trace at the patellae and ankles
- Sensation: reduced to light touch below the chest, reduced vibration and pain sensation in the lower extremities
- Gait: non-ambulatory

MRI Total Spine W/W/O





FINDINGS: Extensive abnormal signal throughout the cord, most pronounced in the cervical and upper thoracic cord with notable expansion of the cervical cord. Notable progression/extension into the medulla and lower thoracic cord as compared to the prior exam. Patchy areas of enhancement are seen in the cord.

IMPRESSION:

Interval progression of nonspecific transverse myelitis involving the spinal cord and medulla.

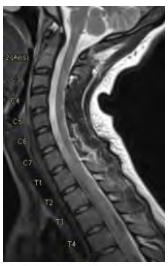
12 yo girl with progression of **longitudinally extensive transverse myelitis**

Workup:	Treatment:	Follow-up:
• CSF: 18 WBC (98% lymph), 2 RBC, protein 105, normal glucose, negative OCBs, IgG index mildly elevated (0.68) • MOG positive (1:100)	• 1 g IV Solumedrol for 5 days followed by 80 mg prednisone tapered over several weeks (tapered more rapidly in IPR) • PLEX (5 sessions) • Cytoxan 700 mg/m^2 every 4 weeks for 3-6 mos (only completed 1 cycle) • Rituximab 1,000 mg x 2 doses (then 1,000 mg every 6 mos)	• Wheelchair dependent with maximum dependence for transfers upon discharge to IPR • Rituximab continued for relapse prevention

3 years later (now 15 yo girl) with **longitudinally extensive transverse myelitis** presents for routine follow-up

- Motor: Moderately increased tone in the lower extremities. Full strength upper extremities. Right hip flexion 3/5, bilateral knee flexion 4+/5, knee extension 5/5, dorsi and plantar flexion 4-/5
- Reflexes: 3+ diffusely, extensor plantar responses bilaterally, ankle clonus (R>L)
- Sensation: reduced vibration, pinprick, and proprioception in the lower extremities
- Gait: able to transfer without assistance, occasionally uses walker at home (otherwise wheelchair)
- Workup: repeat MOG positive low titer (1:20)
- Treatment: Rituximab 1,000 mg every 6 mos
- Imaging: Improvement in cord lesion without residual enhancement

MRI Cervical and Thoracic W/W/O



slightly decreased T2 hyperintensity in the thoracic spinal cord. No associated enhancement.

Transverse Myelitis (including LETM)

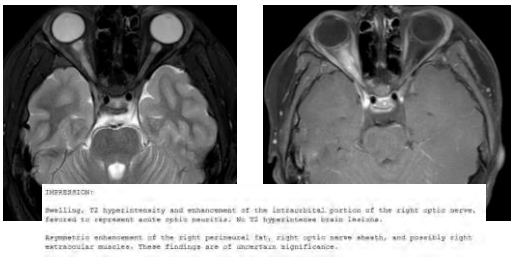
- Isolated TM rare in pediatric MOGAD
- Severe presentation at onset (one third wheelchair bound)
- Involvement of the conus medullaris in (37%) of cases presenting with cord involvement
- Predilection for the central grey matter (can present with flaccid areflexia)
- Tendency to have favorable outcomes in motor function (variable bowel, bladder, and erectile dysfunction)

Bruijstens et al. 2020

13 yo boy presents with 5 days of vision loss and pain with eye movements in all directions in the right eye

- Visual acuity: hand motion superior fields and light perception centrally OD (20/20 OS)
- Right rAPD and pupil sluggishly reactive
- Visual fields: total inferior temporal and inferior nasal deficiencies
- Fundus (OD): 2+ disc edema with mild blurring of vessels and 2 small disc hemorrhages, 2 small retinal hemorrhages along superior arcade, mild tortuosity of vessels

MRI Brain and Orbits W/W/O



IMPRESSION:

Swelling, T2 hyperintensity and enhancement of the intraorbital portion of the right optic nerve, favored to represent acute optic neuritis. No T2 hyperintense brain lesions.

Asymmetric enhancement of the right perineural fat, right optic nerve sheath, and possibly right extraocular muscles. These findings are of uncertain significance.

13 yo boy presents with 5 days of vision loss and pain with eye movements in the right eye, **diagnosed with optic neuritis**

Treatment:	Follow-up:
• 1 g IV Solumedrol for 4 days • Prednisone starting at 40 mg and tapered over 16 days	• Visual acuity 20/20 (-2) OU • Right rAPD • Normal visual fields • Normal fundoscopic exam • MOG antibody not tested and relapse prevention not initiated

Optic Neuritis

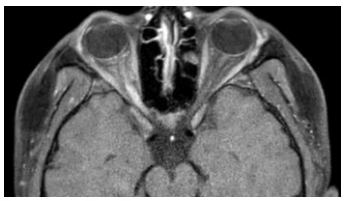
- Can be monophasic or part of several relapsing phenotypes: ADEM-ON, relapsing NMOSD-like, or relapsing ON
- Predominantly in older pediatric patients (ages 13-18)
- Severe vision loss at onset though favorable recovery compared to AQP4 NMOSD, double seronegative NMOSD, and MS patients
- Bilateral involvement is more likely than with MS, but not seen as commonly as it is in adults
- Prominent optic disc edema due to anterior involvement of the optic nerve
- Higher rates of longitudinal involvement of optic nerve on MRI with relative sparing of the chiasm and tracts
- Optic neuritis plus phenotype= perineural enhancement and inflammation of soft orbital tissues on MRI in up to 50% (mainly adults)
- Despite good clinical recovery, can see severe axonal damage on OCT consistent with findings from AQP4 associated ON
- Headache is common and can precede visual symptoms by several days

Bruijstens et al. 2020
Longbrake 2022

3 years later, now 16 yo boy presents with 2 weeks of vision loss and pain with eye movements in all directions in the right eye

- Visual acuity: counts fingers OD (20/20 OS)
- Right rAPD and pupil sluggishly reactive
- Visual fields: total superior temporal, superior nasal deficiencies, partial outer inferior temporal, inferior nasal deficiencies
- Fundus (OD): 2+ disc edema, tortuous vessels

MRI Brain and Orbits W/W/O



IMPRESSION:

Enlargement, T2 hyperintensity, diffusion restriction, and enhancement of the mid and apical portions of the intraorbital right optic nerve as well as the surrounding perineural fat, likely representing acute optic neuritis.

No acute intracranial abnormalities.

16 yo boy presents with **recurrent optic neuritis of the right eye**, 3 years after index event

Treatment:	Follow-up:
• 1 g IV Solumedrol for 3 days • Prednisone 60 mg daily until follow-up 2 weeks later	• Visual acuity 20/40 (+2) OD • Right rAPD • Fundoscopic exam with disc pallor without edema • MOG antibody returned positive (1:40) • Prednisone tapered over ~7 weeks • Relapse prevention discussed but not initiated

Relapsing optic neuritis

- Higher rates of relapse of optic neuritis with MOGAD compared to MS or other optic neuritis in pediatric patients
- Relapses typically very steroid-responsive or steroid-dependent (often meet criteria for chronic relapsing inflammatory optic neuropathy (CRION))
- Typically longer time to first relapse than other MOGAD phenotypes in children

Longbrake 2022

A 19 yo girl presents with several days of severe fatigue and intractable nausea/vomiting

- Discharged from outside ED several times with supportive management only

Brainstem syndromes

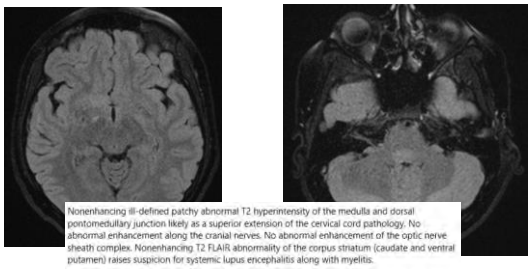
- Rarely observed (in isolation) in pediatric MOGAD (0-4%) (compared to 10-30% in adults)
- Can see area postrema syndrome but thought to be due to disruption of the anatomical connections to the vomiting center (rather than pure inflammation seen in AQP4-NMOSD)

Bruijstens et al. 2020

A 19 yo girl with recent onset intractable nausea/vomiting presents with several days of urinary retention and bilateral lower extremity weakness

- Exam with "mild weakness of the arms and legs." Normal reflexes.
- LP performed due to concern for AIDP. CSF with elevated protein (85), otherwise 0 WBC and normal glucose.

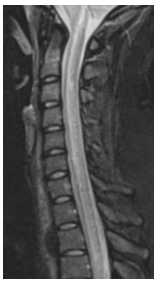
MRI Brain W/W/O



Nonenhancing ill-defined patchy abnormal T2 hyperintensity of the medulla and dorsal pontomedullary junction likely as a superior extension of the cervical cord pathology. No abnormal enhancement along the cranial nerves. No abnormal enhancement of the optic nerve sheath complex. Nonenhancing T2 FLAIR abnormality of the corpus striatum (caudate and ventral putamen) raises suspicion for systemic lupus encephalitis along with myelitis.

MRI Cervical and Thoracic W/W/O

1. Longitudinally extensive patchy central T2 hyperintensity throughout the cervical and upper thoracic cord with ill-defined subtle peripheral, lateral column enhancement and diffuse cord swelling. Postcontrast images are moderately degraded by motion artifacts. Differential consideration includes infectious/viral myelitis (including HTLV-1 myelitis and acute flaccid myelitis), inflammatory myelitis (including anticardiolipin myelitis) or atypical idiopathic transverse myelitis. Overall pattern less typical for sarcoidosis myelopathy. On the MRI of the brain, nonenhancing T2 FLAIR abnormality of the corpus striatum (caudate and ventral putamen) raises suspicion for systemic lupus encephalitis and myelitis.
2. Mild multilevel degenerative changes as detailed above.

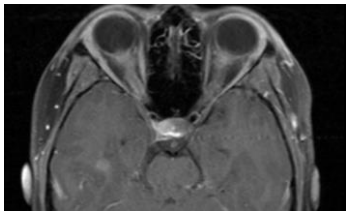


A 19 yo girl with **brainstem syndrome** and **longitudinally extensive myelitis**

Workup:	Treatment	Follow-up:
• Repeat CSF: 241 WBC (diff not available), 36 RBC, protein 51, IgG index 0.50 (normal), cytology negative	• 1 g IV Solumedrol for 5 days • Discharged on Medrol dose pack	• MOG pending at time of discharge to IPR (returned positive) • Required walker to ambulate upon IPR discharge and had neurogenic bladder

A 19 yo girl with **brainstem syndrome** and **longitudinally extensive myelitis** presents one week later with right eye pain and vision loss

MRI Brain and Orbits W/W/O



1. There are imaging findings consistent with active, right-sided optic neuritis.
2. No definite abnormal T2 hyperintensity or enhancement is seen in the left optic nerve.

A 19 yo girl with history of longitudinally extensive myelitis and **new right optic neuritis**

- Treatment
  - 1 g IV Solumedrol for 3 days
- Follow-up:
  - Developed left eye pain ~2-3 weeks later
  - MRI Brain and Orbits W/W/O now with bilateral findings in optic nerve
  - Received another course of IV Solumedrol
  - Maintained on 50 mg prednisone daily until Rituximab started for relapse prevention
  - Prednisone tapered but subjective worsening when prednisone tapered below 10 mg
  - OCT with progressive thinning bilaterally

NMOSD-like phenotype

- Simultaneous ON and TM (including LETM)
- AQP4 antibodies rare in children (3-6% of those with acute demyelinating syndromes and 11% of NMOSD)
- MOG antibodies are found in 56% of pediatric patients with NMOSD phenotype
- Relapsing forms can present with isolated optic neuritis episodes or simultaneous ON and (LE)TM
- Only half of MOG positive pediatric forms of NMOSD (fulfilling Wingerchuk diagnostic criteria) or limited forms of NMOSD relapse (compared to 100% of AQP4)

Bruijstens et al. 2020

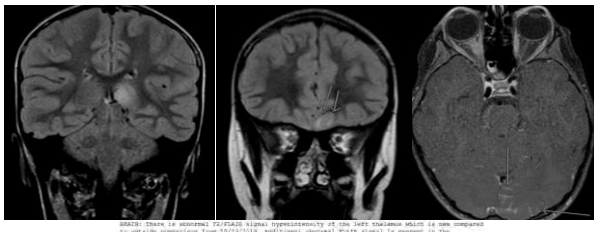
A 6 yo girl presents with new right eye vision loss and pain and is found to have optic neuritis in the setting of **several months of focal neurologic symptoms**

Exam with visual acuity 20/200 OD and grade 1 edema

Further history notes:

- 3 months of right-sided facial pain
- Transient alteration of awareness that was prolonged at times and episodes of sustained left wrist flexion
- EEG noted right hemispheric focal slowing and ultimaltely diagnosed with focal seizures (now responsive to leviteracetam)

MRI Brain W/W/O



BRAIN: There is abnormal T2/FLAIR signal hyperintensity of the left thalamus which is new compared to certain comparison from 10/25/2019. Additional abnormal FLAIR signal is present in the juxtacortical white matter of the medial right parietal lobe (coronal FLAIR series 12 image 24) and juxt cortical white matter of the inferomedial, left frontal lobe (image 9), and anterior medial portions of the right frontal lobe (images 5, 7). There is abnormal leptomeningeal enhancement within left occipital sulci (series 14 image 12), and involving the medial right parietal lobe in the region of parenchymal T2 signal abnormality (series 14 image 17). No evidence of hemorrhage or acute infarction. The ventricles are normal in size and morphology.

A 6 yo girl presents with new right optic neuritis is found to have findings of **encephalitis** on imaging

Workup	Treatment	Follow-up
• CSF with 20 WBC (8% PMNs) and 97 RBC. Protein and glucose normal. IgG index 0.75 (elevated). Negative OCBs.	• 5 days IV Solumedrol (30 mg/kg/day) • Discharged on prednisone taper over 7 weeks	• MOG returned positive (1:1000) • Vision improved to 20/20 by 6 months • No further clinical events • Relapse prevention not started

Atypical and emerging phenotypes

- Encephalitis (focal and atypical)
- Leukodystrophy-like
- "CLIPPERS" phenotype
- Combined central and peripheral demyelination

Bruijstens et al. 2020
Longbrake 2022

Atypical and Emerging Phenotypes: Encephalitis

FLAMES (focal encephalitis)

- FLAIR-hyperintense lesions in anti-MOG-associated encephalitis with seizures
- Decreased consciousness, seizures, and focal weakness
- MRI with hyperintense cortical FLAIR abnormalities (usually unilateral) and may have corresponding leptomeningeal enhancement

Atypical Encephalitis

- presenting with altered consciousness, seizures, or brainstem syndrome
- not meeting ADEM or FLAMES criteria
- MRI findings can include bilateral cortical abnormalities and/or isolated deep grey matter (thalamic or basal ganglia)
- Some may have minimal MRI changes despite severe phenotypes including refractory status epilepticus

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Atypical and emerging phenotypes: Leukodystrophy-like

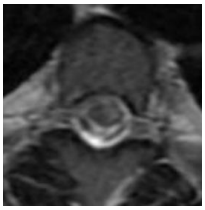
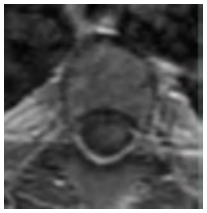
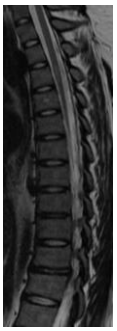
- Initial presentation can be consistent with ADEM phenotype
- Poor recovery from initial event with progressive disability
- MRI suggestive of a genetic leukodystrophy
- Can be stabilized by immunotherapy

Bruijstens et al. 2020
Longbrake 2022

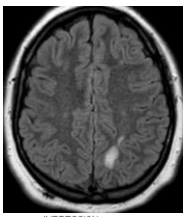
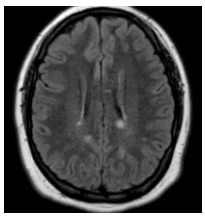
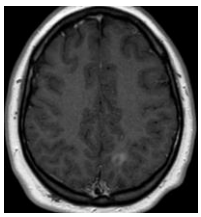
15 yo girl presents with 1 week of paresthesias on the right side below the chest several days following a GI illness

- Sensation: impaired to all modalities on the right, T3 sensory level

MRI Thoracic W/W/O

MRI Brain W/W/O

IMPRESSION:

Numerous T2/FLAIR hyperintense brain lesions, including lesions involving juxtacortical white matter, periventricular white matter and in the spinal cord, some with incomplete ring enhancement, and others with no enhancement. Findings meet the revised radiographic McDonald criteria for dissemination in both time and space.

15 yo girl with transverse myelitis and periventricular and juxtacortical brain lesions

Workup:	Treatment:	Follow-up:
• NMO negative • MOG positive; low titer (1:20) • CSF not obtained	• 1 g IV Solumedrol for 3 days	• Diagnosed with RRMS and started on oral DMT (switched to Ocrevus due to issues with compliance and new lesions)

MOG Antibodies and MS

- One study of pediatric acute demyelinating conditions found positive MOG antibodies in 8% of children with MS
- Low titers of MOG (1:20-1:40) aren't specific for MOGAD when MS is suspected
- Possible spectrum (classic MOGAD on one end and MS without MOG antibodies on the other, with low titer MOG and MS somewhere in the middle)
- MS overrepresented in cases of false positive results (clinicians should be dissuaded from ordering MOG testing in classic MS presentations)

Hennes et al. 2017
Sechi et al. 2021
Levy et al. 2022

Acute treatment is similar to other demyelinating syndromes

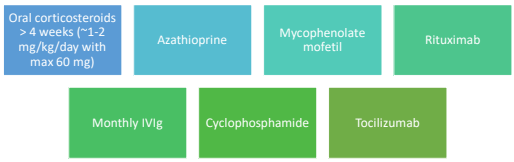
- IV methylprednisolone for 3-5 days (~20-30 mg/kg/day)
- IVIg
- Plasma exchange

Long-term maintenance treatment to prevent relapses comes from cohort studies

- No completed RCTs
- Most studies report different treatment outcomes which limits guidance
- Many off-label treatments help (ARR is reduced), but many patients still relapse (20-75%)
- DMTs approved for MS are strongly discouraged due to lack of efficacy and potential worsening
- European Union pediatric MOG consortium suggest waiting to initiate relapse prevention until the second clinical attack (first relapse)

Klein da Costa et al. 2021
Longbrake 2022

Long-term maintenance treatment to prevent relapses comes from cohort studies



Monitoring: Imaging in MOGAD

- Less likely to have subclinical disease activity (screening MRI not as important or recommended)
- Can see asymptomatic lesions on MRI during first few months after initial attack that are not always predictive of future relapsing disease

Longbrake 2022

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CNS Vasculitis: Case Based Review

Vicky L. Chen, MD
OHSU Department of Neurology / Portland VA Medical Center

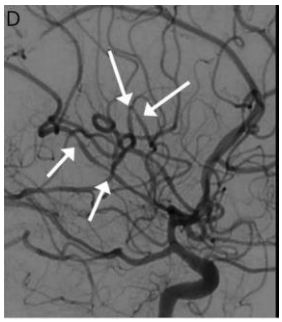
Overview

- Background
- Diagnostic Criteria
- Clinical features
- Labs/Imaging
- Histopathology
- Treatment
- Mimics

23-year-old right-handed man presented to the hospital with acute onset of left hemiparesis, numbness, and dysarthria. CT head showed a right frontal IPH.

- 4 months ago presented with GTC to OSH, CT showed right parietal IPH. MRI brain WWO multiple microhemorrhages in deep white matter, leptomeningeal enhancement of the right parietal lobe, and parenchymal enhancement right temporal lobe. DCA with multifocal narrowing in the right MCA.

- DCA –subtle areas of multifocal narrowing in the right MCA



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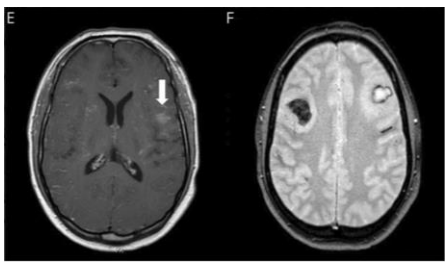
- 2 months later: acute onset word finding difficulties and headache in setting of left frontal IPH. Repeat angiogram with resolution of prior segmental vessel narrowing. Diagnosed with RCVS precipitated by daily cannabis use.
- 4 months later: left sided weakness and dysarthria. MRI with multiple areas of superficial and deep microhemorrhage. Multiple curvilinear areas of contrast enhancement.



T1 post contrast: left frontal and diffuse leptomeningeal enhancement
T2* weighted image: multiple hemorrhages of different ages in right and left frontal lobes

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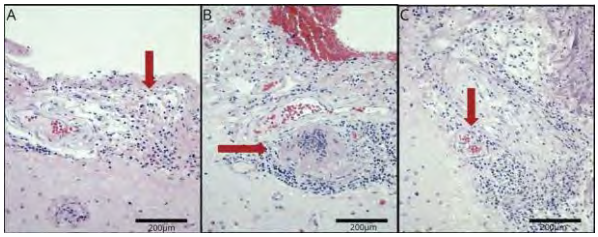
LP: R 3000/WBC 67 (94% lymph)/P 94, OCB +3,

ESR, CRP, ANCA, ANA, Hep b/c, HIV, RPR, HSV, quant gold negative

CT C/a/p with contrast normal.

Biopsy: small vessel inflammation consistent with a chronic and active vasculitis. Focal granuloma formation with associated Leptomeningitis and cerebritis. AFB, funal, and bacterial cultures had no growth. 15s ribosomal RNA infection panel was negative. Bacterial PCR negative.



- (A) Leptomeningeal surface with diffuse mononuclear infiltrate (arrow, upper portion of figure) extending into superficial cortex (lower portion of figure).
- (B) Leptomeningeal vascular and perivascular inflammation with focal granuloma formation (arrow).
- (C) Some leptomeningeal vessels show complete obliteration with fibrotic lumens and transmural inflammation (arrow).

Treatment

- Induction:
  - 1g IV methylprednisolone IV x5 days with
  - cyclophosphamide 600g/m2 monthly x6 doses
- Maintenance:
  - oral prednisone taper x5 weeks.
  - Azathioprine

PACNS

- 2.4/1 million person-years
- Medium and small vessels
- CNS (brain and spinal cord)
- Challenging to diagnose

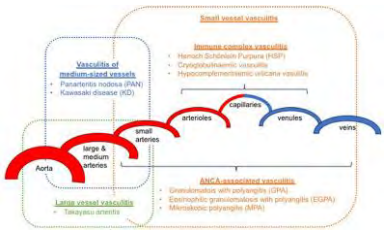


Image credit: Schnabel A, Hedrich CM. Childhood Vasculitis. Front Pediatr. 2019 Jan 10;6:421. doi: 10.3389/fped.2018.00421. PMID: 30687686; PMCID: PMC6335362.

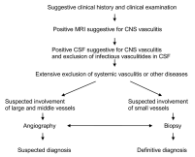
Diagnostic Criteria

1) Unexplained neurologic deficit
2) Classic findings of CNS vasculitis on angiogram **or** histopathology
3) No evidence of a systemic vasculitis or any other condition

Findings consistent with PACNS on: angiogram, MRI, **and** CSF Biopsy Confirmed?

Yes ↙ ↘ No

Definite PACNS **Probable** PACNS



Calabrese and Mallek
1988

2009
Birnbaum and Helman

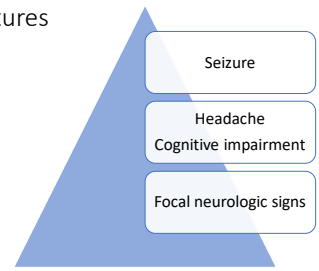
Berlit and Kramer
2021

Cleveland Clinic | Johns Hopkins University

PACNS: Clinical Features

- M>F
- Mean age 42 yo
- Onset: insidious/progressive

Red flags: signs of systemic disease
- B-symptoms
- Rash
- Abdominal pain
- Arthritis/arthralgia
- Myalgias
- Renal disease (proteinuria, hematuria)
- Ulcers
- Sinusitis



CSF

- Abnormal in ~2/3 patients
- 47% CSF pleocytosis
- **Takeaway: although included in 2009 updated criteria…**
  - CSF is not sensitive or specific for PACNS
  - may be normal in 1/3 of patients

Radiographic Features

- MRI
  - Nonspecific T2 lesions
  - Leptomeningeal and/or parenchymal contrast enhancement
  - Mass lesions
  - infarcts
- Vessel Imaging:
  - Alternating vascular stenosis/dilation (beads on a string)
  - Vessel wall enhancement (MRI Vasculitis Protocol)

Diagnostic Cerebral Angiography

- Limited sensitivity 50-90%
- Lacks resolution for small vessel PACNS

MRI Vasculitis Protocol

- "Black blood imaging": high resolution, contrast enhanced, compensated and fat saturated MRI of the blood vessel walls
- Vessel wall enhancement
  - Frequent in large/medium vessel PACNS
  - Infrequent in small vessel PACNS
- Not specific to vasculitis (see next slide)
- Distinguishing features
  - concentric vessel wall thickening and enhancement (vs. eccentric plaque enhancement in atherosclerosis)
- Use as biomarker for treatment response is unclear
  - Resolution/improvement of VWE associated with lower rate of relapse
  - Radiographic progression associated with higher rate of relapse
  - Persistent VWE seen in both stable and relapsing vases
  - **Takeaway**: resolution/improvement generally reassuring, progression is a bad sign, persistence is common and not helpful

Vasculopathies with VWE

Primary angiitis of the central nervous system	Infectious vasculopathies
	Viral infections (e.g. VZV, HSV, HIV, SARS-CoV 2)
CNS vasculitis as part of a primary systemic vasculitis	
Giant cell arteritis	Basal meningitis caused by tuberculosis or fungal infections
ANCA-associated vasculitides	Bacterial infection (e.g. borreliosis, lues)
Systemic autoimmune and rheumatic diseases	Radiation-induced vasculopathy
Neurosarcoidosis	Noninflammatory vasculopathies
Neuro-Behcet	RCVS
Systemic Lupus erythematodes	Atherosclerosis
Systemic sclerosis	
Other autoimmune diseases	CADASIL
Susac syndrome	Moyamuya angiopathy
Cryopyrin-associated periodic syndrome	Metabolic diseases
	Fabry disease
	Malignant diseases
	Vascular lymphoma

Biopsy

- Yield
  - Segmental/skipping pattern along vessels -> sampling error
  - Sensitivity may be <50%
- Targets: cortex and leptomeninges
- Histopathology
  - Granulomatous vasculitis > lymphocytic vasculitis > necrotizing vasculitis
- Biopsy is imperfect but important diagnostic tool
  - There is a reasonable false negative rate
  - There is a reasonable ~30-50% identify a cause other than PACNS

PACNS Subtypes

	Small Vessel PACNS	**Medium Vessel PACNS**
Clinical Presentation	Cognitive impairment Seizures	Focal neurologic symptoms
MRI Features	Meningeal and parenchymal contrast enhancement	Ischemic infarction
Angiography consistent with vasculitis?	+	+++
Biopsy consistent with vasculitis?	+	-
+Vessel Wall Enhancement	-	+

Relapse Rates

- 1/3 relapse during the first years after diagnosis
- Mortality after diagnosis is up to 1/4

Treatment

- No prospective randomized studies exist
- Induction
  - IV glucocorticoids
  - IV Cyclophosphamide: median dosing 1g monthly x6 months
  - Other: oral cyclosphosphamide x 6-10 months, azathioprine, mycophenolate, rituximab, methotrexate, IVIG, infliximab, PLEX
- Maintenance
  - Oral glucocorticoids: gradual taper
  - Immunosuppression: azathioprine, mycophenolate, methotrexate, rituximab*
  - *pts with disease resistant to conventional immunotherapy then treated with rituximab were found to have improvement of neuro findings, imaging, and reduction of relapses.

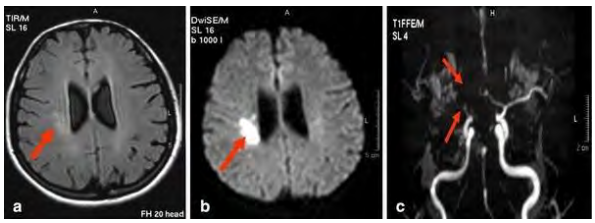
Case Quickfire

- Thunderclap headache
- Mini chocolate chips
- B-symptoms
- Snowballs

Case: thunderclap headache!

37 year old woman with depression who presents to the ER screaming in pain with worst headache of her life. Onset is hyper-acute, occurred while folding her laundry, duration x12 hours

- Medications: mirena IUD, sertraline
- Exam: left lower facial paralysis
- CT Head and CSF normal
- MRI/A Head WWO: acute ischemia within the right centrum semiovale, multiple stenotic segments in both anterior and posterior circulations.



A) FLAIR
B) DWI - acute ischemia within the right centrum semiovale
C) MRA with stenotic segments both in anterior and posterior circulations particularly in the right arteria cerebri media

(a different case… but good example of reversible vasoconstriction)

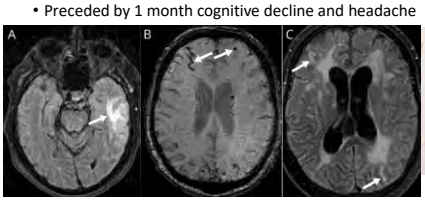
RCVS

- Thunderclap headache
- Reversible vasoconstriction
- Identifiable trigger
- Improves with removal of trigger and CCB
- VWE: none or mild/moderate enhancement

Case: Mini chocolate chips

73-year-old man presented with sudden right-sided weakness, aphasia, and low-grade headache

- Preceded by 1 month cognitive decline and headache



Case: Mini chocolate chips

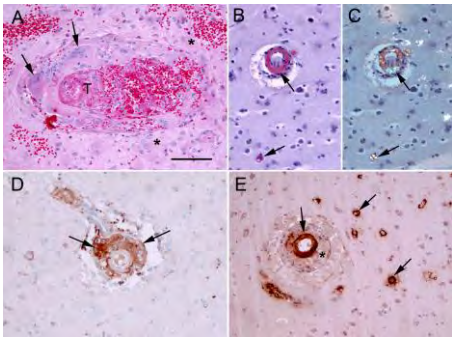
- Vessel imaging was normal
- Symptoms resolved within 24 hours
- 3 weeks later a second episode of aphasia and right sided weakness occurred, resolving within hours
- Serum studies normal: ESR, CRP, ANA, ANCA, HIV, RPR
- CSF: Protein **187**. WBC, RBC, normal. No OCB.
- biopsy…

Typical Findings
-transmural infiltration of vessel walls by lymphocytes and macrophages

Formation of granuloma and multinucleated giant cells

Background of cerebral amyloid angiopathy

IHC stains show A beta in vessel walls, CD68+ macrophages



Cerebral Amyloid Angiopathy (CAA) related inflammation

- Reversible inflammatory vasculopathy as reaction to amyloid deposition in CNS vessels
- 2 forms:
  - Aβ-related angiitis (ABRA): vessel wall inflammation
  - CAA-related inflammation (CAAri): perivascular inflammation without vessel wall involvement
- Responds to steroids and immunotherapy


Seminars in Arthritis and Rheumatism

Amyloid Beta-Related Angiitis—A Case Report and Comprehensive Review of Literature of 94 Cases

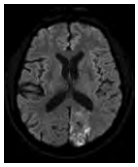
Cerebral Amyloid Angiopathy (CAA) related inflammation

- resembles PACNS: involves small and medium leptomeningeal and superficial cortical arteries
- Usually in older adults age >40
- CSF: protein typically elevated, may have some pleocytosis
- Angiography usually normal
- MRI: **microhemorrhages**, lobar/confluent WM lesions involving U fibers, +/- leptomeningeal enhancement
- Histopathology
  - **ABRA**: histologically identical to granulomatous subtype of PACNS + amyloid deposits
  - **CAAri**: amyloid deposits + perivascular lymphocytic inflammation
- Most cases monophasic after tx, ¼ may relapse
- Treatment: steroids +/- cyclophosphamide + other steroid sparing agent

Case: B symptoms

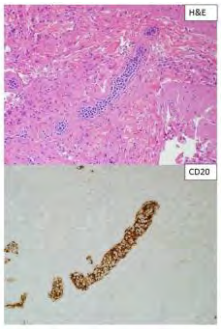
- 68-year-old man, was admitted for homonymous hemianopsia, headaches and subacute progressive cognitive decline.
- Past 8 months word finding difficulty and forgetfulness
- Exam: RHH otherwise nonfocal
- ROS: weight loss, malaise
- Serum CRP 92 (H) ESR 110 (H)

- MRI Brain: patchy acute infarction involving the left occipital lobe, left occipital cortex, a remote right frontal cortical infarct and scattered chronic appearing cortical infarcts most in the right parietal cortex.
- MRA Head: bilateral scattered areas of mild vascular narrowing of the M2 and M3 branches of the middle cerebral artery. Large vessels were normal.
- DCA: evidence of diffuse tapering in the mid to distal distribution of multiple vessels.



Intravascular Lymphoma

- CSF: Protein 103, otherwise normal
- Biopsy: Consistent with intravascular lymphoma.
- H&E stain showed brain parenchyma and several small blood vessels with intravascular infiltrates of large atypical lymphoid cells with vesicular chromatin and prominent nucleoli. CD20 immunohistochemical stain showed that the intravascular large lymphoid cells represent CD20 positive B-lymphocytes.

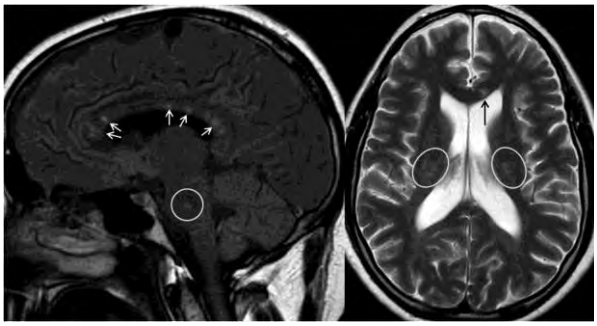


Intravascular lymphoma

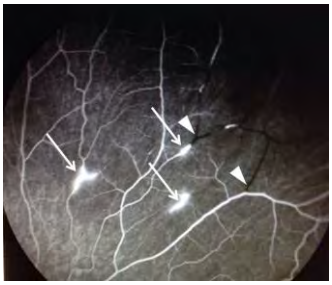
- Often represents disseminated disease (can have skin involvement)
- Represents luminal proliferation of lymphoid cells (capillaries and medium sized vessels)
- Clinical presentation can vary
  - Focal neurologic symptoms due to multifocal infarcts
  - Can also present with progressive symptoms: cognitive impairment, headache
  - Constitutional symptoms are common (fever, malaise, weight loss)
  - Acute phase reactants are elevated
- Requires biopsy for diagnosis

Susac Syndrome

- 27 year old woman with 1 week headache, tearfulness, difficulty speaking and nonspecific cognitive complaints.
- 2 years prior had episode of monocular vision loss of left eye (superonasal quadrant)
- Exam: Delayed processing speed, stuttering slowed speech without aphasia, vision: patchy VF deficits od, DTRs 3+ throughout.



- Retinal Fluoroscein Angiography: multiple **branch retinal artery occlusions**
- Audiometry: mild sensorineural hearing loss L>R ears



Susac Syndrome

- Immune mediated microvascular endotheliopathy
- Involves CNS, inner ear, and retina
- MRI: snowball lesions of corpus callosum, can also have leptomeningeal enhancement.
- Angiography: normal
- Histology: perivasascular and or/leptomeningeal infiltrates, arteriolar wall thickening, or normal.
- Systemic findings: livedo reticularis

2016 EuSaC Criteria

- *Definite SuS*: Patients with an unequivocal clinical and/or paraclinical involvement of all three main organs (ie, fulfilling the typical clinical triad).
- *Probable SuS*: Patients with an unequivocal clinical and/or paraclinical involvement of two of the three main organs.

Organ	Clinical	Paraclinical
Brain	New cognitive impairment and/or Behavioral changes and/or New headache	MRI Brain with typical findings: hyperintense, multifocal, round, small lesions. At least 1 in the corpus callosum ('snowball') in T2/FLAIR
Retina	Not required	BRAOs or arterial wall hyperfluorescence on fluorescein angiography or characteristic sign of retinal branch ischemia on funduscopy or SD-OCT
Vestibulocochlear	New tinnitus and/or Hearing loss and/or Peripheral vertigo	Hearing loss must be supported by audiogram Vestibular vertigo must be supported by caloric testing of the vestibular organ

PACNS has a broad differential

- Non inflammatory vasculopathy: RCVS, PRES
- Inflammatory vasculopathies: CAA inflammation, Susac Syndrome
- Malignancy: intravascular lymphoma
- Secondary vasculitis (not discussed in depth here… thus important to involve rheumatology and infectious disease colleagues)


Differential diagnosis of PACNS.

- Systemic vasculitides: Behçet's syndrome, polyarteritis nodosa, granulomatosis with polyangiitis (Wegener), EGPA (Churg Strauss), Urticarial hypocomplementemic vasculitis, Cogan's syndrome.
- Systemic inflammatory diseases: systemic lupus erythematosis, Sjögren's syndrome, Crohn's disease, sarcoid granulomatosis and angiitis.
- Infections: viral (e.g. herpes zoster, HIV), bacterial (e.g. tuberculosis, syphilis, neuroborreliosis), fungal (e.g. aspergillosis, nocardiosis, cryptococcus, histoplasmosis).
- Conditions with cerebral angiographic abnormalities: reversible cerebral vasoconstriction syndrome, premature intracranial atherosclerosis, fibromuscular dysplasia, moyamoya disease and syndrome, small-vessel arterial dissection, angiotropic and intravascular lymphoproliferative disorders, radiation vasculopathy.
- Brain diseases with MRI lesions that can mimic PACNS: brain neoplasms, e.g. intravascular lymphoma, gliomatosis cerebri, generic conditions, e.g. CADASIL, HERNS, COL4A1 mutation, posterior reversible encephalopathy syndrome, Susac syndrome, chronic hypertension ('microvascular cerebral ischemia'), demyelinating diseases: multiple sclerosis, acute disseminated encephalomyelitis, progressive multifocal leukoencephalopathy.
- Miscellaneous: hyperhomocysteinemia, thrombocytic purpura, porphyria, antiphospholipid antibody syndrome, Kohlmeier Degos.
- Conditions with multi-focal cerebral thrombo-embolism: atrial fibrillation and cholesterol atheroembolism, endocarditis, left atrial myxoma and other cardiac tumors.

Summary

- History is important (thunderclap headache, systemic symptoms)
- Angiography can be normal
- Biopsy is imperfect but critical diagnostic tool
- Vessel wall enhancement is not specific to vasculitis ☹
- PACNS likely represents multiple disorders
- Clinical/Radiographic presentation varies with vessels involved
  - Small vessel: HA, cognitive sxs, subacute/progressive onset, seizure, leptomeningeal enhancement, normal angio, biopsy positive
  - Medium vessel: Focal neuro sxs, ischemic strokes, acute onset, angio +, biopsy usually negative
- You may need to treat empirically

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Closing Remarks

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