Update in Immune Axonal Neuropathies

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Objectives

- Learn the different causes of immune axonal neuropathies
- Learn the diagnostic work-up of immune axonal neuropathies
- Learn the best evidence-based options for when and how to treat immune axonal neuropathies

Outline

- Introduction to immune axonal neuropathies
- Rapid recognition of immune mediated neuropathy
- Differential diagnosis
- Discussion of illustrative cases of immune axonal neuropathies with brief overview/updates in specific subtypes of immune axonal neuropathies
- Take home messages

Immune Axonal Neuropathies: Introduction

- A diverse group of peripheral neuropathies (PN) where the immune system directly or indirectly damages the nerve axons (in contrast to an immune attack on the myelin covering of nerves)
- These are important to recognize and treat early, otherwise there is irreversible axonal loss
- Can be difficult to recognize in comparison to immune demyelinating neuropathies, which are recognized by changes in nerve conduction(e.g. Chronic Immune Demyelinating Polyneuropathy)
- Untreated, advanced demyelinating PN can be difficult to differentiate from axonal PN

Immune Axonal Neuropathies

Associated with systemic disease

- Vasculitis (autoimmune, infectious, drug-related)
- Connective tissue disease (e.g. Sjogren)
- Sarcoid disease
- Caused by cancer (e.g. anti-HU syndrome)
- Celiac disease

Isolated to the nervous system

-Axonal form of Guillain-Barré Syndrome
-Diabetic amyotrophy
-Non diabetic immune plexopathy (post surgical, Parsonage Turner syndrome, Hereditary Neuralgic Amyotrophy)
-Multifocal acquired motor axonopathy

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Rapid recognition of immune mediated neuropathy

Research

Neurology® Clinical Practice

Rapid screening for inflammatory neuropathies by standardized clinical criteria

Chafic Karam, MD; Louis A. Tramontozzi III, MD

Neurol Clin Pract 2016;6:384-388

Danger signs in PN: ODS Criteria

- Onset-Develops quickly
- Distribution-Non length dependent
- Systemic features-Problems outside of nerves as well

Research
Neurology® Clinical Practice

Rapid screening for inflammatory neuropathies by standardized clinical criteria

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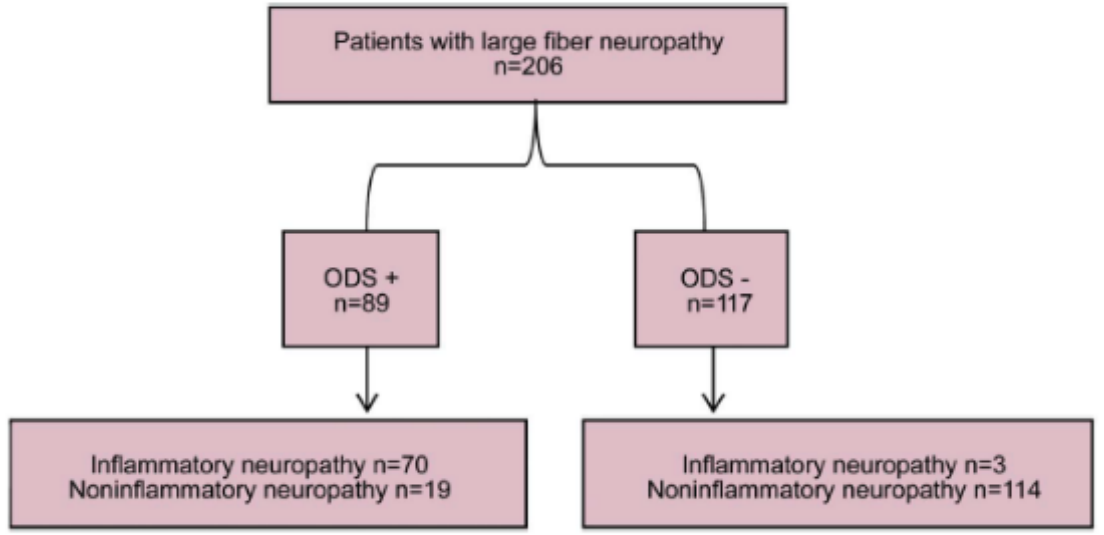
- ODS POSITIVE if any of these criteria are present

Figure Flow chart summarizing the study population



ODS = onset, distribution, and systemic features.

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Results

- ODS Sensitivity (detecting an inflammatory neuropathy) **96%**
- ODS Specificity **85%**
- ODS Positive Predictive Value **0.8**, Negative Predictive Value was **0.97**

Illustrative case 1: Use of ODS clinical criteria for autoimmune neuropathy screening

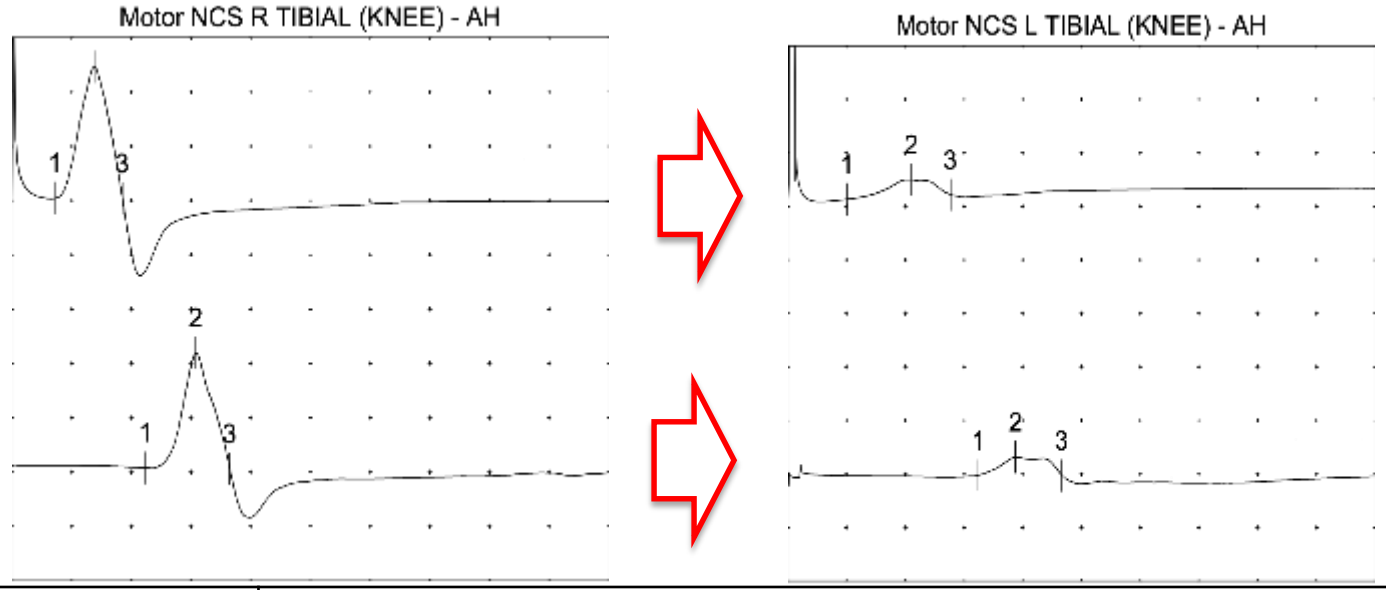
Illustrative Case #1: History

- 33-year-old man with **acute** left foot pain and weakness (Onset/Distribution)
- Episodes of **fever and sweating** (Systemic Symptoms)
- Testicular pain mistaken for torsion
- Muscle pain
- Abdominal pain
- Treated with minocycline for acne for 2years
- Sister has Rheumatoid Arthritis

- **This patient is ODS + due to acute onset and systemic symptoms**

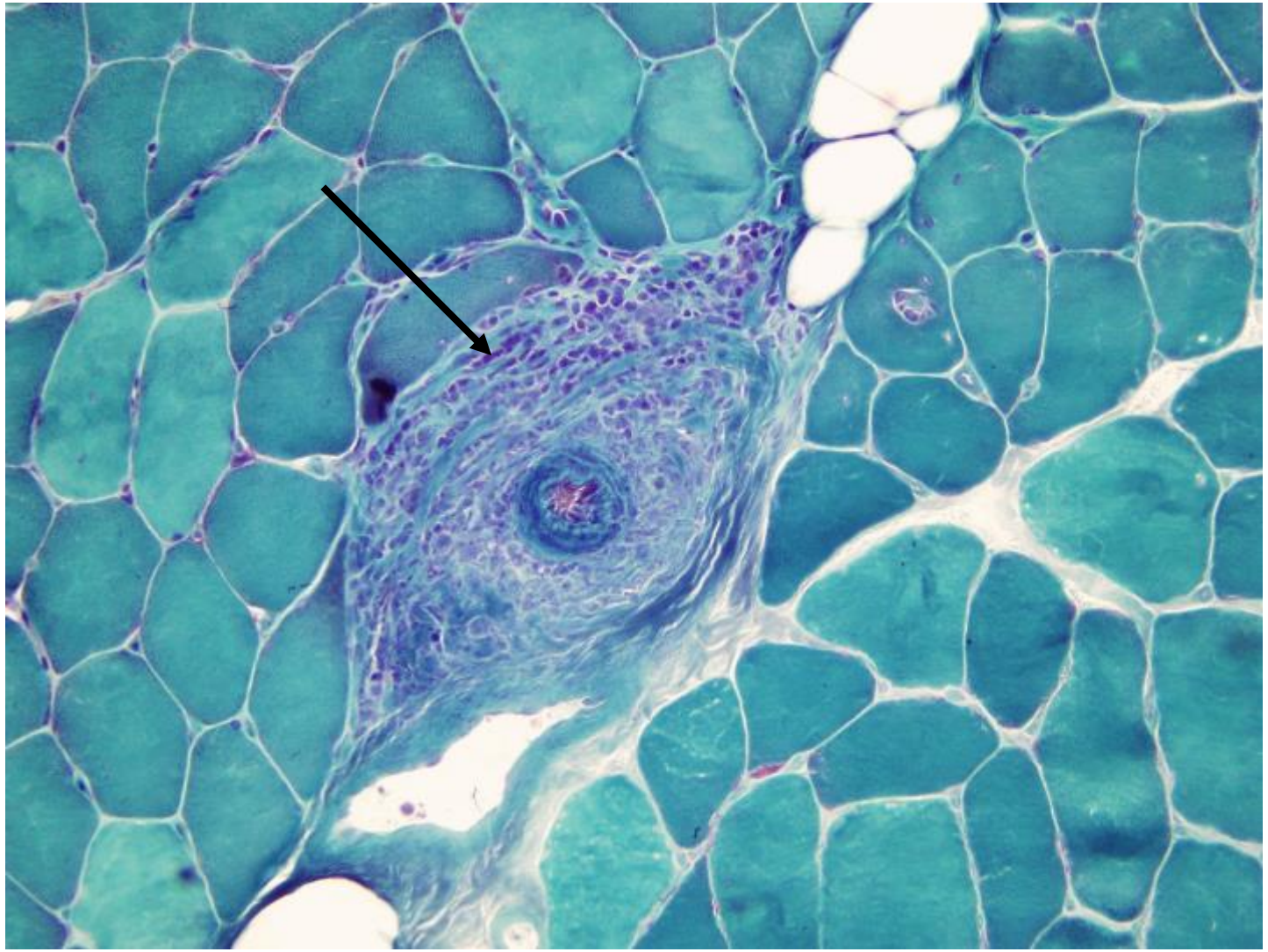
Illustrative Case #1: Exam and EMG

- Exam: left foot weakness in (in tibial nerve distribution) with sensory loss
- Electrical study of both tibial nerves shows that few nerve axons are firing on the left as compared to right nerve and some muscles contacted by tibial nerve have lost their incoming nerve signals



	Spontaneous					MUAP				Recruitment
	IA	Fib	PSW	Fasc	H.F.	Amp	Dur.	PPP	Stability	Pattern
L. TIB ANTERIOR	N	None	None	None	None	N	N	N	Stable	N
L. GASTROCN (MED)	N	1+	1+	1+	None	N	1+	1+	Stable	N
R. GASTROCN (MED)	N	None	None	None	None	N	N	N	Stable	N
L. VAST LATERALIS	N	None	None	None	None	N	N	N	Stable	N
L. BIC FEM (S HEAD)	N	None	None	None	None	N	N	N	Stable	N
L. TIB POSTERIOR	N	1+	2+	1+	None	1+	1+	1+	Stable	Reduced

Illustrative Case #1: Muscle Biopsy shows inflammation (arrow) around a blood vessel



Illustrative Case #1: Follow-up

- Most blood tests for potential causes (HBV and HCV, HIV, kidney function tests, ENA, CBC, LFTs, CK) were all normal or negative

- But blood test for vasculitis inflammation around blood vessels (Antineutrophil cytoplasmic antibodies (ANCA)) was positive perinuclear pattern
- Muscle biopsy confirmed inflammation around blood vessels (vasculitis), so treated with Cytoxan and prednisone to reduce inflammation
- Improvement of foot pain and resolution of weakness

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Vasculitic neuropathy following exposure to minocycline

OPEN

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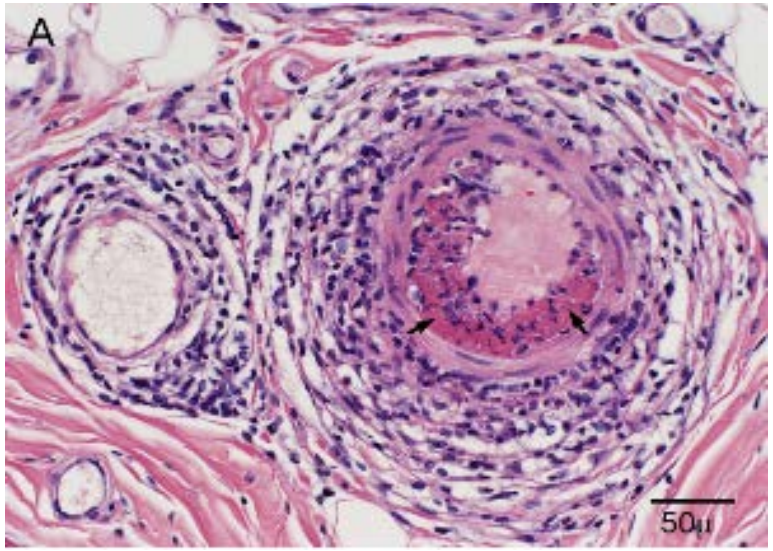
ABSTRACT

Objective: To report 3 patients with minocycline-induced autoimmunity resulting in peripheral nerve vasculitis.

Methods: We report 3 patients who, during minocycline treatment for acne vulgaris, developed subacute onset of pain and weakness caused by vasculitis in single and multiple mononeuropathy patterns.

Results: Each patient underwent either a nerve or muscle biopsy that confirmed vasculitis. One patient additionally developed systemic symptoms (including fever, fatigue, and night sweats) and another had a posterior circulation stroke. Symptoms developed with either early or prolonged use of minocycline. Despite withdrawal of minocycline, patients needed long-term immunotherapy to gain neurologic improvement.

Conclusions: Our findings suggest that the typical neuropathy associated with minocycline use is painful single or multiple mononeuropathy due to peripheral nerve vasculitis, which may also be accompanied by presumed CNS vasculitis (presenting as stroke). ***Neurol Neuroimmunol Neuroinflamm*** **2016;3:e180; doi: 10.1212/NXI.0000000000000180**



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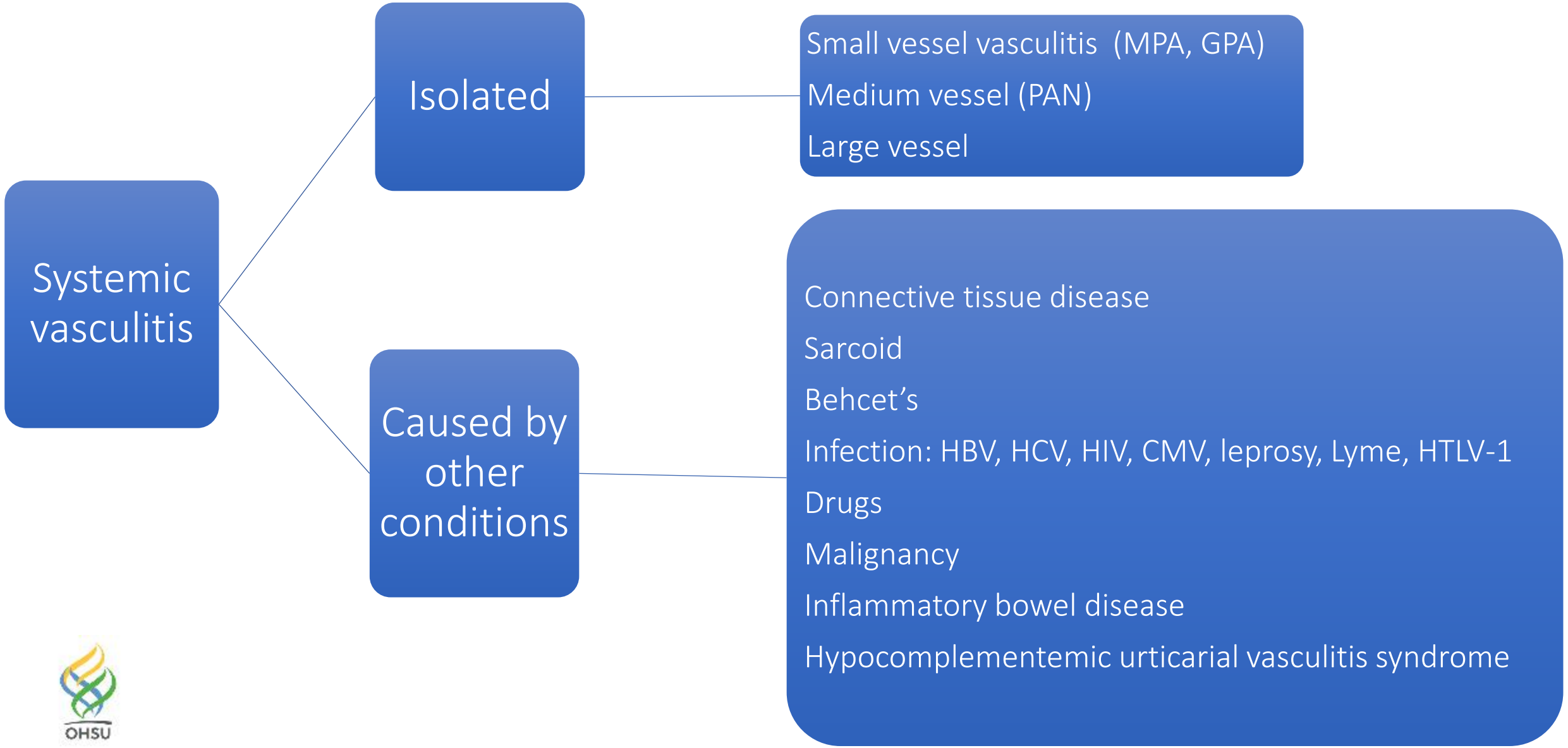
Updates in Vasculitic Neuropathy

Systemic Vasculitis: Overview



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ANCA Vasculitis-Related Peripheral Neuropathy

- Small blood vessels (arterioles, capillaries and venules)
- cANCA (PR3) → Granulomatosis with polyangiitis (Wegener's)
- pANCA (MPO) → Microscopic polyangiitis (MPA)
- ANCA PN
  - most common neurological complication in ANCA vasculitis
  - occurs in about 10-20% of patients
  - most common type is mononeuritis multiplex
  - Commonly first manifestation of the disease
  - 1/3 have complete resolution of neuropathy with appropriate treatment

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Rheumatology (Oxford). 2011 Dec;50(12):2214-22

Vasculitic PN: Typical Diagnostic Tests

- ANCA, cryoglobulin
- Rheumatological markers: ENA, ANA, RF
- Infectious diseases: HCV, HBV, HIV, Lyme
- Blood tests: CBC, SPEP/IFE, FLC
- Kidney function, Urine Analysis
- Inflammation markers: ESR, CRP, C3,4 levels
- CAT Scan chest (+/- Abdomen and pelvis) with contrast
- Nerve and muscle biopsy
- Brain MRI with contrast

Vasculitic PN: Utility of Nerve Conduction Study

- Important to determine the axonal nature of the neuropathy

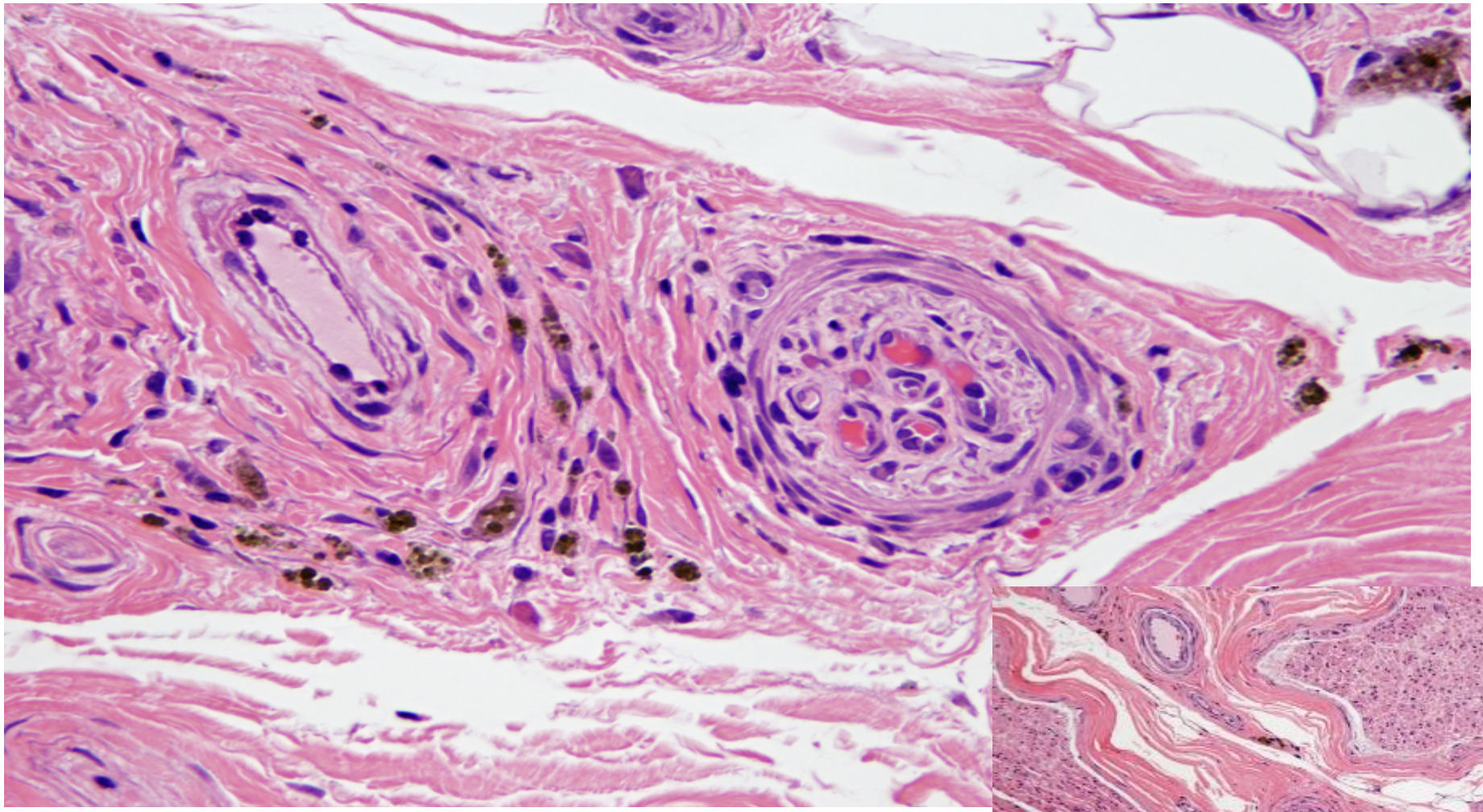
- Important to help show asymmetry
  - Will miss multifocal neuropathy if done on only one side, even in normal values
  - Severe, advanced vasculitic PN will eventually look symmetric

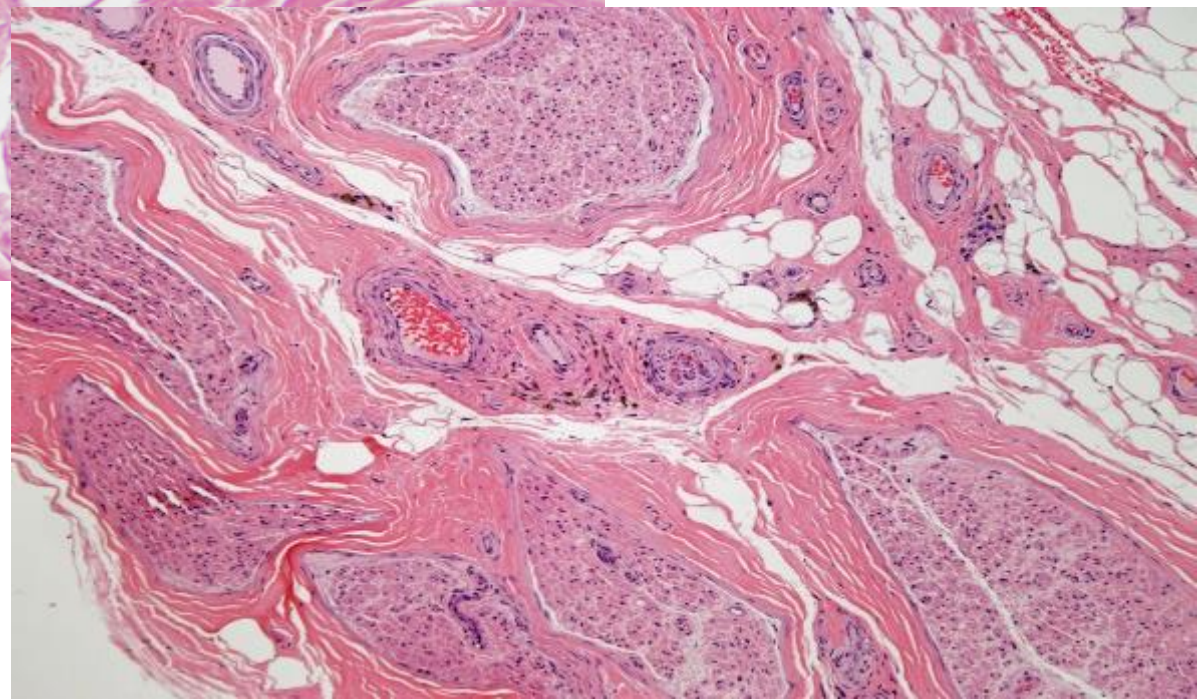
- Can help determine which nerve to biopsy

Vasculitic PN: Nerve biopsy

- Essential for diagnosis of peripheral nerve vasculitis
- Can be avoided if patient already has a biopsy proven (other organ) systemic vasculitis
- Sensitivity for definite vasculitis around 30-50%
- Nerve + Muscle biopsy increases sensitivity for definite vasculitis ~ 20%
- Nerve + Muscle Biopsy probable or definite vasculitis ~85% sensitive

Neurology. 2000 Sep 12;55(5):636-43





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ANCA Vasculitis-Related PN: Treatment

- Classic 3-drug treatment: Steroids (oral or IV) or Plasma Exchange + cyclophosphamide (oral or IV) + azathioprine oral
- Recent: Using rituximab instead of cyclophosphamide for induction and rituximab for maintenance instead of azathioprine
- Future: ? Use of avacopan, a complement 5a inhibitor instead of steroids for induction and potentially maintenance (phase III study ongoing)

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Non-ANCA Vasculitis-Related PN: Treatment

- Often similar to ANCA but some additional considerations

- Infectious vasculitis PN: Need to treat infection
  - HCV- Rituximab + interferon-α alone or combined with ribavirin

- Non-systemic vasculitic neuropathy (**NSVN**): may consider steroid monotherapy

Non-systemic Vasculitic Neuropathy (NSVN)

- No non-PNS organ involvement
- Serological markers usually negative
- Examples
  - Inflammatory neuropathy caused by surgery
    - Staff NP, Engelstad J, Klein CJ, Amrami KK, Spinner RJ, Dyck PJ, et al. Post-surgical inflammatory neuropathy. Brain. 2010;133(10):2866-2880.
  - Painful diabetic radiculoplexus neuropathy (cervical, thoracic or lumbosacral)
  - Painless diabetic radiculoplexus neuropathy
  - Non diabetic multifocal neuropathy

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Illustrative case 2: Post-surgical inflammatory neuropathy

- HISTORY
  - A 58-year-old man undergoing cardiac bypass surgery
  - 3 days after surgery he developed pain in his left shoulder and forearm, numbness and tingling in the left hand and weakness of his left hand and fingers.
  - Symptoms have progressed and weakness has become more profound. He also developed atrophy in his left forearm. He has been requiring opiates for the pain.

Illustrative case 2: Post-surgical inflammatory neuropathy

- EXAM
  - Severe weakness in the hand (movement only without gravity)
  - Deep tendon reflexes were normal
  - Reduced sensation in the left hand

- STUDIES
  - MRI Cervical spine and brachial plexus +/- contrast: Normal
  - EMG: multiple, severe, acute, axonal mononeuropathies in the left upper extremity.

Post-surgical inflammatory neuropathy

- Important to differentiate from mechanical neuropathies
- Typically develops within 30 days post procedure
- Patients present with acute pain and weakness
- Nerve conduction study shows an axonal focal or multifocal neuropathy (including plexopathy)
- No randomized control trial evidence, but since most will have increased epineurial perivascular lymphocytic inflammation, a treatment trial with steroids is justified

Brain. 2010 Oct;133(10):2866-80

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Updates on Management of Brachial Plexitis (Parsonage-Turner syndrome)

- No randomized control trials
- One large retrospective study
  - 50 treated patients (within 1 month of symptoms) vs 203 historical controls
  - 13-days oral prednisolone: 60 mg/day x 1 wk, tapered by 10 mg/day x 5 days, 5 mg on day 13

Table 2 Outcomes for the study (prednisolone) group (SG) and the historical controls (HC)

	Study group	Historical controls	
Median time (days) until initial pain relief (mean)	12.5 (17.1)	20.5 (37.2)	Not significant, $p = 0.13$
Recovery of strength within 1 month	9/50 (18.0%)	11/174 (6.3%)	$p = 0.011$
Full functional recovery within the first year	6/50 (12.0%)	2/189 (1.0%)	$p<0.001$
Good (but not full) self-reported recovery within			
6 months	16/50 (32%)	3/103 (2.9%)	$p<0.001$
12 months	22/50 (44.0%)	11/103 (10.7%)	$p<0.001$

JNNP 2009; 80:1120-1124

Updates in Axonal Guillain-Barré Syndrome variants

Illustrative case 3: GBS (Pharyngeal-cervical-brachial variant)

- 52-year-old diabetic woman with acute, progressive difficulty swallowing and speaking, upper extremity weakness and difficulty breathing

- HISTORY AND EXAM
  - Presented to outside emergency department for weakness and difficulty breathing.
  - Within one week, she required a ventilator to breath, then transferred to our hospital
  - Called the next day because of severe weakness in UE, face and neck
  - Normal strength in legs
  - Absent reflexes

Illustrative case 3: GBS (Pharyngeal-cervical-brachial variant)

- TESTING
  - MRI brain + c spine w/o contrast: Normal
  - EMG :
    - ARMS→ Severe sensory motor polyradiculoneuropathy with absent motor responses
    - LEGS → Normal motor responses
  - LABS
    - CSF: RBC 2208/mm3; WBC 31/mm3, Protein 175mg/dL and glucose 62
    - Paraneoplastic panel: Slightly elevated antibodies to neuroal VGKC protein, with no LGi1 or CASPR2 abs
    - West Nile virus Ab: Negative
    - Ganglioside antibodies GD1b, GT1a, GQ1b: Negative

Illustrative case 3: GBS (Pharyngeal-cervical-brachial variant)

- MANAGEMENT
  - Treated with Intravenous Immunoglobulin (IVIG) (2 gms/kg)
  - Extubated 6 days later
  - Within 10 days, Deltoid strength went from 0/5→4+/5 and normal strength distally

Guillain Barre Syndrome

- Classic GBS
  - AIDP (Acute Inflammatory Demyelinating Polyneuropathy
- Other GBS Variants
  - AMAN (Acute motor axonal neuropathy)
  - AMSAN
  - Pharyngeal-cervical-brachial (PCB)
  - Acute Pharyngeal
  - Paraparetic (muscle weakness)
  - Bifacial weakness with paresthesia (abnormal skin sensations)

Miller Fisher Syndrome

- Classic MFS
  - Ataxia, eye muscle weakness, absence of normal muscle reflexes
- Other MFS Variants
  - Acute eye muscle weakness
  - Acute ataxic neuropathy
  - Acute eyelid drooping
  - Acute pupil dilation
  - Bickerstaff brainstem encephalitis
  - Acute ataxic sleepiness

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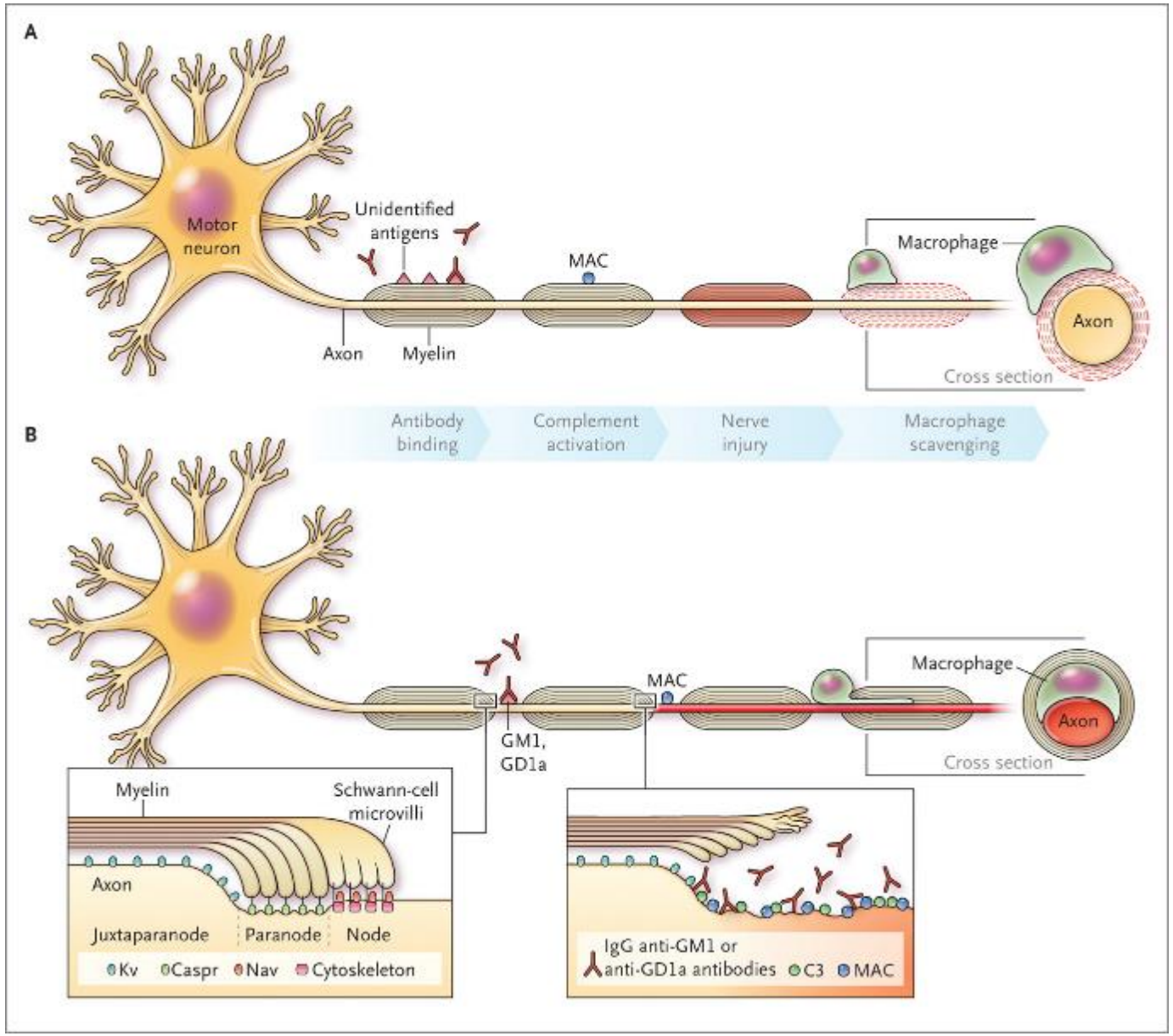
Nat. Rev. Neurol. 10, 537–544 (2014)



Yuki N, Hartung H. N Engl J Med 2012;366:2294-2304.

Gangliosides antibodies in GBS variants/MFS

	GM1	GD1A	GT1a	GQ1b	GD1b
AMAN	x	x			
AMSAN	x	x			
ASAN					x
PCB			x	x	
MFS			x	x	

Guillain-Barre Syndrome: General remarks

- This is a clinical diagnosis! Early in disease cerebrospinal fluid and nerve conduction tests may be normal
- Dynamic disease: One reassuring pulmonary function test early in the disease does not mean patient won't need to be intubated
- Deep tendon reflexes can be present very early in the disease
- 5% patient have weakness spreading in a descending pattern
- Pain is common
- 20–30% of patients develop respiratory failure and need ventilation at an intensive care unit
- 15% patient have a mild increase in cells in cerebrospinal fluid (5 to 50 cells/µl CSF)

Lancet 2016; 388: 717–27

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GBS general remarks

- 25% patients deteriorate during/shortly after treatment with IVIg or PE
- 10% patients relapse (“Treatment-Related Fluctuation” [TRF])
- 5% Mortality
- ~20% GBS patients cannot walk unaided 6 months after onset
- Most have residual pain and fatigue
- Most improvement happens in the first year, but some show further recovery even after 3 or more years.

Lancet 2016; 388: 717–27

Prediction of Respiratory Insufficiency in Guillain-Barré Syndrome

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Judith Drenthen, MD,[1] Rinske van Koningsveld, MD,[3]
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Ewout W. Steyerberg, PhD,[2] and Bart C. Jacobs, MD[1,5]

Objective: Respiratory insufficiency is a frequent and serious complication of the Guillain-Barré syndrome (GBS). We aimed to develop a simple but accurate model to predict the chance of respiratory insufficiency in the acute stage of the disease based on clinical characteristics available at hospital admission.

Methods: Mechanical ventilation (MV) in the first week of admission was used as an indicator of acute stage respiratory insufficiency. Prospectively collected data from a derivation cohort of 397 GBS patients were used to identify predictors of MV. A multivariate logistic regression model was validated in a separate cohort of 191 GBS patients. Model performance criteria comprised discrimination (area under receiver operating curve [AUC]) and calibration (graphically). A scoring system for clinical practice was constructed from the regression coefficients of the model in the combined cohorts.

Results: In the derivation cohort, 22% needed MV in the first week of admission. Days between onset of weakness and admission, Medical Research Council sum score, and presence of facial and/or bulbar weakness were the main predictors of MV. The prognostic model had a good discriminative ability (AUC, 0.84). In the validation cohort, 14% needed MV in the first week of admission, and both calibration and discriminative ability of the model were good (AUC, 0.82). The scoring system ranged from 0 to 7, with corresponding chances of respiratory insufficiency from 1 to 91%.

Interpretation: This model accurately predicts development of respiratory insufficiency within 1 week in patients with GBS, using clinical characteristics available at admission. After further validation, the model may assist in clinical decision making, for example, on patient transfer to an intensive care unit.

ANN NEUROL 2010;67:781–787

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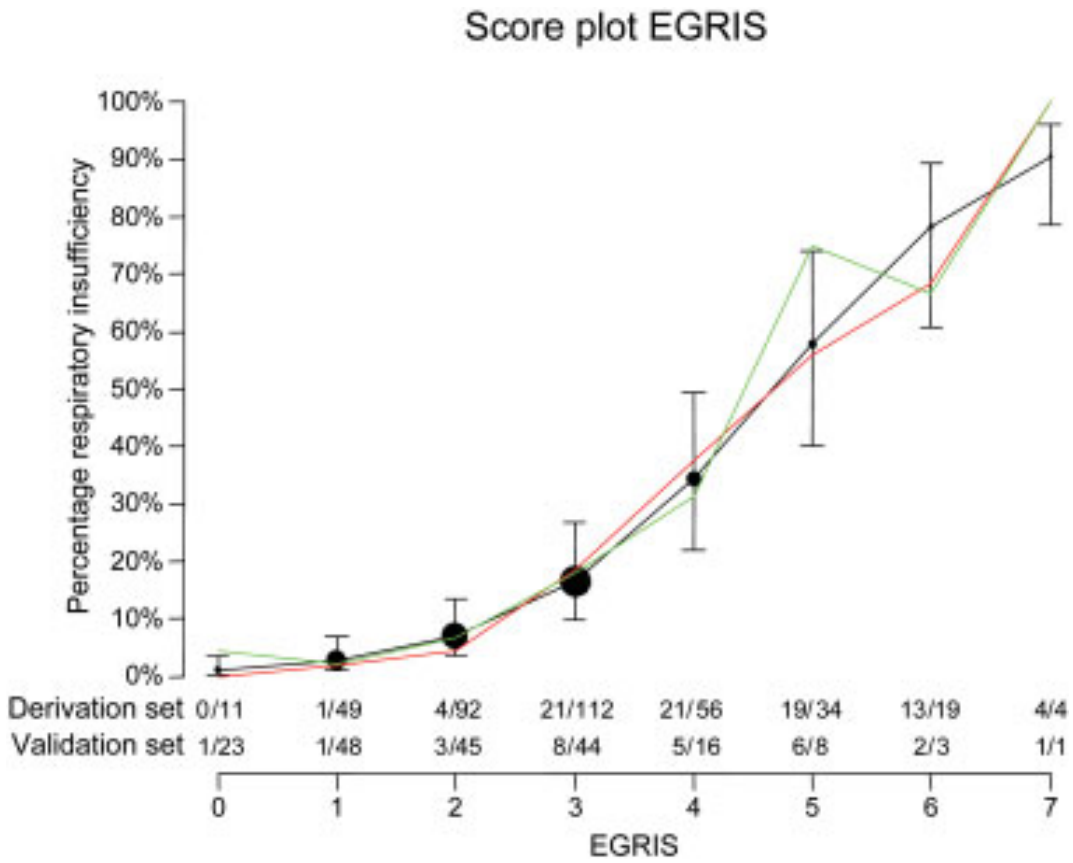
Prediction of Respiratory Insufficiency in Guillain-Barré Syndrome

TABLE 2: EGRIS

Measure	Categories	Score
Days between onset of weakness and hospital admission	>7 days	0
	4–7 days	1
	≤3 days	2
Facial and/or bulbar weakness at hospital admission	Absence	0
	Presence	1
MRC sum score at hospital admission	60–51	0
	50–41	1
	40–31	2
	30–21	3
	≤20	4
EGRIS		0–7

EGRIS = Erasmus GBS Respiratory Insufficiency Score; MRC = Medical Research Counsel.



MRC Sumscore= SA+EF+WE+HP+KE+DF (Bilateral)
Normal = 60, Quadriplegic = 0

TABLE 3: Risk Categories for Respiratory Insufficiency According to EGRIS

Category	Derivation Set	Validation Set	Combined Sets
Low risk (EGRIS 0-2)	5/152 (3%)	5/116 (4%)	10/268 (4%; 95% CI, 1–6%)
Intermediate risk (EGRIS 3–4)	42/168 (25%)	13/60 (22%)	55/228 (24%; 95% CI, 19–30%)
High risk (EGRIS 5–7)	36/57 (63%)	9/12 (75%)	45/69 (65%; 95% CI, 54–76%)
Total	83/377 (22%)	27/188 (14%)	110/565 (19%; 95% CI, 16–23%)

Probability of respiratory insufficiency in the first week of hospital admission in the derivation, validation, and combined sets stratified for EGRIS and expressed as number of mechanically ventilated patients/total number of patients (%). EGRIS = Erasmus GBS Respiratory Insufficiency Score; CI = confidence interval for combined sets.

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Management

- Equal efficacy of IVIg and plasmapheresis in terms of reducing the duration of mechanical ventilation, improving disability at 4 weeks, reducing residual disability and preventing death.
- No more benefit in doing plasma exchange then IVIG
- No benefit in giving corticosteroids
- In TRF, may repeat IVIG course
- **Prevent** deep vein thrombosis, dysautonomia and pain management
- **Prevent** bed sores and contractures

THE LANCET
Neurology

ARTICLES | VOLUME 17, ISSUE 6, P519-529, JUNE 01, 2018

Safety and efficacy of eculizumab in Guillain-Barré syndrome: a multicentre, double-blind, randomised phase 2 trial

Japanese Eculizumab Trial for GBS (JET-GBS) Study Group

- RCT: 34 pt, IVIg + either eculizumab (900 mg) or placebo (2:1)
- Week 4 Independent Ambulation (functional grade ≤2) :
  - Eculizumab group → 61% (90% CI 42–78; n=14)
  - Placebo group → 45% (90% CI 20–73; n=5)
  - Did NOT meet primary end point
- Week 24 Running: 74% Eculizumab vs. 18% in placebo
- AE: Eculizumab group → Anaphylaxis x1, intracranial hemorrhage x1
- Issues: Small number of patients, more severely affected than historical controls, IVIG may interfere with eculizumab

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Update in Paraneoplastic Neuropathy

Illustrative case 5: Paraneoplastic PN

Illustrative case 5: Paraneoplastic PN

- HISTORY
  - 62 y/o M with h/o DM, CKD, smoker who presented with 3.5 months of progressive painful dysesthesias.
  - Started with uncomfortable tingling in his right face that then progressed to numbness.
  - Developed feelings of burning and coldness that progressed from hands to shoulders, to elbows, to knees, to hips.
  - Multiple episodes daily of feeling like his skin is on fire, requiring a cool cloth, alternating with abruptly feeling freezing cold.

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Illustrative case 5: Paraneoplastic PN

- HISTORY CONTINUED
  - Endorsed 30lb unintentional weight loss, mild dry mouth, constipation, urinary changes, change in taste, early satiety and spasms in his hands.
  - Admitted to hospital and d/c with referral to psych for functional gait d/o
  - CT chest: New lung nodule from last year which was stable over 3 mos

This patient is ODS +

Illustrative case 5: Paraneoplastic PN

- EXAM
  - Loss of temperature, vibration in his extremities
  - Absent proprioception at the toes and impaired at the ankles
  - Pseudoathetosis
  - Ataxic gait with unsteady turns.
  - Diffusely areflexic
  - Normal strength

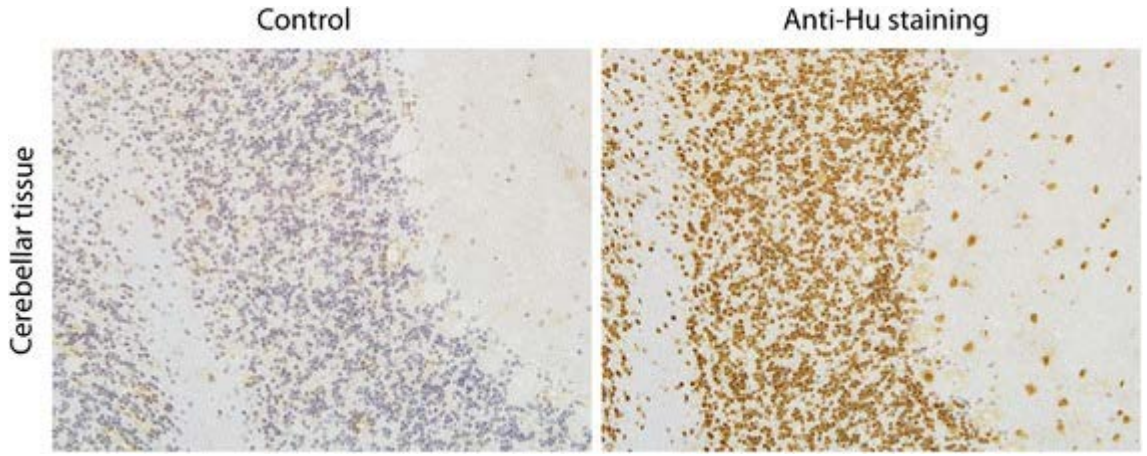
Illustrative case 5: Paraneoplastic PN

MNC								
Nerve	Latency		Amplitude		Conduction Velocity			Neg Area
	Onset Lat. ms	Normal ≤	mV	Normal ≥	Distance mm	m/s	Normal CV ≥	ms*mV
Fibular (Peroneal).R Extensor digitorum brevis.R								
Ankle	4.2	6.0	4.2	2.00	60			11.2
Fibula (head)	12.5		3.6		430	52	40.0	10.9
Above Knee	14.4		3.5		80	42	40.0	11.1
Tibial.R Abductor hallucis.R								
Ankle	4.3	6.0	5.6	4.00	60			13.2
Knee	16.7		4.4		450	36*	40.0	10.4
Median.R Abductor pollicis brevis.R								
Wrist	5.7*	3.8	4.7*	5.00	60			10.7
Elbow	12.4		3.8		310	46*	50.0	10.2
Ulnar.R Abductor digiti minimi (manus).R								
Wrist	2.7	3.2	6.4	4.00	60			20.5
Below elbow	8.1		5.6		275	51	50.0	19.1
Above elbow	9.8		4.6		100	59	50.0	15.0

SNCS							
Nerve	Peak Latency		Amplitude		Conduction Velocity		
	Neg Peak Lat ms	Normal ≤	µV	Normal ≥	Distance mm	m/s	Normal CV ≥
Sural.R to Lat Mal.R							
Post Calf	NR		NR		140		
Median.R to Digit II (index finger).R							
Wrist	NR		NR		130		
Ulnar.R to Digit V (little finger).R							
Wrist	NR		NR		110		
Radial.R to Anatomical snuff box.R							
Forearm	NR		NR		100		

Illustrative case 5: Paraneoplastic PN

- ANNA-1 (anti-hu) Positive 1:7680



BMC Neurol. 2016; 16: 136.

Neuropathies in cancer

- Neuropathies caused by cancer itself:
  - Paraneoplastic
  - Infiltrative
- Neuropathies caused by cancer treatment:
  - Toxic
  - Autoimmune
  - Opportunistic infections (CMV)
  - Trauma from surgery, bone fracture
  - Malnutrition, vitamin deficiency
  - Radiation

Paraneoplastic neuropathies

- Autoimmune neuropathy (mostly axonal)
- Tumor antigen is identical to the neural antigen
- Either neuronopathy or polyneuropathy
- Motor (rare), Sensory (common) with or without autonomic involvement
- Other syndrome may be associated such as LEMS, Encephalitis etc .
- Anti-Hu (ANNA-1) most common antibody, 2nd comes anti-CRMP5 (CV-2) (may look demyelinating)
- The tumor is often occult, and the neurologic disorder typically precedes the diagnosis of cancer
- In patient felt to be in remission, paraneoplastic neuropathy usually means relapse

Arch Neurol . 2010;67(3):330-335

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Table 4. Tumor Types in the PNS Euronetwork Database

Tumor Type	Patients, No. (%) (n=899)
Small cell lung cancer	345 (38.4)
Ovary	94 (10.5)
Breast	87 (9.7)
Non–small cell lung cancer	71 (7.9)
Non-Hodgkin lymphoma	31 (3.4)
Hodgkin lymphoma	27 (3.0)
Thymoma	24 (2.7)
Prostate	23 (2.6)
Metastasis from unknown primary	18 (2.0)
Colorectal	16 (1.8)
Esophagus or gastric	16 (1.8)
Testicular	15 (1.7)
Kidney or bladder	11 (1.2)
Neuroblastoma	7 (0.8)
Merkel carcinoma	6 (0.7)
Melanoma	4 (0.4)
Other	104 (11.6)

Arch Neurol . 2010;67(3):330-335

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Paraneoplastic neuropathies

- Antibodies may be absent
- Patients with paraneoplastic neurologic disorders have a better prognosis than patients with histologically identical tumors but without paraneoplastic syndrome
- No evidence that immunosuppression for treatment of the paraneoplastic syndrome stimulates the growth of the tumor
- However immunotherapy is not very effective (unless, perhaps the patient is treated very early)
- Treatment of the tumor may stabilize the neuropathy

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Take home messages

- Large groups of potentially treatable PN
- Use of clinical criteria may help early identification
- Laboratory testing can be helpful in some but not all cases
- Early recognition and treatment will help improve outcome