Refractory CIDP: CIDP Variants, Look-alikes, Evaluation and Treatment

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None

Objectives

- To discuss clinical features of classical CIDP.
- To discuss different varieties of CIDP.
- To discuss treatment of classical CIDP and its varieties and an approach for dealing with refractory CIDP.
- To discuss other types of neuropathy that resemble CIDP and how to identify and treat them.

Treatment of Inflammatory Neuropathies

- Only a small number of drugs are well studied:
  - IVIg
  - Plasma exchange
  - Corticosteroids
  - Azathioprine
  - Cyclophosphamide
- Newer treatments are less well studied:
  - Rituximab (B cell antibody)
  - Interferons
  - Tumor necrosis factor α antagonists (etanercept, infliximab)
  - Autologous stem cell transplant

Case 1

- 49 year old woman referred for CIDP because of demyelinating nerve conduction studies.
- She has several years of burning pain in feet and mild distal weakness.
- Neurological examination showed:
  - Sensory loss to touch, pin and vibration in feet.
  - Weakness in hand and foot muscles.
  - Mild high arches and thin ankles.

49 F

MNC Record # 4 Data on Local Hard Disk Ulnar.L 09:22:34

Switch: STOP Stim: 1	Rate: 0.5 Hz	Level: 53.3 mA	Dur: 0.1 ms	Single
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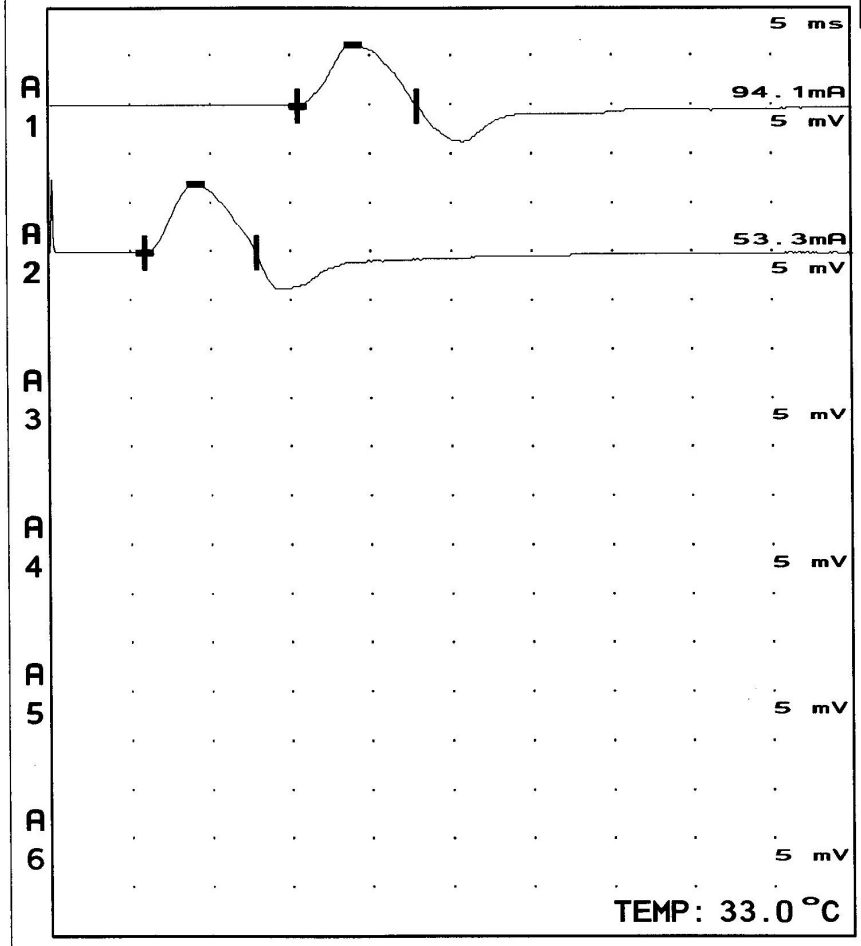


Recording Site : ADM

STIMULUS SITE	LAT1 ms	DUR ms	AMP mV	AREA mVms	TEMP °C
A1: Elbow	15.4	7.4	6.380	26.20	33.5
A2: Wrist	5.8	7.0	7.200	27.88	33.6
A3: B. Elbow					
A4: Upper Arm					
A5: Supraclavi					
A6:					

SEGMENT	DIST mm	DIFF ms	CV m/s
Elbow-Wrist	263	9.6	27
Wrist-ADM	68	5.8	
B. Elbow-Wrist			
Upper Arm-Wrist			
Supraclavicular-Wrist			
A6-Wrist			

Case 1

- Nerve conduction studies showed uniform demyelination (no temporal dispersion).
- Family Hx
  - No one with symptoms like hers (burning feet).
  - Mother had “ugly feet”, foot drop and foot ulcers (no pain).
  - Daughter was asymptomatic (high arches, skinny ankles, hammertoes on exam).
- Diagnosis:
  - Charcot Marie Tooth 1A (duplication of PMP-22).
  - Not CIDP.

Lessons from Case 1

- The first step in treatment is the correct diagnosis.
- CMT (inherited neuropathy) unlike CIDP does not respond to immunotherapy.
- Many cases thought to have CIDP really have another diagnosis (such as inherited neuropathy).
- One of the main reasons for treatment non-responsiveness (refractory CIDP) is because the CIDP diagnosis is wrong.

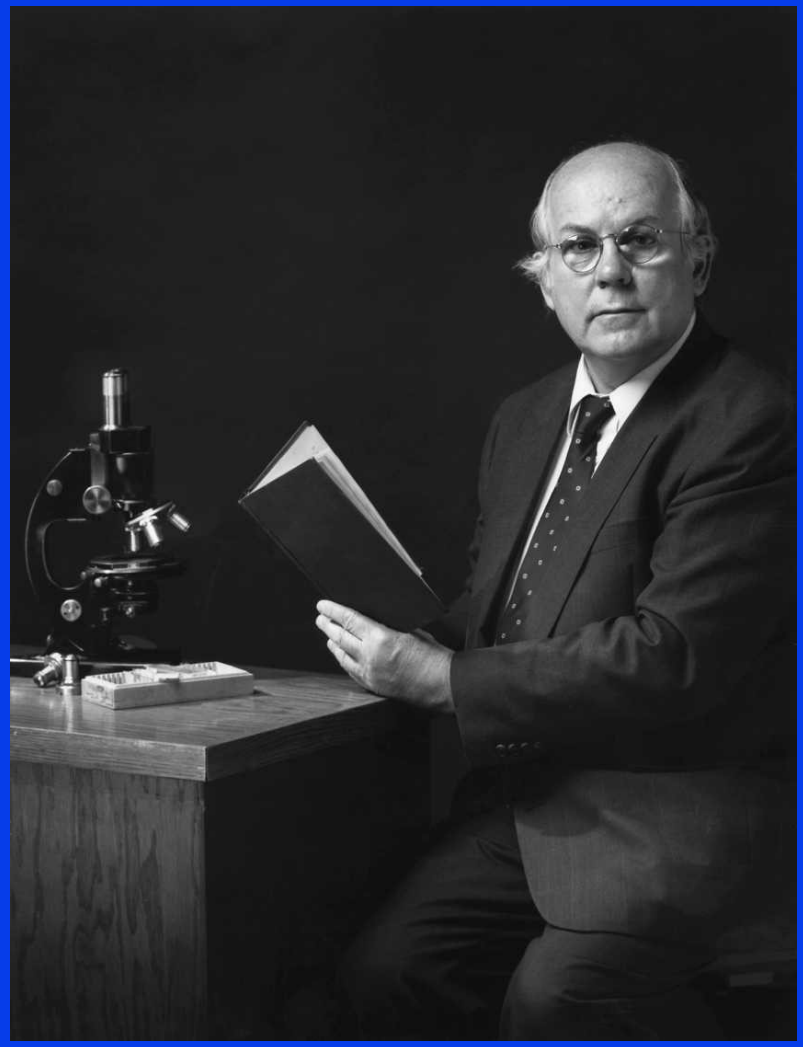
Wrong Diagnosis of CIDP

- Allen and Lewis (Neurology 2015) found that 27 of 57 (47%) patients referred for CIDP failed to meet diagnostic criteria.
- In wrongly diagnosed CIDP:
  - Mild CSF protein elevation was present in 50%.
  - Mild demyelinating findings were found.
  - Patients reported subjective improvement with treatment.
- The authors conclude that CIDP is over-diagnosed because of over-reliance of mild elevated CSF protein, over-reliance of self-reported improvement and liberal electrophysiological interpretation of demyelination.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

History

- A recurrent treatment responsive polyneuropathy was first recognized by Austin in 1958.
- In 1975 Peter J. Dyck and co-workers named the condition CIDP by describing the natural history, clinical, electrodiagnostic, CSF and pathological findings in 53 personally seen patients.



Peter J. Dyck

Classical CIDP

Clinical Features

- CIDP is usually a slowly worsening neuropathy (in contrast to AIDP).
- CIDP is characterized by progressive weakness and sensory loss that worsens for at least 8 weeks.
- A symmetrical polyradiculoneuropathy – proximal and distal involvement of upper and lower extremities.
- Motor and sensory fibers are involved (usually motor predominant).
- Large fiber predominant – muscle weakness and sensory ataxia.

Classical CIDP

Clinical Features

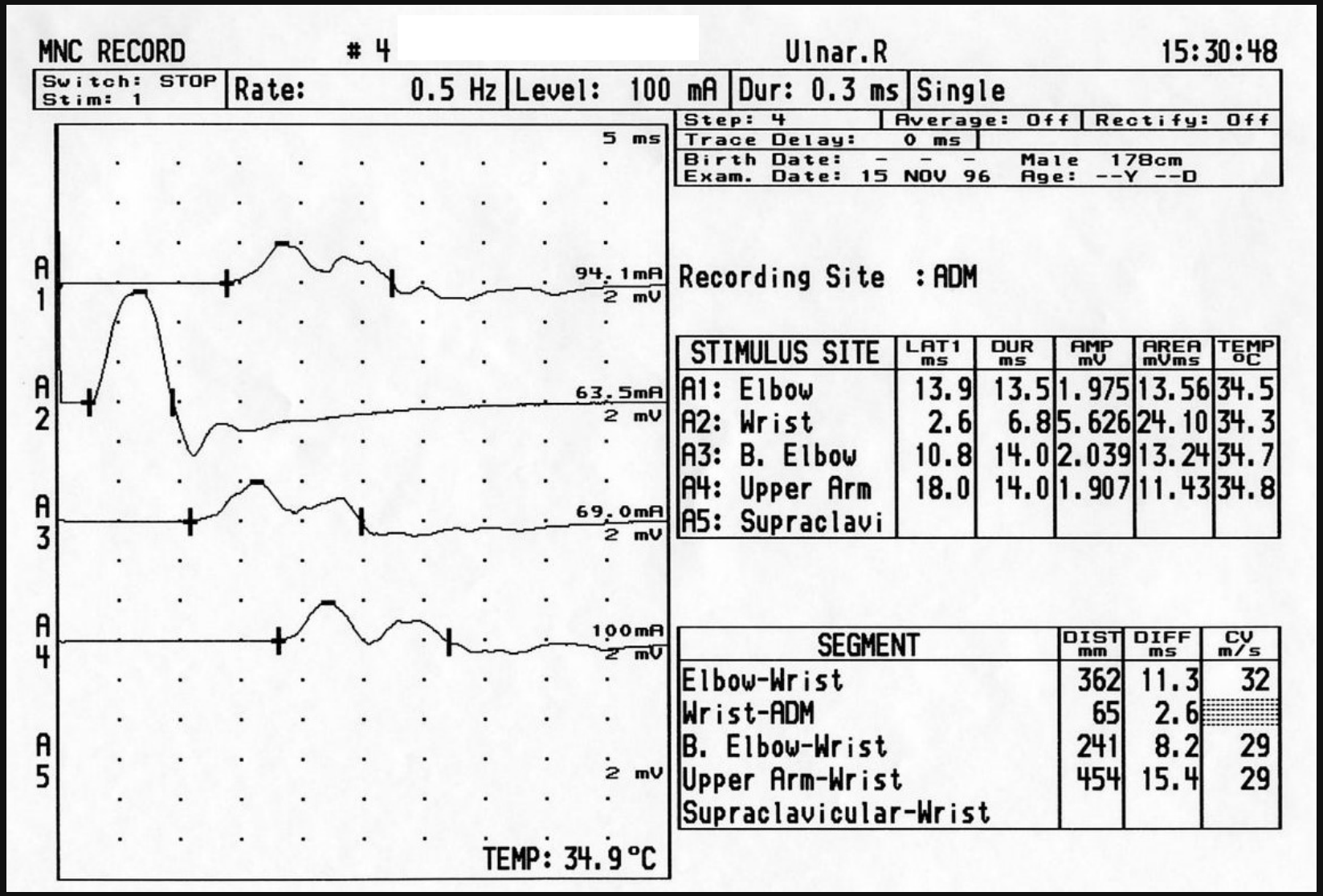
- Sensory loss and prickling are common.
- Pain and autonomic symptoms are uncommon (mild small fiber dysfunction).
  - Painful small fiber neuropathies are unlikely to be CIDP.
- Three usual types of course:
  - Relapsing remitting
  - Stepwise
  - Gradually progressive
- More common in adults than children.
- In older adults it is usually progressive, whereas in children it is usually relapsing remitting.

Classical CIDP

Clinical Features

- Patients present with progressive weakness or sensory ataxia.
- On exam, symmetrical proximal and distal weakness, large fiber (vibration and JPS) sensory loss, and reduced reflexes are common.
- Small fiber sensation (temperature and pain) are only mildly involved.
- Nerve conduction studies show demyelination (slow conduction velocities, long distal latencies, long F-waves, conduction blocks and temporal dispersion).

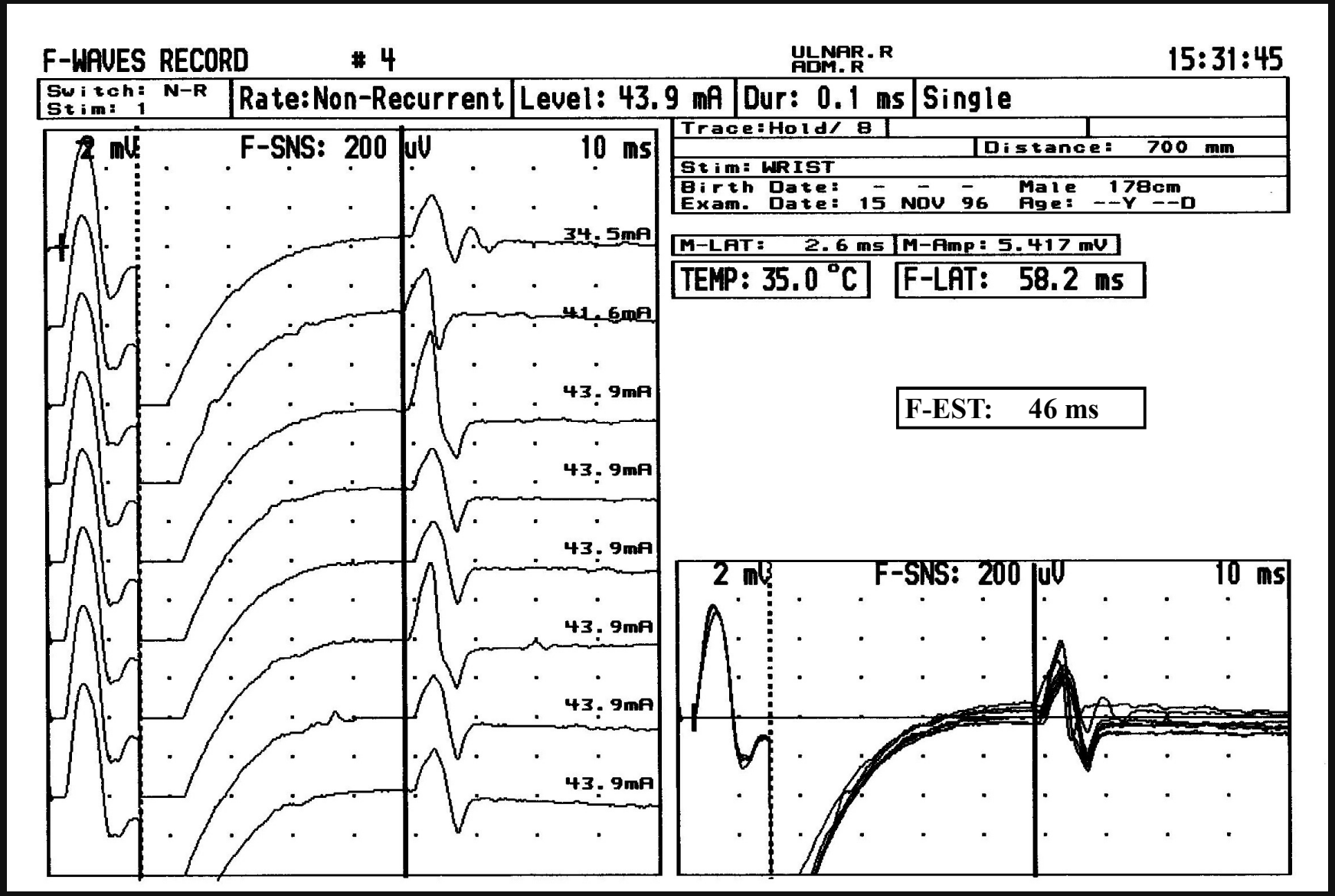
CIDP, 55 M
Temporal Dispersion and CB



STIMULUS SITE	LAT1 ms	DUR ms	AMP mV	AREA mVms	TEMP °C
A1: Elbow	13.9	13.5	1.975	13.56	34.5
A2: Wrist	2.6	6.8	5.626	24.10	34.3
A3: B. Elbow	10.8	14.0	2.039	13.24	34.7
A4: Upper Arm	18.0	14.0	1.907	11.43	34.8
A5: Supraclavi					

SEGMENT	DIST mm	DIFF ms	CV m/s
Elbow-Wrist	362	11.3	32
Wrist-ADM	65	2.6	
B. Elbow-Wrist	241	8.2	29
Upper Arm-Wrist	454	15.4	29
Supraclavicular-Wrist			

CIDP, 55 M
Prolonged F-wave Latency



CIDP

Laboratory Features

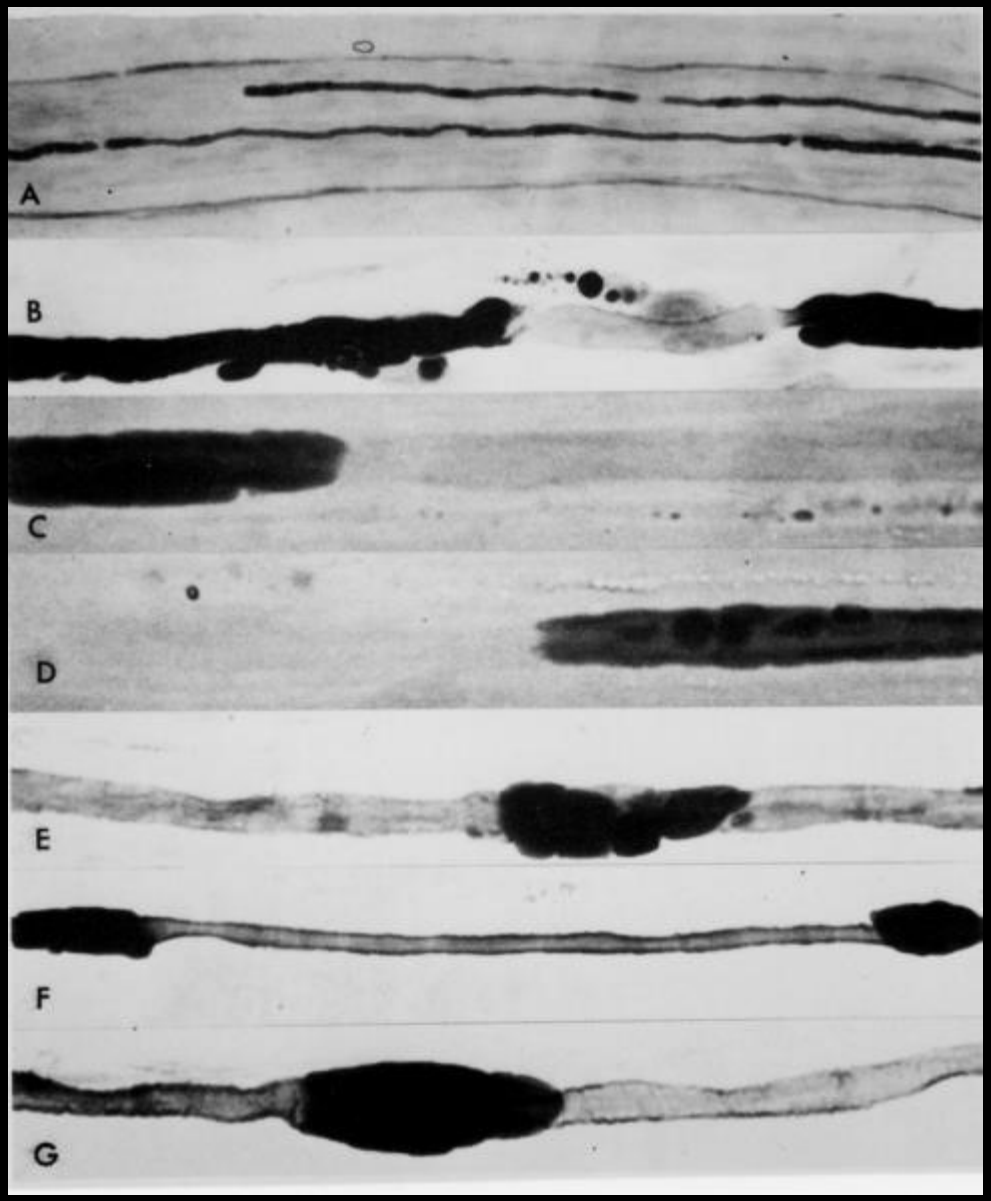
- CSF protein is elevated (>45 mg/dL) in 90% of CIDP but this is not specific. A high CSF cell count makes lymphoma, sarcoid, Lyme disease, malignancies more likely.
- HIV can present as a CIDP-like neuropathy.
- Monoclonal gammopathy (IgA, IgM and IgG) can be found in association with a CIDP-like neuropathy.
  - Lambda light chain and elevated VEGF levels seen in POEMS syndrome but not CIDP.
  - IgM neuropathy responds less well to immunotherapy.
- Diabetes mellitus has been reported to be associated with CIDP.

CIDP

Nerve Pathology

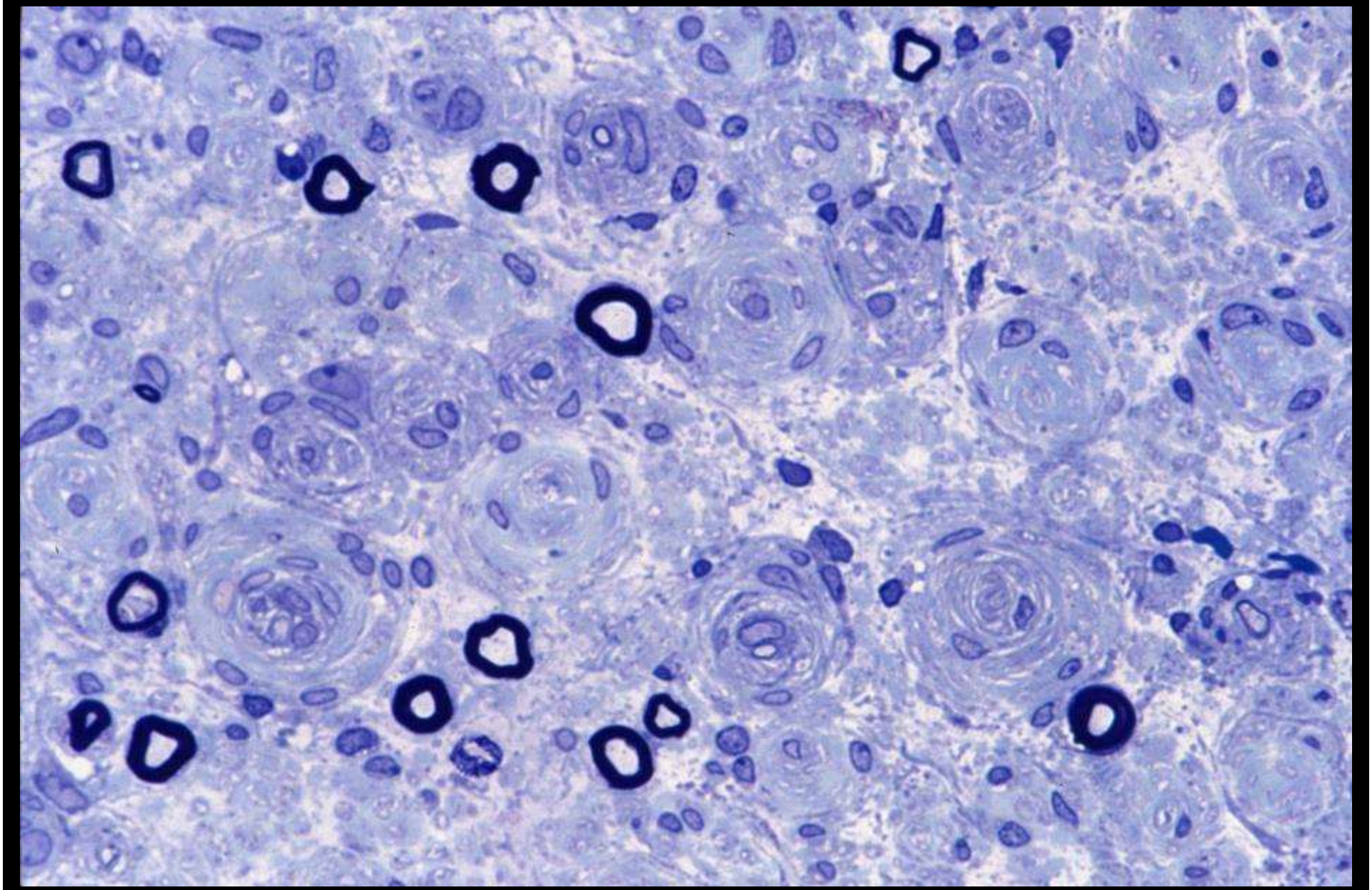
- CIDP is caused by inflammatory/immune demyelination.
  - Teased fibers show segmental demyelination.
- The pathological process typically involves:
  - Motor more than sensory fibers.
  - Large more than small fibers (myelinated fibers).
  - Proximal more than distal nerves.
- With repeated demyelination and remyelination, stacks of Schwann cell processes pile up and form onion-bulbs (hypertrophic neuropathy).

Demyelination in CIDP



Dyck et al, Mayo Clinic Proc, 1968

CIDP (Mixed Pattern of Onion-bulbs) – Unequal Demyelination



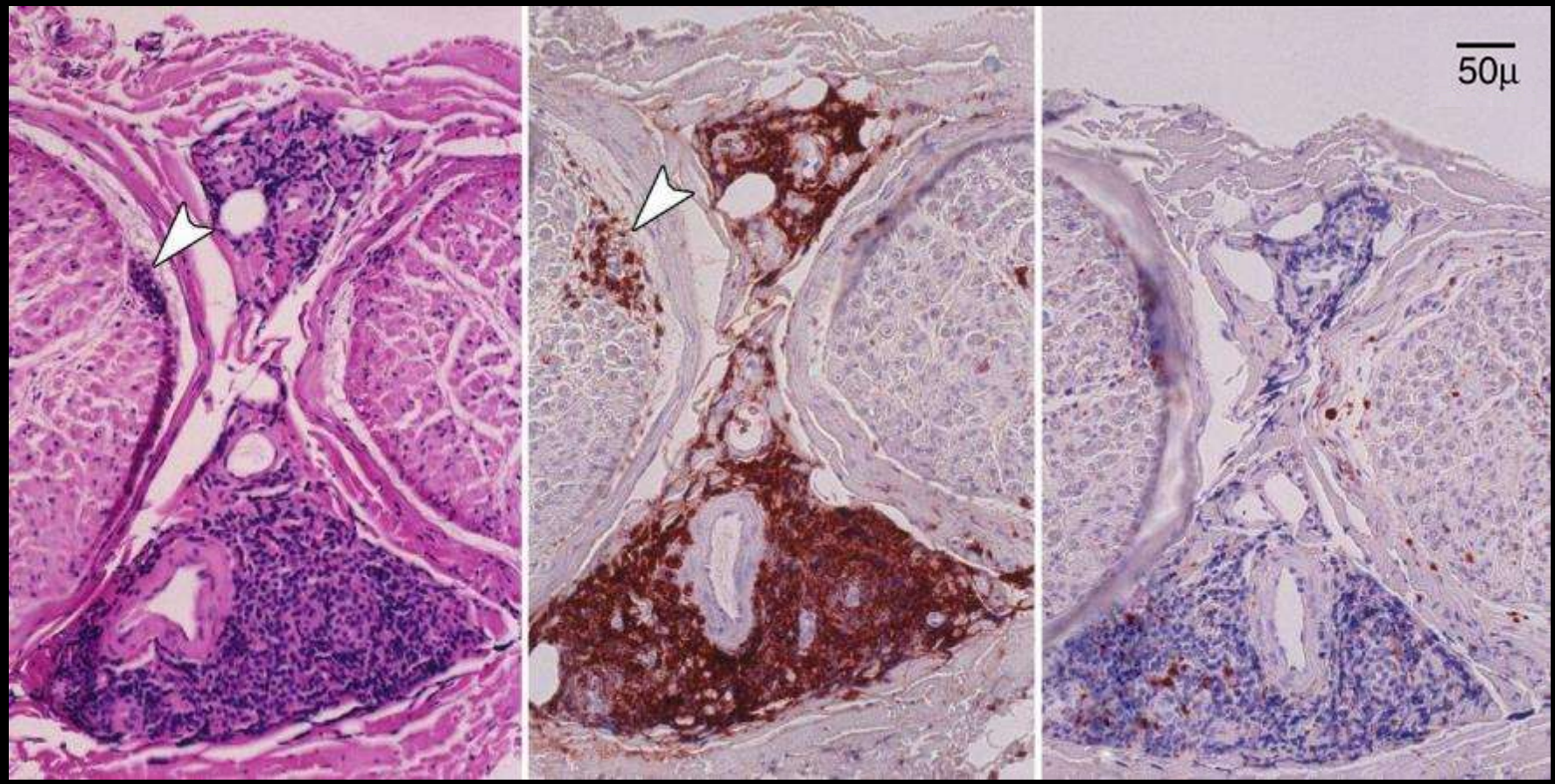
CIDP

Interstitial Pathology

- Interstitial abnormalities include:
  - Edema
  - Inflammatory infiltrates, both endoneurial and epineurial (macrophage mediated demyelinating).
  - The inflammation is lymphocytic predominant and perivascular.
- Because CIDP typically preferentially involves proximal nerves, sural biopsies may not show inflammatory demyelination, whereas proximal fascicular biopsies may.

Proximal Fascicular Biopsy in CIDP
Epineurial and Endoneurial Inflammation

H&E CD45 CD68



Dyck et al, PN4 textbook, 2005

CIDP Varieties

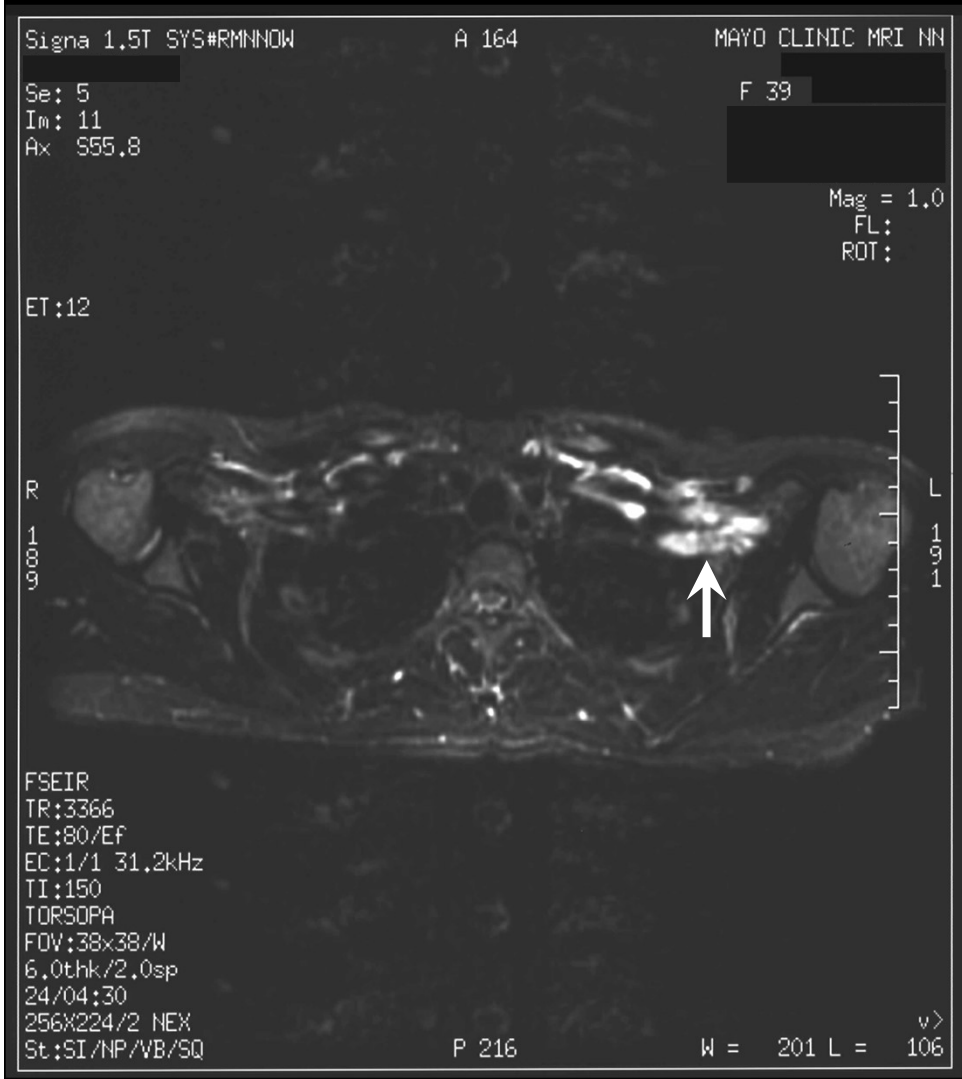
- Classical – symmetrical polyradiculoneuropathy pattern (both proximal and distal weakness) – most common form.
- Other varieties of CIDP:
  - Multifocal CIDP (Lewis-Sumner syndrome, MADSAM).
  - Purely motor or purely sensory CIDP.
  - Isolated sensory root involvement (chronic immune sensory polyradiculopathy – CISP).
  - Diabetic CIDP.
- Varieties resembling CIDP:
  - IgM MGUS (anti-MAG) neuropathy (DADS).
  - Multifocal motor neuropathy.
  - POEMS syndrome.

Case 2

- 39 year old woman with a progressive left ulnar neuropathy (20 years) and a more recent left sciatic neuropathy (5 years).
- She fell and “bruised” her ulnar nerve 20 years earlier.
- Ulnar nerve was transposed and was markedly enlarged (10 years earlier). Nerve biopsy was consistent with “plexiform neurofibroma”.
- She had acute worsening of her left sided weakness after a viral illness. She was diagnosed with AIDP and treated with IVIg.

Case 2 (cont.)

- With treatment, her weakness improved and she was stronger than at baseline.
- Neurological exam and EMG showed left sided multiple mononeuropathies or plexopathies. She had no café au lait spots.
- CSF protein was 90 mg/dL. No cells.
- MRI showed marked enlargement of the left brachial plexus and lumbosacral plexus.
- A left ulnar fascicular biopsy was obtained.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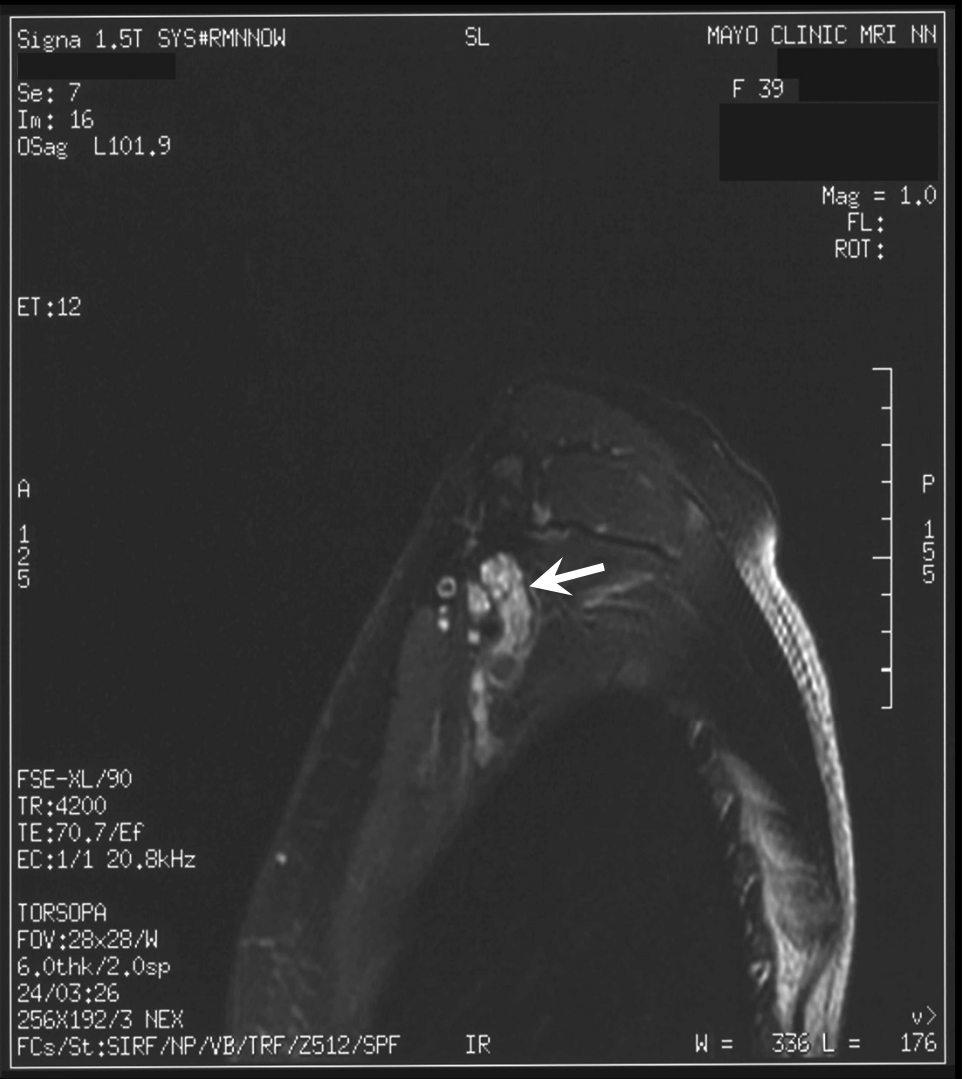
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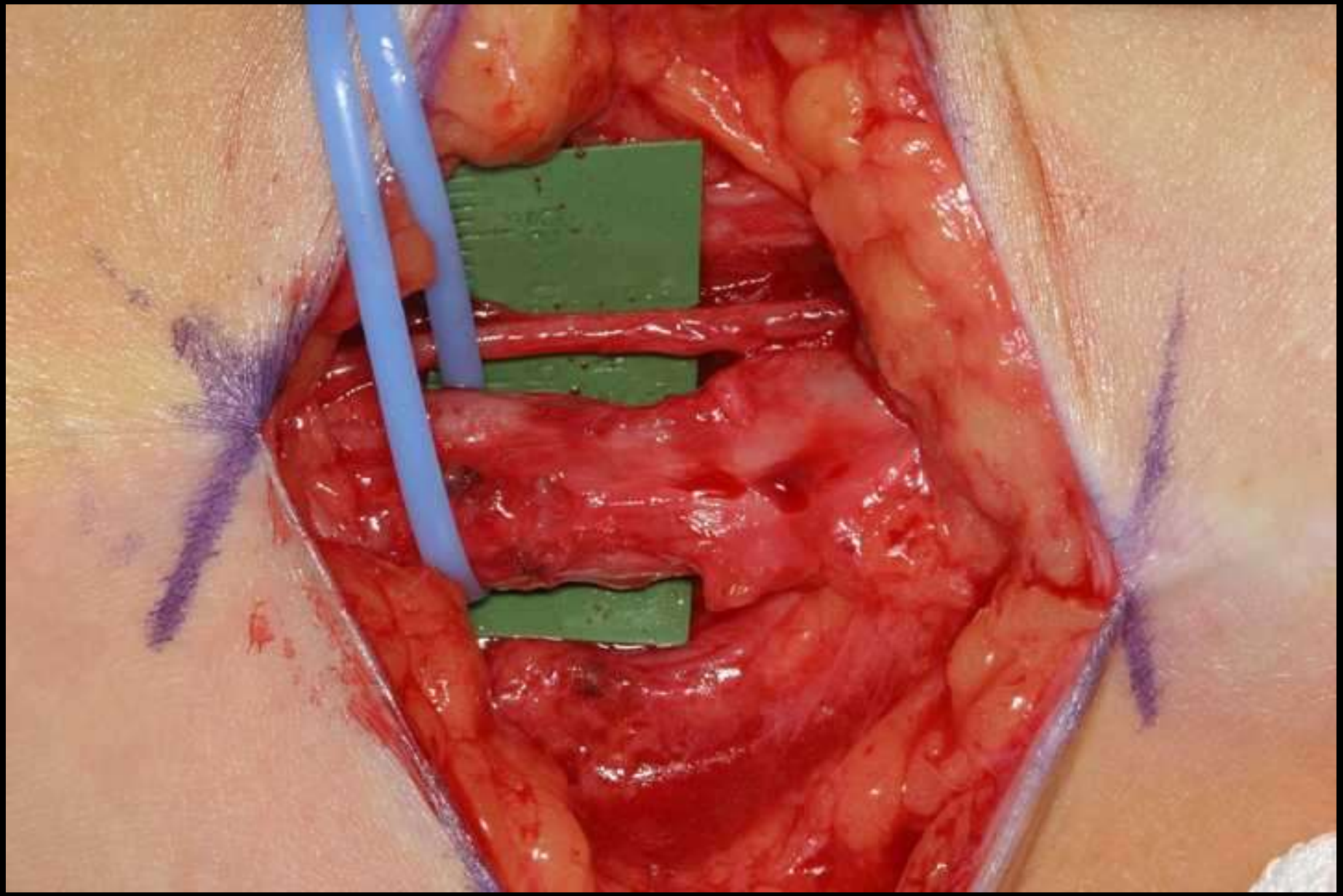
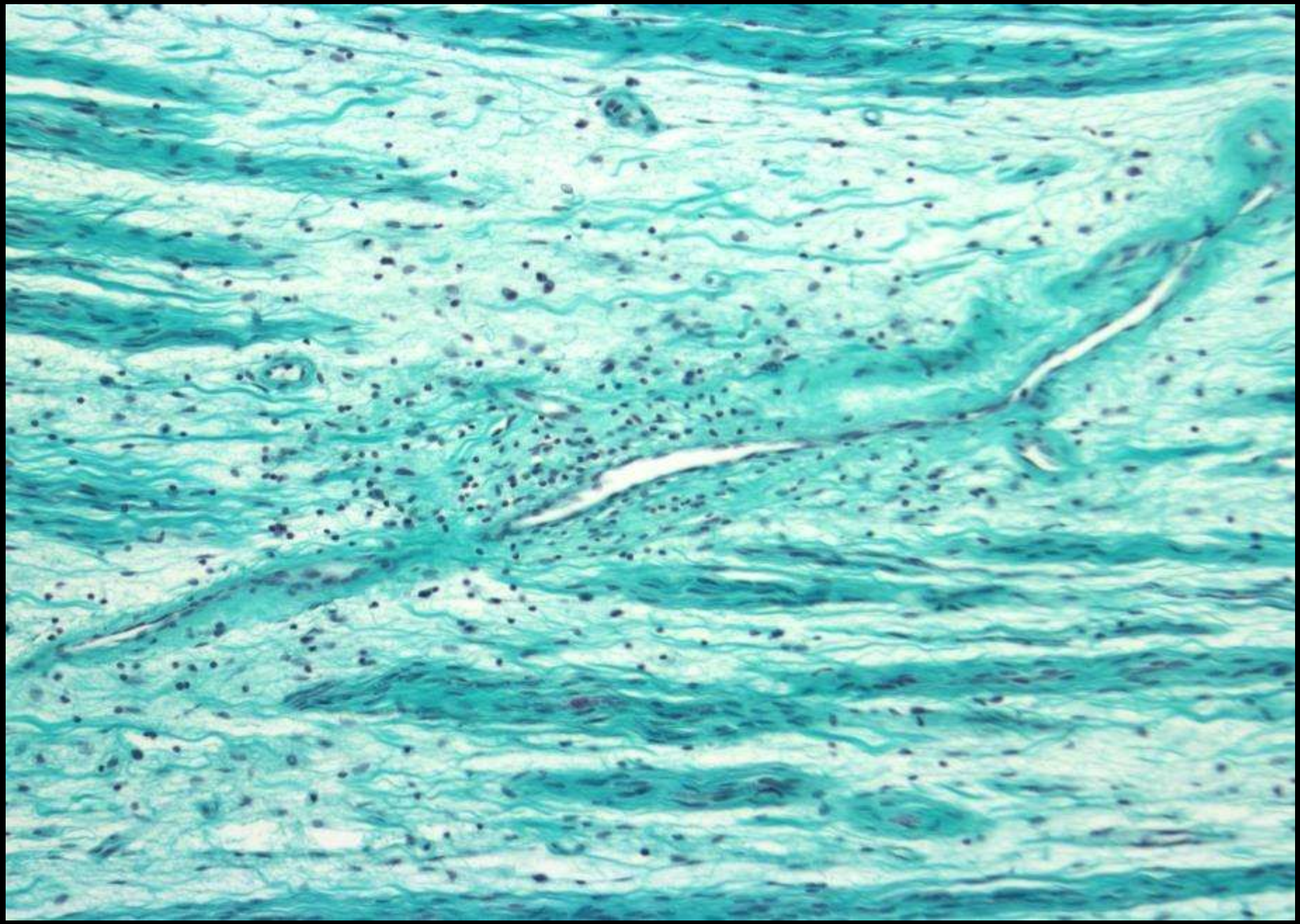
Ulnar Nerve at Biopsy



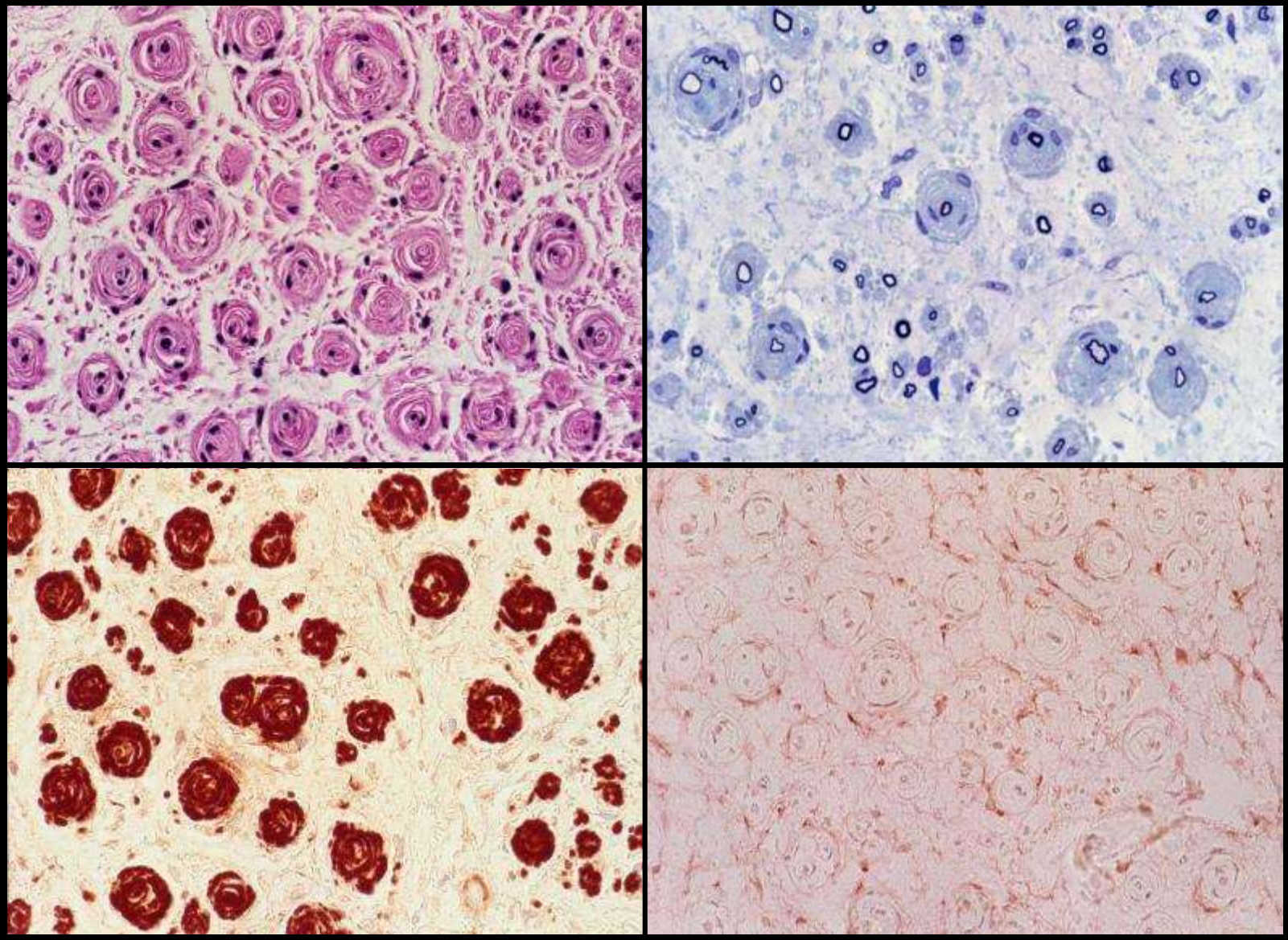
Masson Trichrome – Endoneurial Inflammation



CIDP – Onion-bulbs

H&E

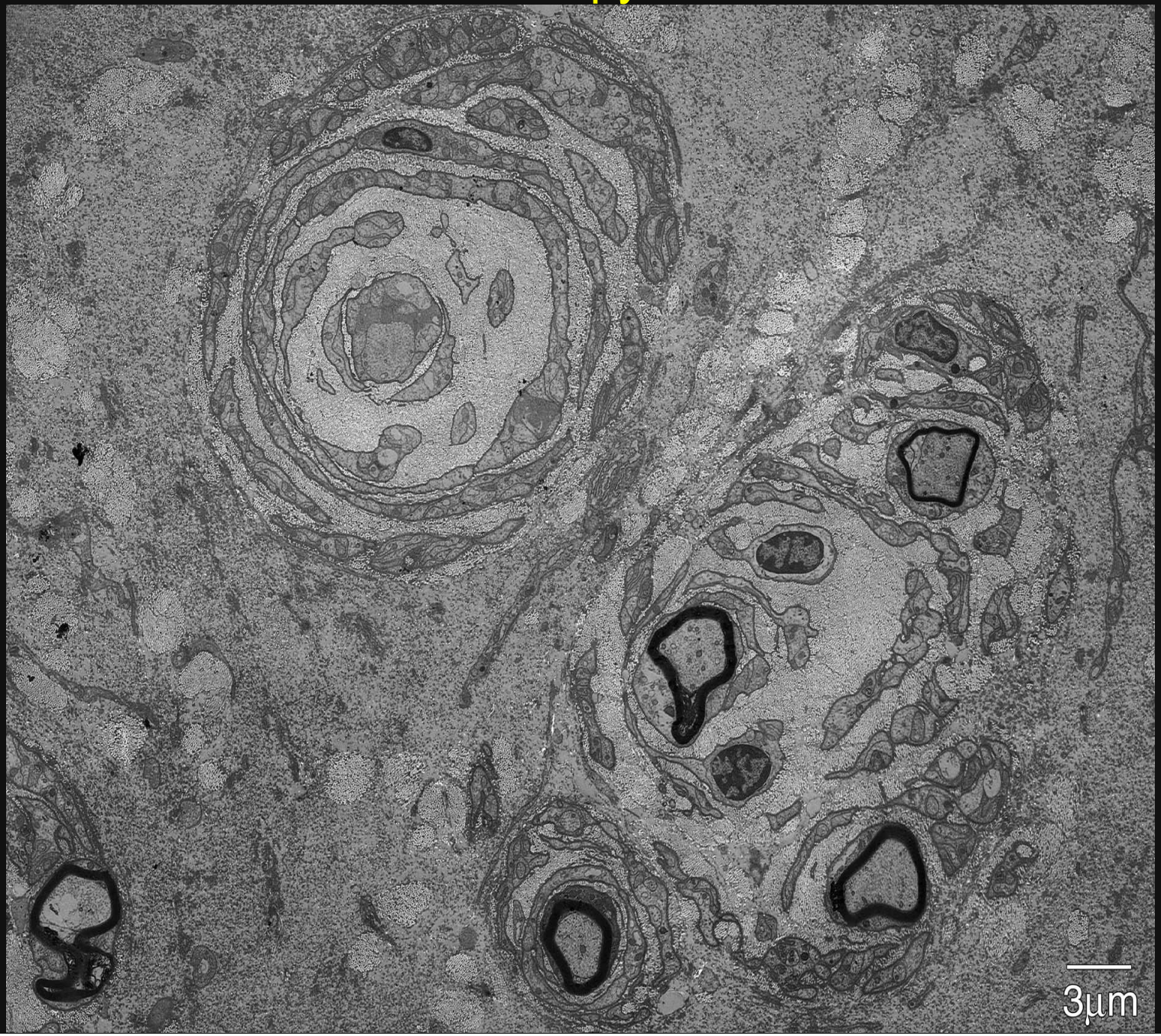
Methylene Blue



S-100

EMA

Electron Microscopy – Onion-bulbs



Case 2

- Pathology: hypertrophic nerve with edema, endoneurial inflammation and onion-bulbs.
- Diagnosis: Multifocal CIDP.
- Treatment: IVIg 0.4 gm/kg twice weekly for 4 weeks, then once weekly for 8 weeks.
- Response: strength in arm and leg improved though hand still somewhat weak.

Multifocal CIDP

- Also called Lewis-Sumner syndrome and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM).
- Described originally by Lewis, Sumner, Brown and Asbury in 1982.
- After classical CIDP, multifocal CIDP is the next most common subtype.
- An asymmetrical form of CIDP in which individual nerves become involved in an overlapping and patchy way.
- Similar presentation to multifocal motor neuropathy but multifocal CIDP has sensory involvement.

Multifocal CIDP

- Upper limb nerves are usually more involved than lower limb nerves.
- CSF protein is usually elevated (82%) in contrast to multifocal motor neuropathy (MMN).
- There is prominent sensory nerve involvement clinically, electrophysiologically and pathologically.
- Nerve conduction studies show asymmetrical demyelination in motor and sensory nerves – unlike MMN which is pure motor.
- Motor conduction blocks are seen in both multifocal CIDP and MMN.

Motor Conduction Block

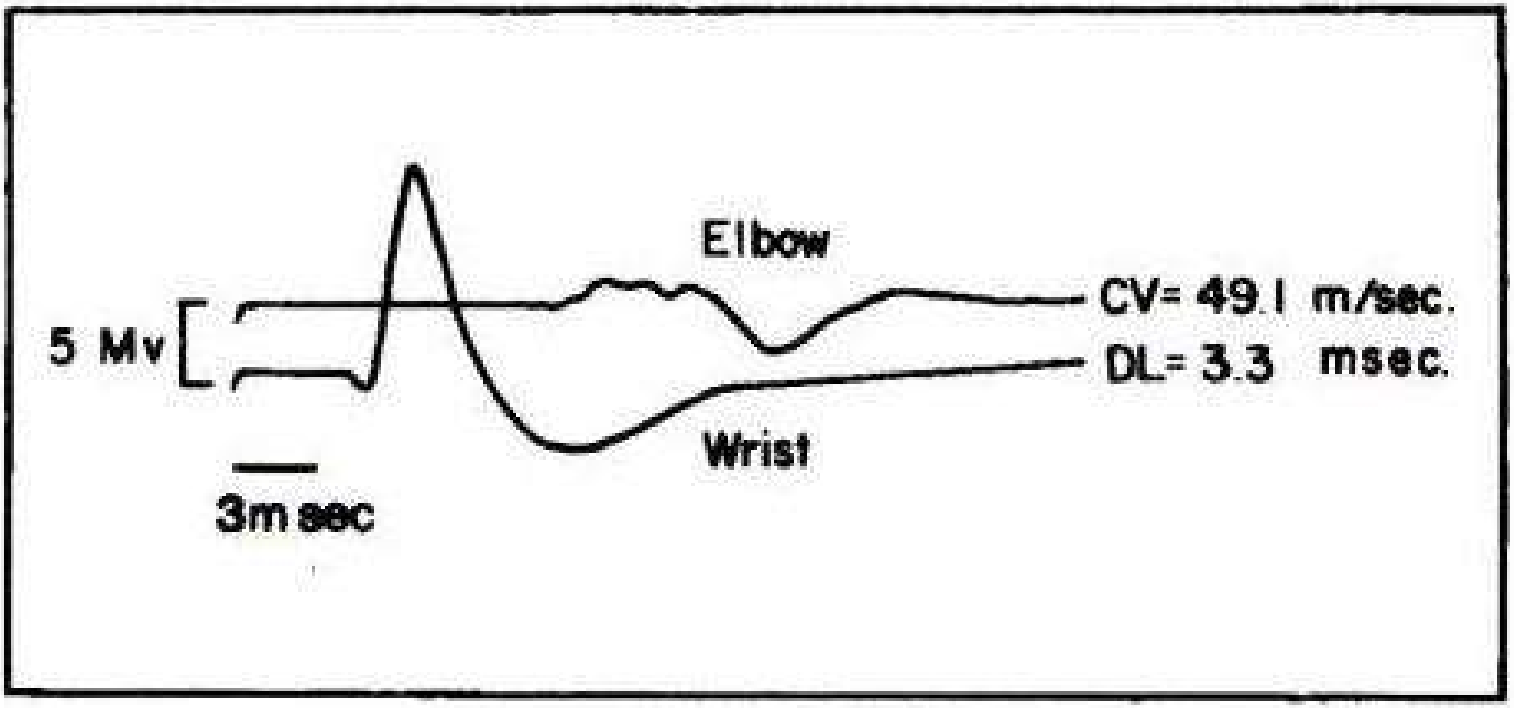


Figure 1. Left median motor conduction study of patient 3, demonstrating partial conduction block. Area beneath the negative (above the baseline) potential representing the response on proximal stimulation is 40% of the area of the response on distal stimulation.

Lewis, R. et al, Neurology 1982;32:958-64

Multifocal CIDP

- Anti-GM1 antibodies are usually normal (in contrast to MMN).
- Pathology is the same as classical CIDP with inflammatory demyelination.
- Patients respond to IVIg, plasma exchange and prednisone (like classical CIDP).
- In contrast, MMN patients do not usually improve with steroids.
- Multifocal CIDP probably is a form of CIDP (whereas MMN probably is not).

Case 3

- 66 year old woman with sensory ataxia for 10 years (needed two canes).
- Absent vibration, JPS and reflexes with normal strength.
- EMG was normal, tibial SSEP showed delayed responses, and CSF protein was elevated (103 mg/dl).
- MRI showed enlarged and enhancing roots in her cauda equina.
- A dorsal lumbar rootlet biopsy was performed.

Nerve Conduction Studies (normal)

Stimulate (Record)	A (mV/μV)	CV (m/s)	DL (ms)	F (ms)
L. Median motor (APB)	9.9 (>4)	52 (>48)	3.2 (<4.5)	25.5 (<32)
L. Median sensory (Index)	27 (>15)		3.0 (<3.6)	
L. Tibial motor (AH)	11.3 (>4)	47 (>40)	5.5 (<6.1)	50.4 (<58)
L. Peroneal motor (EDB)	4.4 (>2)	45 (>41)	4.9 (<6.6)	53.1 (<58)
L. Sural sensory (Ankle)	13 (>0)	54 (>40)	3.5 (<4.5)	

EMG (normal)

Muscle	Insertional activity	Fibrillation	Fasciculation	MUP
L. Abductor hallucis	Normal	0	0	Normal
L. Tibialis anterior	Normal	0	0	Normal
L. Peroneus longus	Normal	0	0	Normal
L. Gastrocnemius medialis	Normal	0	0	Normal
L. Vastus lateralis	Normal	0	0	Normal
L. Lumbar paraspinal	Normal	0	0	Normal

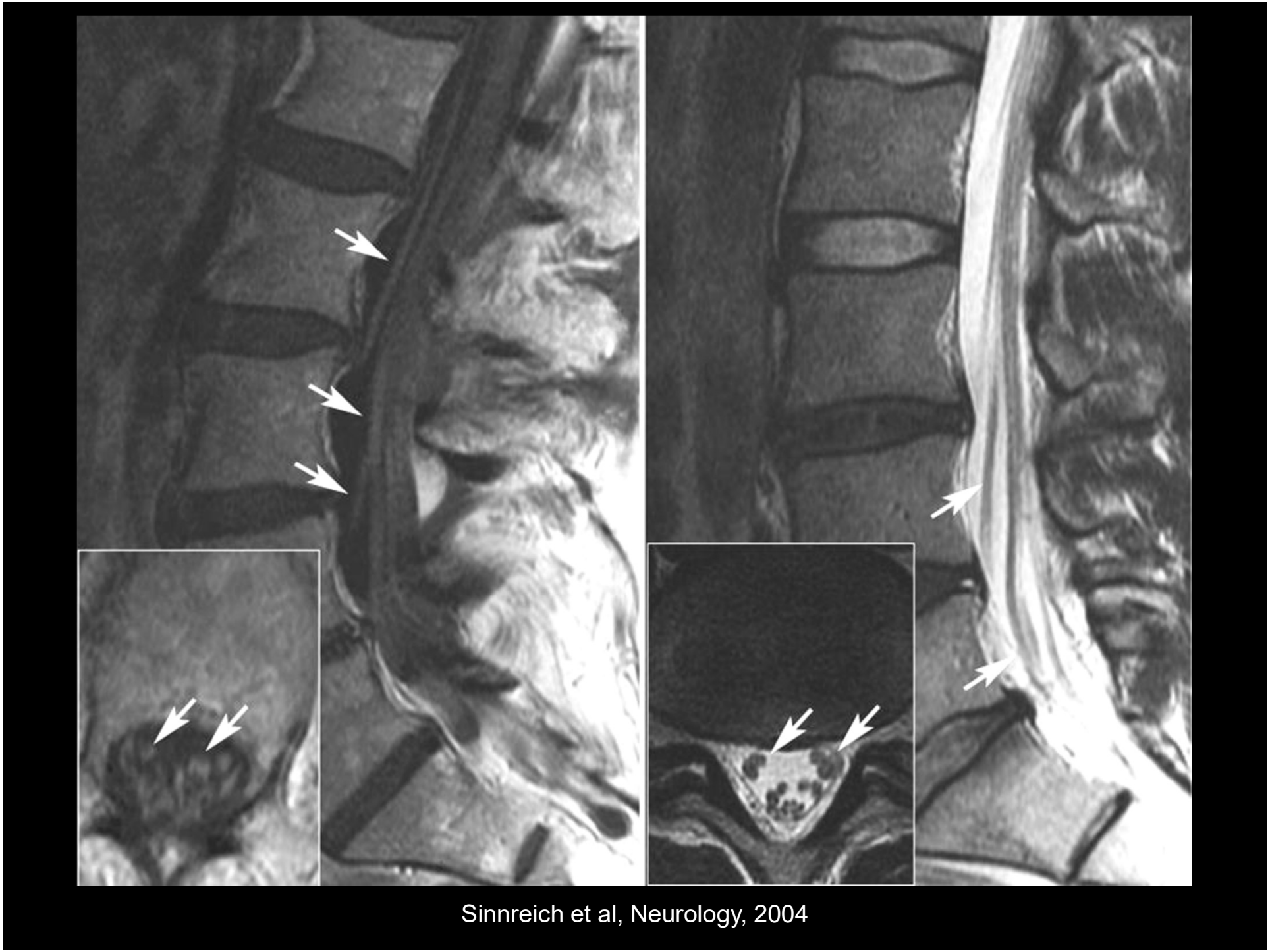
Median and Tibial SSEPs

MEDIAN SOMATOSENSORY EVOKED POTENTIALS

Record	Amplitude, uv			Latency, ms		
	Right	Left	Normal	Right	Left	Normal
Clavicle, N9		1.9	1.0-6.5		10.2	8.2-11.7
Cervical, N13		1.4	0.9-3.0		13.3	11.3-15.5
Cerebral, N20		2.4	0.5-8.7		18.6	16.9-21.9
N9-N13 Interval					3.1	2.2-4.7
N13-N20 Interval					5.3	4.7-6.6
N9-N20 Interval					8.4	7.8-10.5

TIBIAL SOMATOSENSORY EVOKED POTENTIALS

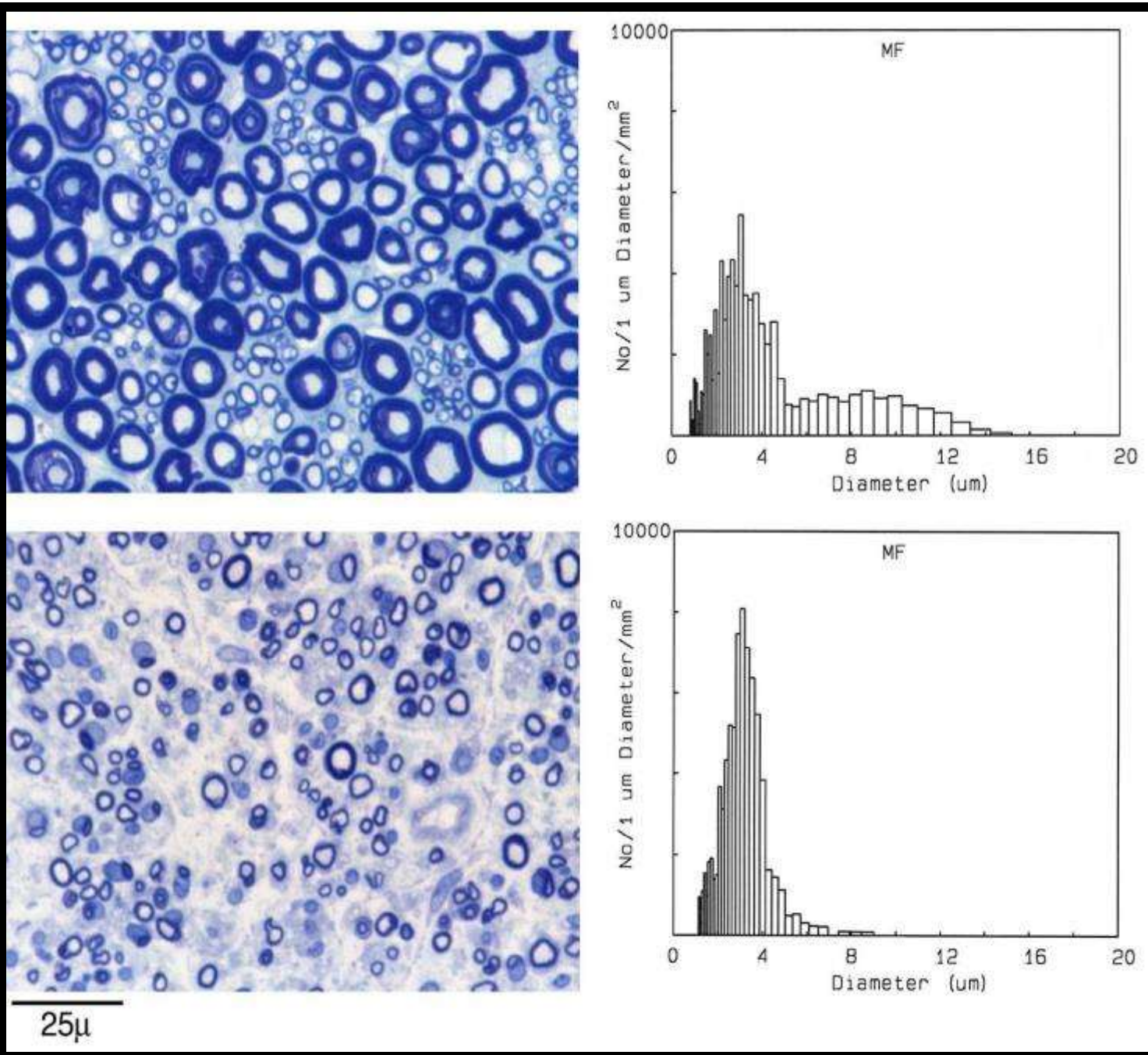
Record	Amplitude, uv			Latency, ms		
	Bilateral	Left	Normal	Bilateral	Left	Normal
Lumbar, N22	0.0	0.0	0.0-2.8	NR	NR	18.0-28.0
Cervical, N30	0.0	0.0	0.4-1.5	NR	NR	24.0-37.0
Scalp, P38	1.0	0.1	0.6-6.5	53.0	52.8	32.0-46.0
N22-N30 Interval				NR	NR	5.5-11.0
N30-P38 Interval				NR	NR	5.0-12.0
N22-P38 Interval				NR	NR	12.2-20.0



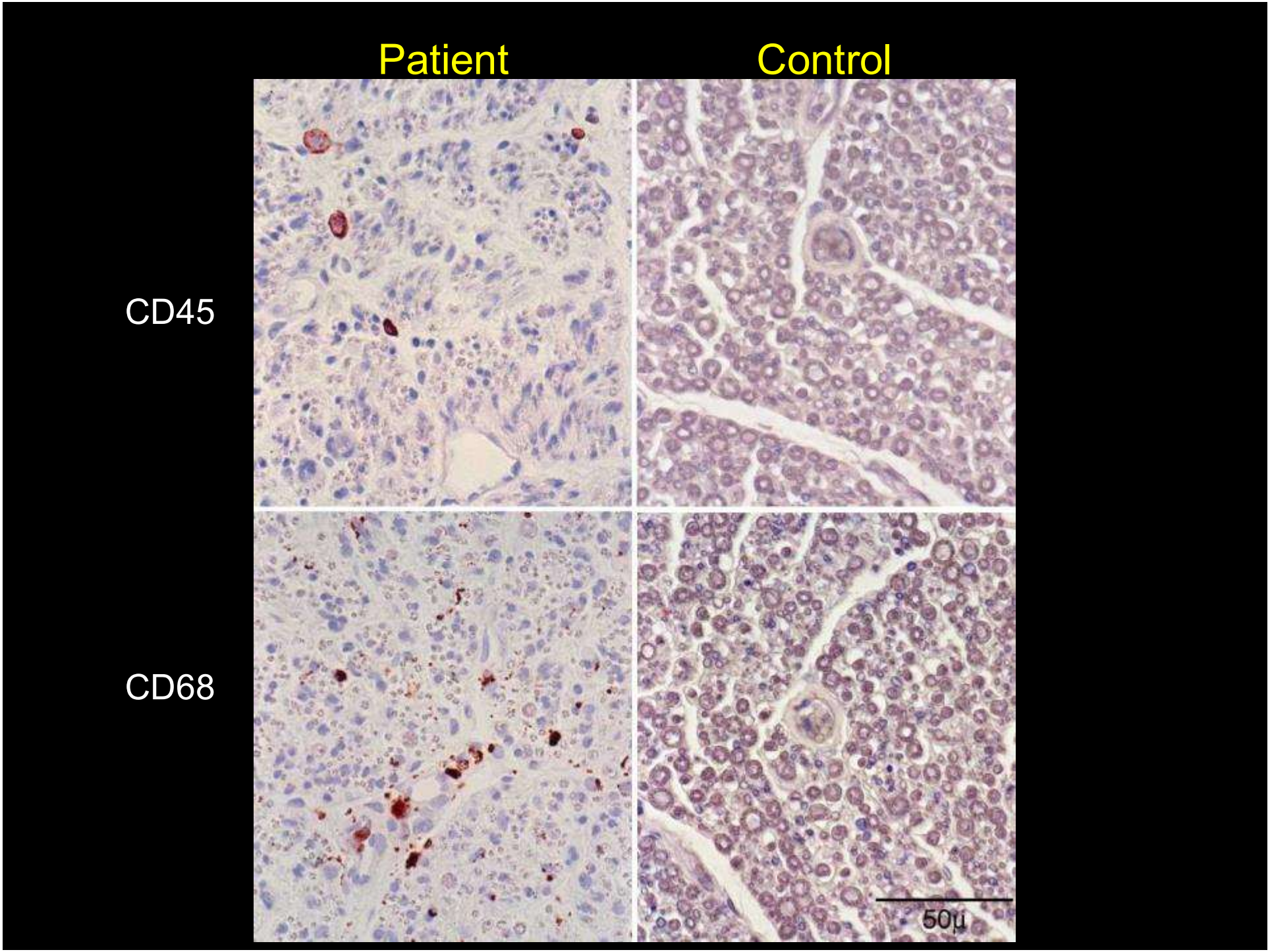
Sinnreich et al, Neurology, 2004

Control

Patient



Sinnreich et al, Neurology, 2004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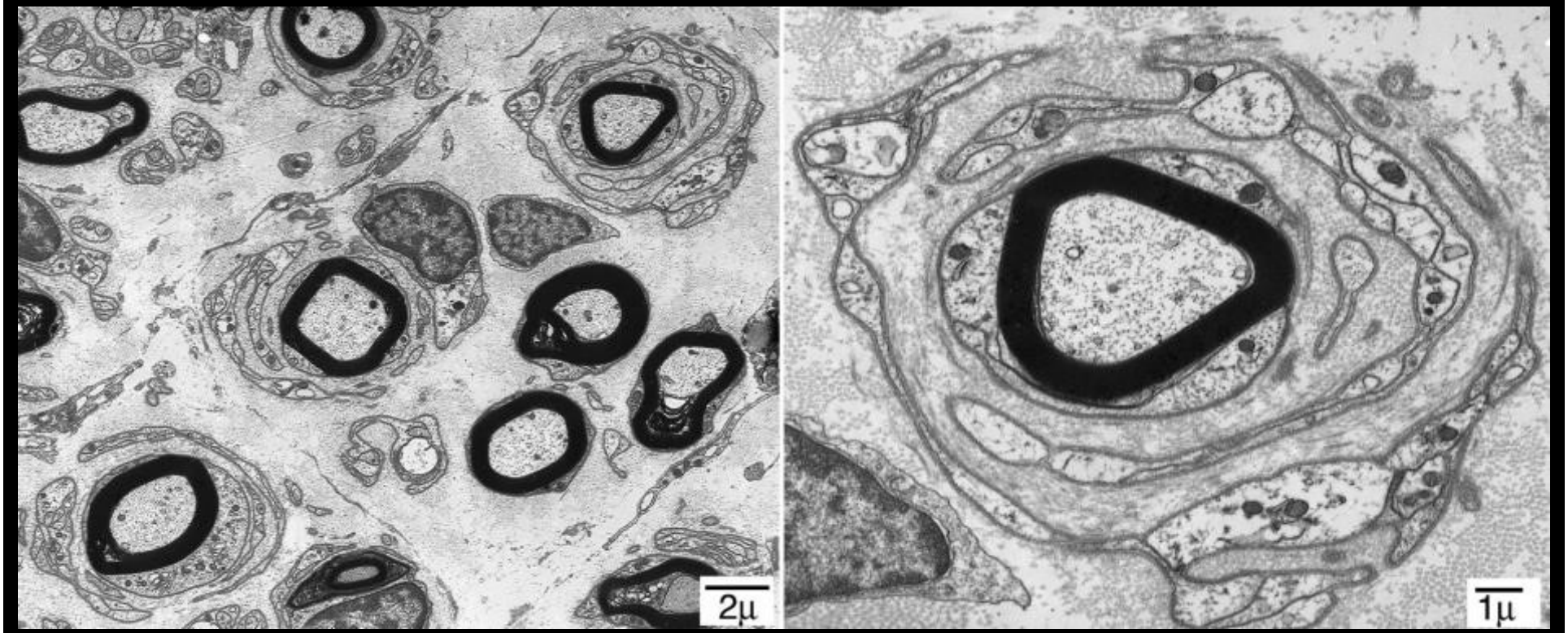
Onion-bulbs on EM



Sinnreich et al, Neurology, 2004

Case 3

- Pathology:
  - Loss of large fibers
  - Endoneurial macrophages
  - Onion-bulbs
- Diagnosis: chronic immune sensory polyradiculopathy (CISP).
- Treatment: IVIg 0.4 gm/kg twice weekly for 8 weeks and then once weekly.
- Response: she resumed walking independently without ataxia.

Chronic immune sensory polyradiculopathy

A possibly treatable sensory ataxia

M. Sinnreich, MD, PhD; C.J. Klein, MD; J.R. Daube, MD; J. Engelstad, HT; R.J. Spinner, MD; and P.J.B. Dyck, MD

Abstract—*Background:* Chronic inflammatory neuropathies can present with a sensory ataxia due to involvement of dorsal root ganglia (DRG) or sensory nerves. Selective inflammatory involvement of sensory nerve roots proximal to the DRG has been postulated. *Methods:* The authors identified 15 patients with a sensory syndrome and normal nerve conduction studies. Sensory nerve root involvement was suggested by either somatosensory evoked potential (SSEP) or imaging abnormalities. CNS disease was excluded. *Results:* All patients had gait ataxia, large fiber sensory loss, and paresthesias, and nine had frequent falls. The disease course was chronic and progressive (median duration 5 years, range 3 months to 18 years). Sural sensory nerve action potential amplitudes were preserved and SSEP abnormalities were consistent with sensory nerve root involvement. Five patients had enlargement of lumbar nerve roots on MRI with enhancement in three. The CSF protein was elevated in 13 of 14 patients tested. Three patients had lumbar sensory rootlet biopsies that showed thickened rootlets, decreased density of large myelinated fibers, segmental demyelination, onion-bulb formation, and endoneurial inflammation. Six patients who required aids to walk were treated with immune modulating therapy and all had marked improvement with four returning to normal ambulation. *Conclusion:* Based on the described clinical features, normal nerve conduction studies, characteristic somatosensory evoked potential (SSEP) abnormality, enlarged nerve roots, elevated CSF protein, and inflammatory hypertrophic changes of sensory nerve rootlet tissue, we suggest the term chronic immune sensory polyradiculopathy (CISP) for this syndrome. This condition preferentially affects large myelinated fibers of the posterior roots, may respond favorably to treatment, and may be a restricted form of chronic inflammatory demyelinating polyradiculoneuropathy.

NEUROLOGY 2004;63:1662–1669

CISP Clinical Features
(Sinnreich et al. Neurology, 2004)

- 15 patients (5 women, 10 men).
- Median age at onset 63 years (range 30 to 78 years).
- Large fiber sensory symptoms predominated. All 15 patients complained of gait ataxia.
- 9 patients had falls; 3 required wheelchairs and 5 canes.
- In all 15 patients, the course was chronic and progressive without spontaneous improvement (median 5 years, range 3 months to 18 years).

CISP Clinical Features

Neurological Examination

- All 15 patients had gait ataxia and altered large fiber sensation (JPS and vibration) (13 absent) on exam.
- 14 patients had reduced or absent reflexes.
- No patients had weakness.

CSF Findings

- 13 of 14 had elevated CSF protein (median 83 mg/dL, range 31 – 161) and normal cell counts.

CISP Electrophysiology

NCS

- Sensory and motor conduction studies were normal.
- Median sural SNAP 11 μV (range 6 - 20).
- Median tibial CMAP 7.6 mV (range 4.2 - 16.7).

EMG

- The needle examinations were normal.

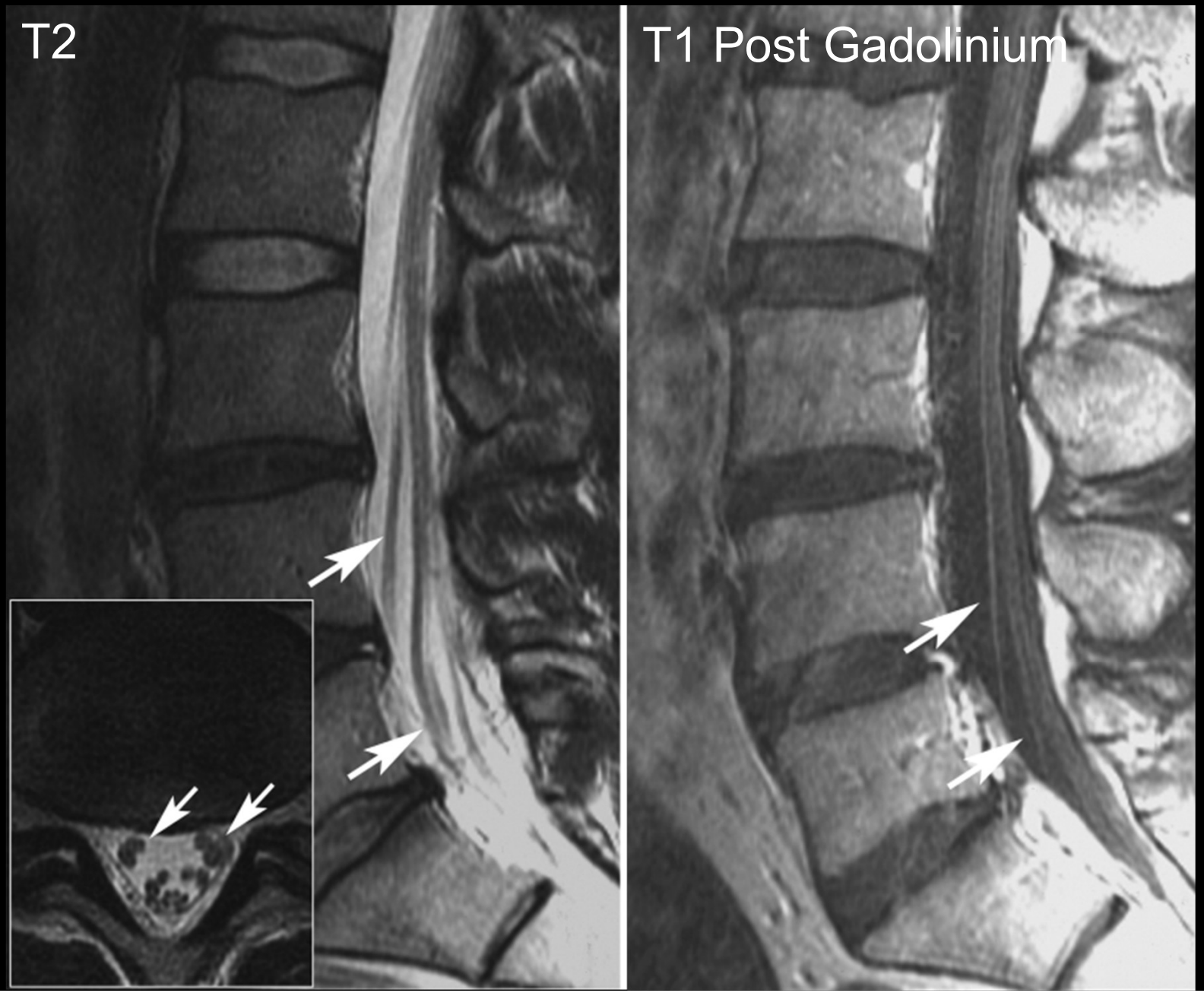
Quantitative Sensory Testing

- Large myelinated fiber abnormality predominated.
  - 10 of 11 had elevated vibration thresholds (>97%).

CISP MR Imaging

- MRIs of brain, cerebellum and spinal cord were normal in all patients.
- 5 patients had thickened lumbar nerve roots.
- 3 patients had Gadolinium enhancement of lumbar nerve roots.

CISP Patient



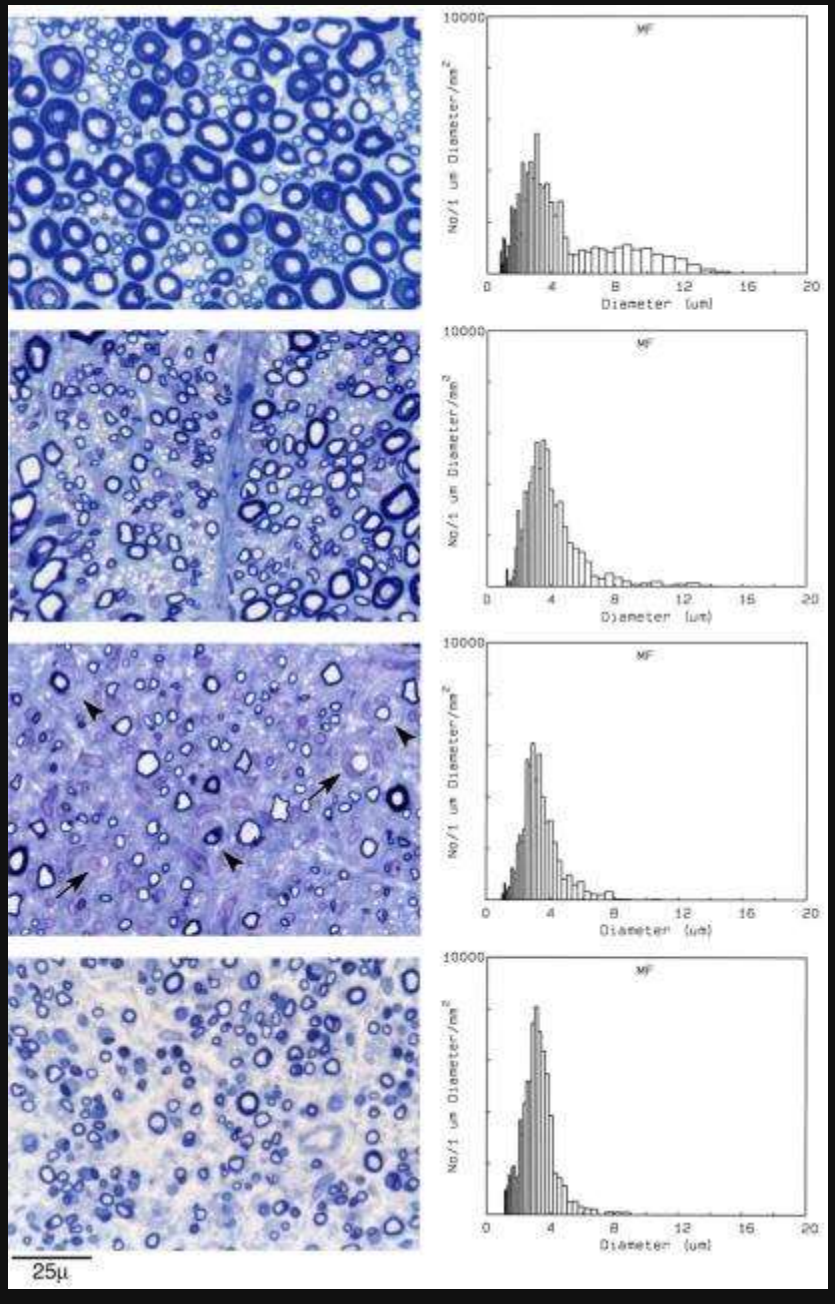
Sensory Rootlet – Loss of Large Fibers

Control (post mortem)

Patient 12

Patient 13

Patient 1



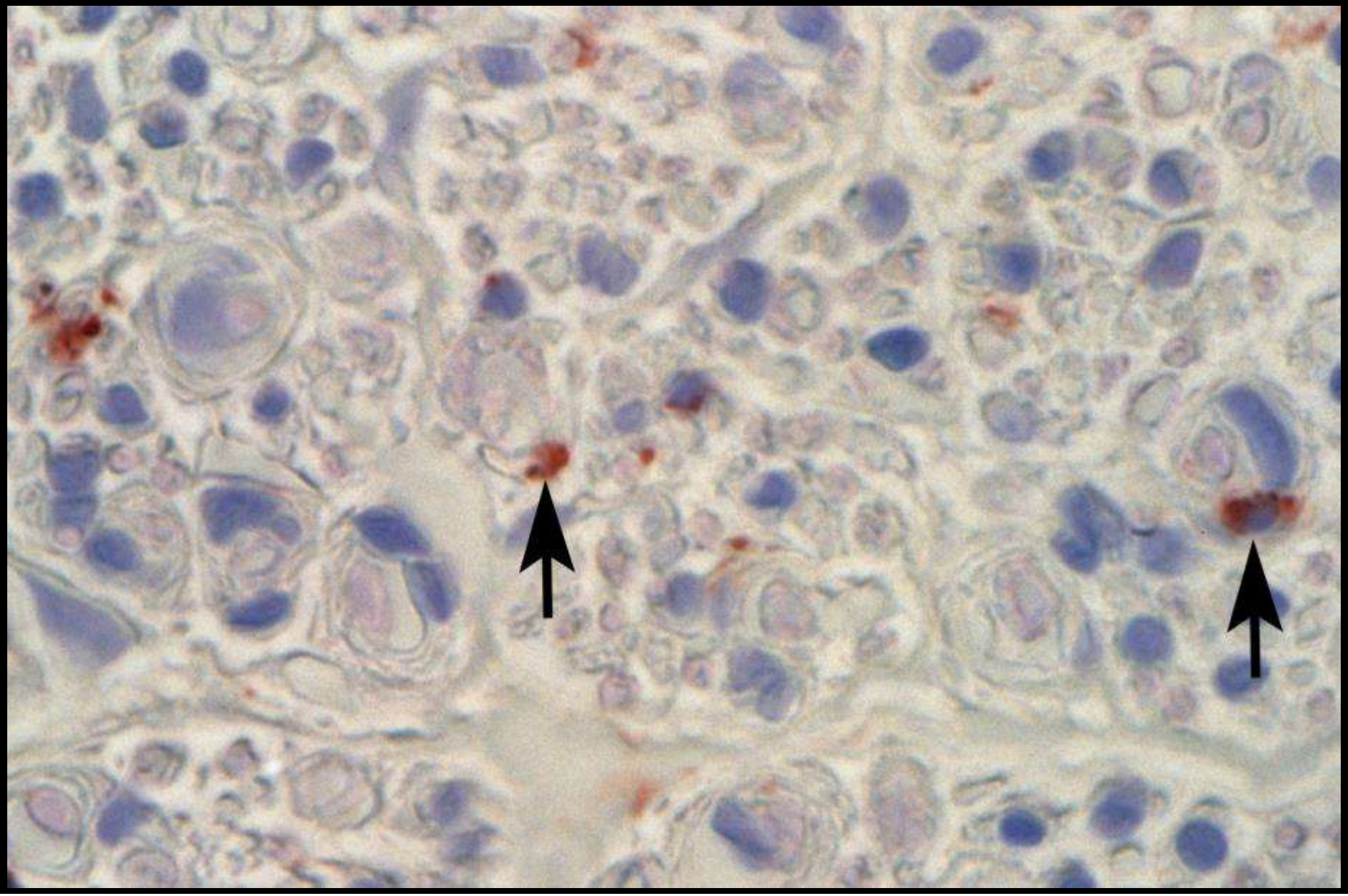
– All 3 CISP rootlet biopsies had reduced large fibers.

– 2 CISP biopsies had endoneurial macrophages and onion-bulbs.

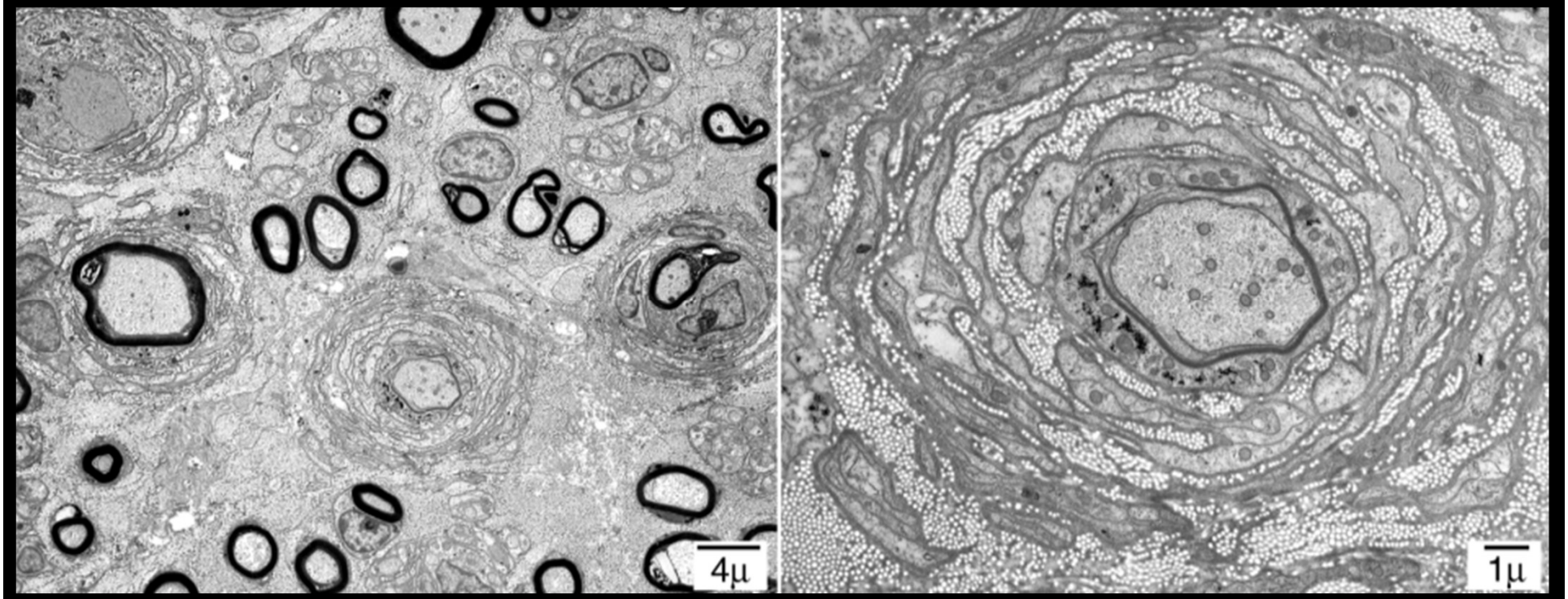
– Teased fibers done in 1 biopsy showed 60% demyelination and remyelination.

CISP – Teased Fibers – Increased Demyelination

CISP – Macrophages (CD68)



CISP – EM Onion-bulbs and Naked Axons



Immune Therapy in CISP

- 6 severely affected, non-ambulatory patients were treated with immunotherapy.
  - 4 received IVIg
  - 2 received IV steroids
- All had rapid and marked improvement in sensory ataxia and gait.
- 4 returned to normal ambulation whereas 2 others improved.

CISP Conclusions

1) Chronic immune sensory polyradiculopathy (CISP) appears to be a restricted form of CIDP localized to the sensory root level that responds favorably to immunotherapy.
2) CISP causes sensory ataxia.
3) CISP has normal nerve conduction studies, delayed SSEP responses, thickened nerve roots on MRI, elevated CSF protein, and inflammatory demyelinating changes on sensory rootlet biopsy.
4) CISP can be easily missed and patients may be incorrectly diagnosed as hysterical (4 of 15).

Treatment of CIDP

- Randomized, controlled trials have shown benefits for:
  - Prednisone
  - Plasma Exchange (PE)
  - IVIg
- CIDP should respond to immunotherapy and if it does not, the diagnosis should be rethought (POEMS syndrome, lymphoma, MGUS associated neuropathies, CMT and others).

Pulsed high-dose dexamethasone versus standard prednisolone treatment for chronic inflammatory demyelinating polyradiculoneuropathy (PREDICT study): a double-blind, randomised, controlled trial

Ivo N van Schaik, Filip Eftimov, Pieter A van Doorn, Esther Brusse, Leonard H van den Berg, W Ludo van der Pol, Catharina G Faber, Joost C H van Oostrom, Oscar J M Vogels, Rob D M Hadden, Bert U Kleine, Anouk G W van Norden, Jan J G M Verschuuren, Marcel G W Dijkgraaf, Marinus Vermeulen

Summary

Background Pulsed high-dose dexamethasone induced long-lasting remission in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in a pilot study. The PREDICT study aimed to compare remission rates in patients with CIDP treated with high-dose dexamethasone with rates in patients treated with standard oral prednisolone.

Lancet Neurol 2010; 9: 245–53
Published Online February 3, 2010
DOI:10.1016/S1474-4422(10)70021-1

Dexamethasone vs prednisolone In CIDP PREDICT study

- 40 patients with CIDP were randomized to receive pulsed high-dose dexamethasone or standard oral prednisolone.
- 24 received dexamethasone and 16 received prednisolone.
- 12 months, 16 patients were in remission –
  10 in dexamethasone and 6 in prednisolone group.
- Side effects not different except Cushingoid face were more common in prednisolone group.
- Pulsed high-dose dexamethasone worked as well as prednisolone.
- Comparison to IVIg needed.

IV Methylprednisolone (IV MP) in CIDP (My Practice)

- To reduce side effects of daily oral steroids, I prefer to use pulse IV MP.
- 1.0 gram given 3 times the first week and then 1.0 gram weekly thereafter is often used.
- See the patient back after 12 weeks to check the Neuropathy Impairment Score (NIS) and titrate the IV MP.
- Agitation and insomnia are common, but many of the other side effects are reduced with IV vs. oral steroids.
- Patients often tolerate long-term IV MP well without serious side effects.

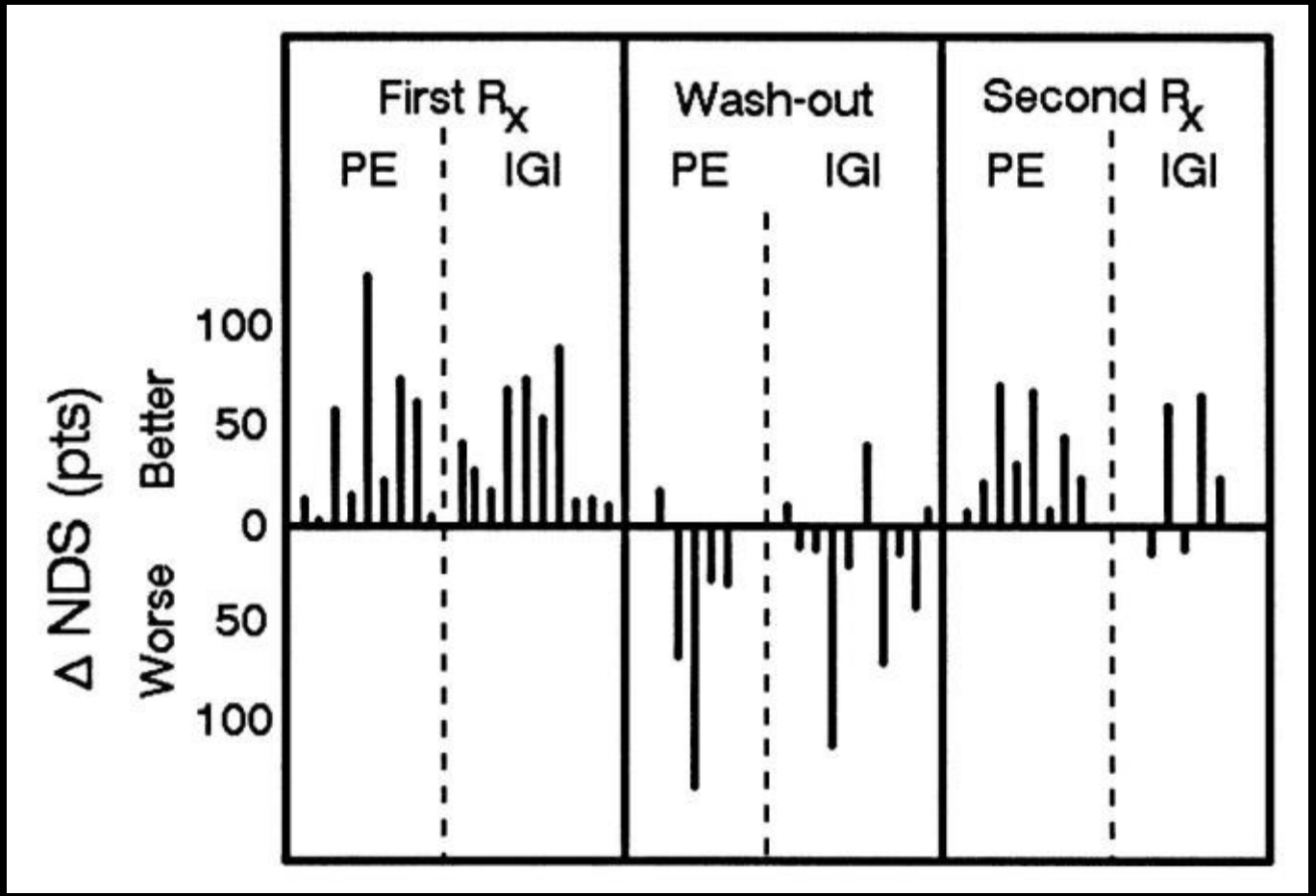
Plasma Exchange (PE) in CIDP

- Two double blind, sham-controlled, randomized studies have shown PE is an effective treatment (Dyck et al 1986, Hahn et al 1996).
- Treatment was effective but beneficial effects wore off after weeks to months.
- Because PE needs to be given in a medical center, it is usually not the first line treatment.
- Important to space out the treatments: twice weekly for 4 weeks, then once weekly for 8 weeks.
- Re-evaluate at 12 weeks with NIS and titrate.

IVIg in CIDP

- IVIg has become mainline treatment for CIDP.
- Several large, randomized, controlled trials have shown IVIg to be effective (Dyck et al 1994, Hahn et al 1996, Mendell et al 2001, Hughes et al 2008).
- In a long-term follow-up study, IVIg was an effective therapy for 81% of CIDP patients, but 86% needed ongoing IVIg (Van Doorn et al, 2003).
- The effect of IVIg is short-lived and patients need ongoing treatment.

PE vs. IVIg in CIDP



Dyck et al, Ann Neurol, 36(6) 838, 1994

Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial

*Richard A C Hughes, Peter Donofrio, Vera Bril, Marinos C Dalakas, Chunqin Deng, Kim Hanna, Hans-Peter Hartung, Norman Latov, Ingemar S J Merkies, Pieter A van Doorn, on behalf of the ICE Study Group**

Lancet Neurol 2008; 7: 136–44
Published Online January 7, 2008
DOI:10.1016/S1474-4422(07)70329-0

Summary

Background Short-term studies suggest that intravenous immunoglobulin might reduce disability caused by chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) but long-term effects have not been shown. We aimed to establish whether 10% caprylate-chromatography purified immune globulin intravenous (IGIV-C) has short-term and long-term benefit in patients with CIDP.

- ICE study lead to FDA approval for IVIg in CIDP.

IVIg in CIDP – ICE study, 2008

- 117 patients participated in randomized, double-blind, placebo-controlled, crossover trial.
- Loading dose of 2g\kg followed by maintenance dose of 1g\kg every three weeks.
- Primary endpoint was percentage of patients who had maintained improvement of INCAT disability score of 1 point through week 24.
- 32 of 59 (54%) treated with IVIg and 12 of 58 (21%) treated with placebo improved at 24 weeks (p=0.0002).
- Patients who continued to receive IVIg took a longer time to relapse than placebo patients (p=0.01).

IVIg in CIDP (My Practice)

- IVIg is the first line of treatment for CIDP for most providers (as well as me).
- Many physicians use IVIg every three week (or monthly) because this dose was used in the ICE study.
- This schedule works for many patients but may produce a "wearing off" effect before the next dose – some patients feel like they are on a rollercoaster.
- Because CIDP is a chronic illness, dosing does not need to be given in large infrequent boluses (as in AIDP) and may be better if given in frequent small doses (weekly infusions).
- Small frequent IVIg infusions decreases the "wearing off" effect.

IVIg in CIDP (My Practice)

- I use different IVIg regimes in different situations.
- In severe worsening cases:
  - 2 gm/kg IVIg over 5 days, then
  - 0.4 gm/kg twice weekly for 4 weeks, then
  - 0.4 gm/kg once weekly for 8 weeks.
- In moderately severe cases, start with 0.4 gm/kg weekly for 12 weeks.
- In mild cases, start with 0.4 gm/kg once every other week for 12 weeks.
- Re-evaluate at 12 weeks. If you re-evaluate too soon, the improvement is hard to appreciate.
- Use NIS and ∑CMAPs to determine improvement.

IVIg in CIDP (My Practice)

- Titrate IVIg dose by treatment response.
- Patients need different dosing of IVIg. Just because a standard dose was used in the ICE study does not mean that one dose works for all CIDP patients.
  - Treat most aggressively at first (first few months) to try to get maximal improvement, then wean.
  - Goal is ~ 90% better. It is usually unrealistic to try to regain 100% of function.
  - Adjust dosage and frequency of IVIg based on patient's response.
  - Reassess regularly (every three months initially then every 6 months).
- Ultimately, the goal is to maintain patients on as little IVIg as possible keeping patients at a high function and the physician should continue try to wean IVIg.

Subcutaneous Immunoglobulin (SCIG) in CIDP

- Several small studies suggest that SCIG is an attractive alternative to IVIg (Markvardsen et al. EJN, 2013, 2014).
- Most the patients included had previously responded to IVIg.
- Patients were treated with a weekly dosage of SCIG (compared to once every 3 weeks on IVIg).
- In general, the patients studied did not have worsening of neurological examination when switched to SCIG.
- Major advantage is that patients can self-administer SCIG at home.
- The efficacy seems similar to IVIg but further study is needed.

Secondary Immunosuppressive Agents in CIDP

- Other agents often used in combination with IVIg, PE or prednisone to reduce dosage of primary agents.
- Azathioprine (Imuran)
  - Start at 50 mg/day and titrate to goal of 2-3 mg/kg/day in divided doses.
- Mycophenolate mofetil (Cellcept)
  - Usual dose is 1.0 gram twice daily.
- I use these two agents with IVIg as a way of decreasing the amount of IVIg needed.

Secondary Immunosuppressive Agents in CIDP

- Cyclophosphamide (Cytoxan)
  - Has been used orally 1-2 mg/kg/day (50-150 mg/day) or intravenously in pulsing.
- Rituximab – control studies are lacking. It is useful in some cases.
  - Dosed 375 mg/m^2 or 100 mg given weekly for 4 weeks.
  - Can repeat every ~ 6 months.
- In general, one wants to continue primary treatment (IVIg) until other agents take effect.

Autologous Peripheral Blood Stem Cell Transplantation (ASCT) for CIDP

- Case reports and small series report efficacy of ASCT in CIDP.
- Press et al (JNNP 2014) reported on 11 CIDP patients treated with ASCT.
- INCAT and Rankin scores improved significantly within 6 months after ASCT.
- 3 of 11 patients relapsed during follow-up period and 8 of 11 maintained drug-free remission.
- Results suggest that ASCT is a potentially good option for CIDP but controlled studies are needed.
- As of now, insurance will not pay for ASCT in CIDP.

Treatment Strategies for Refractory CIDP

- If the neuropathy is not improving with IVIg (the neurological exam and NIS are getting worse)
  - Increase the dosage and frequency of IVIg.
  - Assess treatment response (three months later).
- If after the IVIg is increased, the patient's neurological exam is still worsening switch to another treatment.
  - IV methylprednisolone can be added.
  - Oral prednisone
  - PE
  - These can be done in isolation or with IVIg.
- Some patients only respond to one treatment - IVIg, PE or steroids but not the other treatments.

Refractory CIDP

- Most patients with CIDP do respond to one of the proven treatments (corticosteroids, IVIg or PE) alone or in combination.
- If a patient does not improve with immunotherapy the diagnosis of CIDP needs to be questioned (further workup may be needed).
- However, relapses or worsening of disease spontaneously or with weaning of treatment are common and should be expected.
- In severe cases, CIDP can be a fatal illness (usually due to respiratory failure).

Refractory CIDP

- Reasons patients are treatment unresponsive or poorly responsive include:
  - Very severe, progressive, active illness.
  - Wrong diagnosis (not CIDP).
  - Not enough treatment (need to use higher amounts or more frequent dosing of steroids, IVIg or PE).
  - Significant secondary axonal loss.
- In CIDP cases with severe weakness, dense fibrillations potentials and muscle atrophy, it is important to discuss with the patient that a prolonged aggressive treatment trial will be necessary (axonal repair takes months to years).

Refractory CIDP

- In severe cases biweekly IVIg or biweekly plasma exchange given for a year may be necessary and I have seen such cases go from being wheelchair dependent to walking.
- Use of combination of treatments is often helpful in such cases.
  - IVIg and IV methylprednisolone used together.
  - PE followed by IVIg.
  - Rituxan with IVIg.
  - Cytoxan with IVIg.
- One should be more aggressive in more severe cases.

Neuropathies Resembling CIDP (CIDP Look-A-Likes)

- Inflammatory neuropathies but not true forms of CIDP.
  - IgM (anti-MAG) neuropathy (DADS phenotype)
  - Multifocal motor neuropathy
  - POEMS syndrome

IgM (anti-MAG) Neuropathy

- A demyelinating polyneuropathy associated with IgM monoclonal gammopathy (often Kappa).
- Many of the cases have antibodies to myelin-associated glycoprotein (MAG).
- This is a sensory predominate syndrome that presents with sensory ataxia.
- These patients presents with a length-dependent, sensory neuropathy with mild weakness confined to distal segments.

IgM (anti-MAG) Neuropathy

- The pattern of involvement of these patients has been described as distal acquired demyelinating symmetric (sensory) (DADS).
- The distal motor latencies of IgM neuropathy tends to be long whereas the conduction velocities are mildly slow.
- There have been reports of deposits of IgM and complement on myelin sheaths and widening of the myelin lamellae.
- This is an inflammatory demyelinating neuropathy.

Widening of Myelin Lamellae

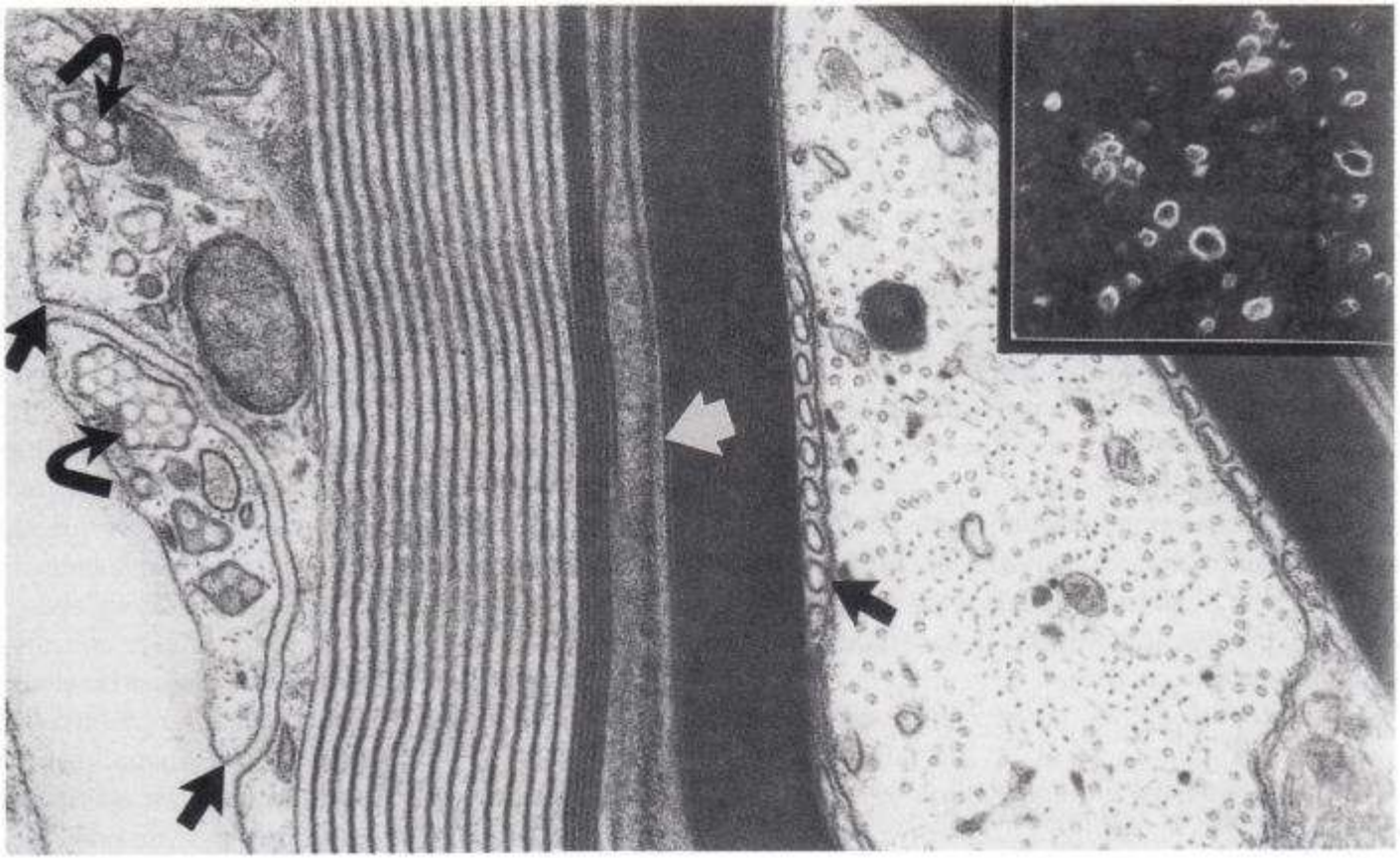


FIGURE 100–9
Myelinated fiber showing different stages of splitting of myelin lamellae. Normal compact myelin is present only in the inner half of the sheath. Note irregularities of outer and inner lips of enveloping Schwann cell (*straight black arrows*). *Curved arrows* point to honeycomb-like inclusions derived from myelin breakdown. Accumulation of proteinaceous material and membranous debris in periaxonal location (*lower right corner*) and between dissociated lamellae of myelin (*white arrow*) (×65,000). **Inset:** Localization of κ light chain at the periphery of myelinated fibers (approximately ×200). (From Lach, B., Rippstein, P., Atack, D., et al.: Immunoelectron microscopic localization of monoclonal IgM antibodies in gammopathy associated with peripheral demyelinating neuropathy. Acta Neuropathol. 85:298, 1993, with permission of Springer-Verlag.)

Lach, B. et al, Acta Neuropathol. 85:298, 1993

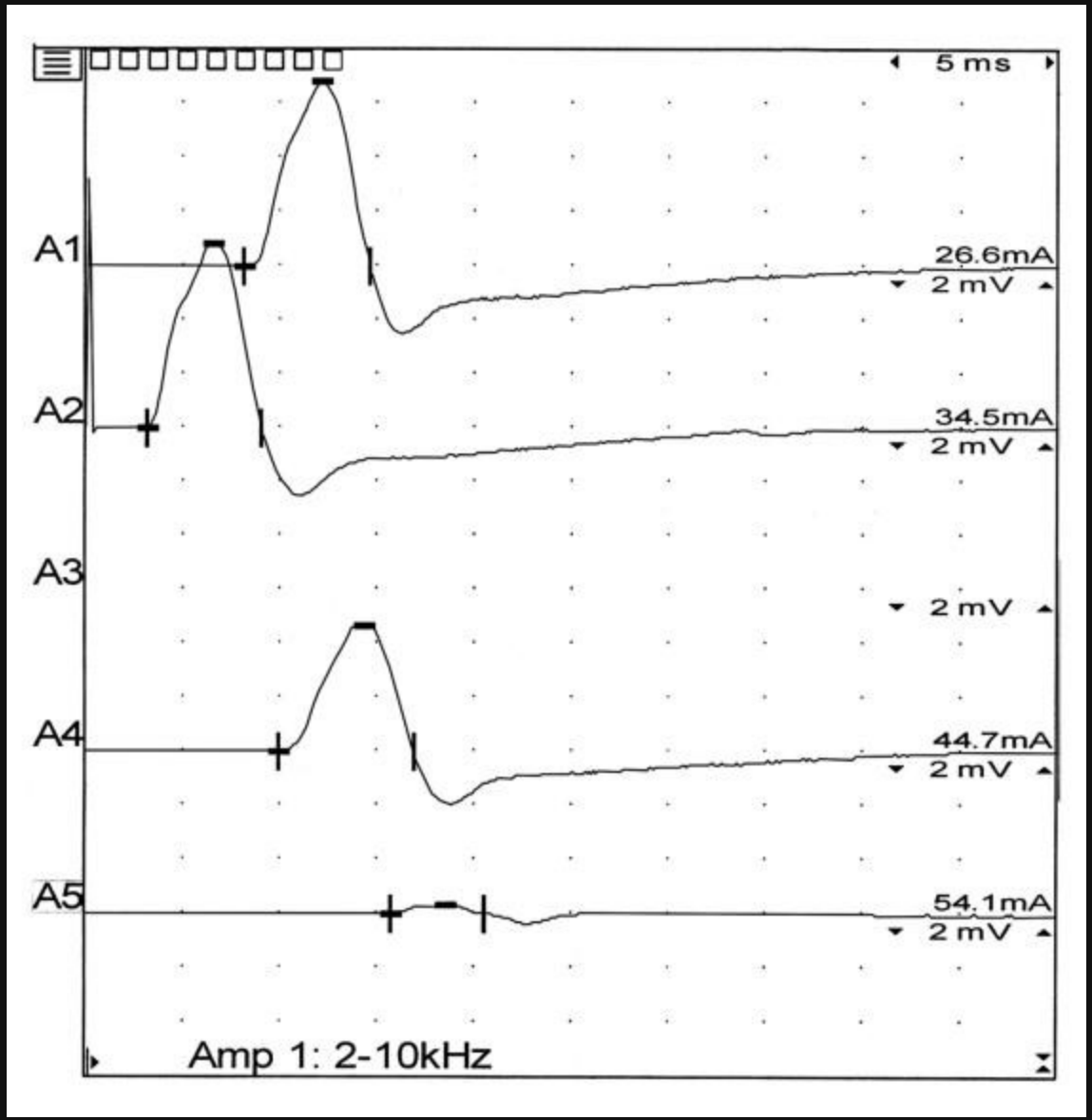
IgM (anti-MAG) Neuropathy

- Responds less favorably to immunotherapy than other forms of CIDP (the IgG and IgA neuropathies responded better to PE than IgM – Dyck et al, NEJM 1991).
- IVIg still helps some of the IgM neuropathy patients.
- Studies with Rituximab in IgM neuropathy showed promising results (Dalakas et al, Ann Neur 2009).
  - 4 of 12 Rituximab patients improved.
  - 0 of 13 placebo patients improved (p=0.04).
- These neuropathies tend to be mild so many experts question if they should be treated at all.
- Physicians and patients should decide together if a treatment trial is warranted. It is okay to observe.

Multifocal Motor Neuropathy (MMN)

- An asymmetrical, upper limb predominant, motor neuropathy with focal conduction block.
- Slowly progressive with weakness and wasting.
- Normal sensory examination.
- Looks like ALS, but only lower motor neuron and affects individual peripheral nerves.
- Originally, MMN was felt to be a subtype of CIDP, but now MMN thought to be a unique and separate disease.

Right Proximal Ulnar Motor Nerve Conduction Block



MMN Pathogenesis

- 40-80% of MMN patients have anti-GM_1 antibodies.
- Does conduction block mean a demyelination?
  - A study of fascicular nerve biopsies from conduction blocks failed to show demyelination (Taylor et al, 2004).
  - Axonal degeneration, multifocal fiber loss and minimal inflammation were seen.
- MMN is probably not a demyelinating neuropathy; probably there is an immune attack on ion (sodium) channels.

Treatment of MMN

- MMN responds to immunotherapy, especially IVIg.
- Four small randomized, double-blind, controlled studies have shown benefit with IVIg.
- Usually there is a rapid improvement that is temporary.
- Since MMN is a chronic gradually worsening disease, I treat with IVIg 0.4 gm/kg weekly for 12 weeks.
- I evaluate with NIS and titrate based on response.

Treatment of MMN

- Treatment of MMN is usually not as effective as CIDP.
- Patients with muscle atrophy respond less well (due to axonal loss) but should still be treated with IVIg.
- IVIg is an effective treatment but does not prevent disease progression.
- Other agents have been used, including oral cyclophosphamide (controversial) and rituximab (monoclonal B-cell antibody).

POEMS Syndrome

- POEMS syndrome is a paraneoplastic neuropathy associated with osteosclerotic myeloma or Castleman's Disease.
- POEMS syndrome is an acronym for:
  - Polyneuropathy
  - Organomegaly
  - Endocrinopathy
  - Monoclonal protein
  - Skin changes
- The most prominent feature of POEMS syndrome is the polyneuropathy.

Criteria for POEMS Syndrome

- The diagnosis of POEMS syndrome is confirmed with by having both mandatory criteria, one major criteria and one minor criteria.

TABLE I. Criteria for the Diagnosis of POEMS Syndrome[a]

Mandatory major criteria	1. Polyneuropathy (typically demyelinating)
	2. Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria (one required)	3. Castleman disease[a]
	4. Sclerotic bone lesions
	5. Vascular endothelial growth factor elevation
Minor criteria	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
	7. Extravascular volume overload (edema, pleural effusion, or ascites)
	8. Endocrinopathy (adrenal, thyroid,[b] pituitary, gonadal, parathyroid, pancreatic[b])
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)
	10. Papilledema
	11. Thrombocytosis/polycythemia[c]
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B_{12} values

Dispenzieri, Angela. POEMS syndrome: Update on diagnosis, risk-stratification, and mangement, American Journal of Hematology, Vol 90, No. 10, October 2015, pages 952 – 962.

Neuropathy Features: POEMS vs. CIDP

- POEMS patients are:
  - older, average age mid 50's (CIDP is 40's).
  - less cranial nerve involvement (2% vs. 18%).
  - more muscle atrophy (52% vs. 24%).
  - more distal weakness.
  - more pain (76% vs. 7%).
  - more positive neuropathic sensory symptoms.

Nasu, et al. Different neurological and physiological profiles in POEMS syndrome and chronic inflammatory demyelinating polyneuropathy, J Neurol Neurosurg Psychiatry 2012;83:476-479.

POEMS Syndrome – Neuropathy

- Usually begins with sensory symptoms (often pain) in the feet (atypical for CIDP).
- Weakness begins distally but becomes severe (patients often in wheelchairs).
- The electrophysiology shows more uniform demyelination and axonal loss than CIDP (Mauermann et al, JNNP, 2012;83:480-486).
  - Greater reduction in motor amplitudes.
  - Greater slowing of motor and sensory CVs.
  - Less prolonged distal latencies.
  - Less frequent conduction blocks or temporal dispersion.

Uniform demyelination and more severe axonal loss distinguish POEMS syndrome from CIDP

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J Neurol Neurosurg Psychiatry 2012;83:480e486. doi:10.1136/jnnp-2011-301472

See Editorial commentary, p 474

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ABSTRACT

Objective POEMS syndrome (the acronym reflects the common features: Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein and Skin changes) is a paraneoplastic disorder with a 'demyelinating' peripheral neuropathy that is often mistaken for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The nerve conduction study (NCS) and electromyography (EMG) attributes that might differentiate POEMS from CIDP and lead to earlier therapeutic intervention were explored.

Methods NCS/EMG of POEMS patients identified through retrospective review from 1960 to 2007 were compared with matched CIDP controls.

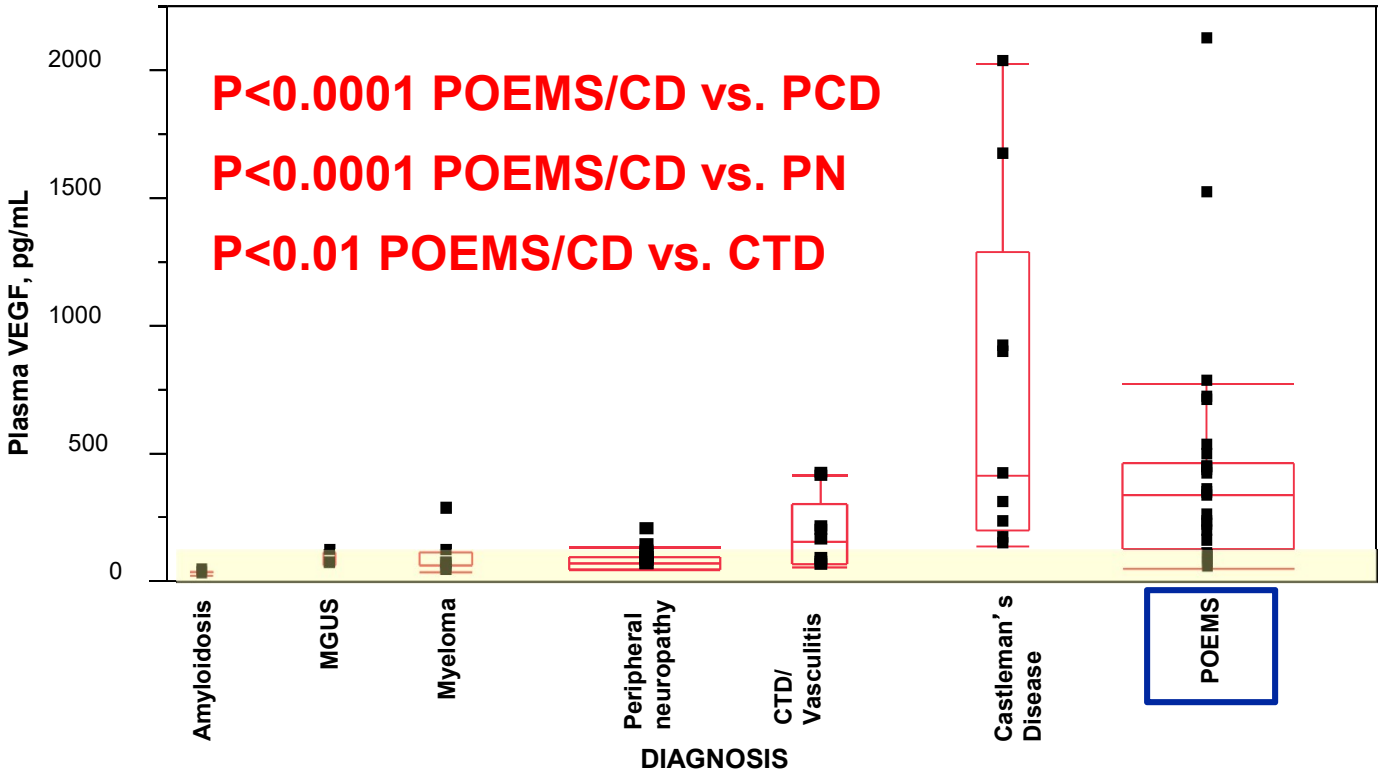
Results 138 POEMS patients and 69 matched CIDP controls were compared. POEMS patients demonstrated length dependent reduction in compound muscle action potentials, low conduction velocities, prolonged distal latencies and prolonged F wave latencies. Compared with CIDP controls, POEMS patients demonstrated: (1) greater reduction of motor amplitudes, (2) greater slowing of motor and sensory conduction velocities, (3) less prolonged motor distal latencies, (4) less frequent temporal dispersion and conduction block, (5) no sural sparing, (6) greater number of fibrillation potentials in a length dependent pattern and (7) higher terminal latency indices (TLI). TLI $ 0.38 in the median nerve demonstrated a sensitivity of 70% and specificity of 77% in discriminating POEMS from CIDP.

Conclusions NCS/EMG of POEMS syndrome suggests both axonal loss and demyelination. Compared with CIDP, there is greater axonal loss (reduction of motor amplitudes and increased fibrillation potentials), greater slowing of the intermediate nerve segments, less common temporal dispersion and conduction block, and absent sural sparing. These findings imply that the pathology of POEMS syndrome is diffusely distributed (uniform demyelination) along the nerve where the pathology of CIDP is probably predominantly proximal and distal. Median motor TLI may be useful in clinically distinguishing these disorders.

Biomarkers in POEMS Syndrome: VEGF

- A hallmark of POEMS syndrome (multisystem disease) is the presence of angiogenic and proinflammatory cytokines.
- Levels of vascular endothelial growth factor (VEGF), IL-1β, IL-6, and TNF-α are all increased in POEMS.
- Elevated VEGF level is a good biomarker in POEMS.
- Elevated platelet (thrombocytosis) level is also a good biomarker for POEMS.

Plasma VEGF in POEMS Syndrome

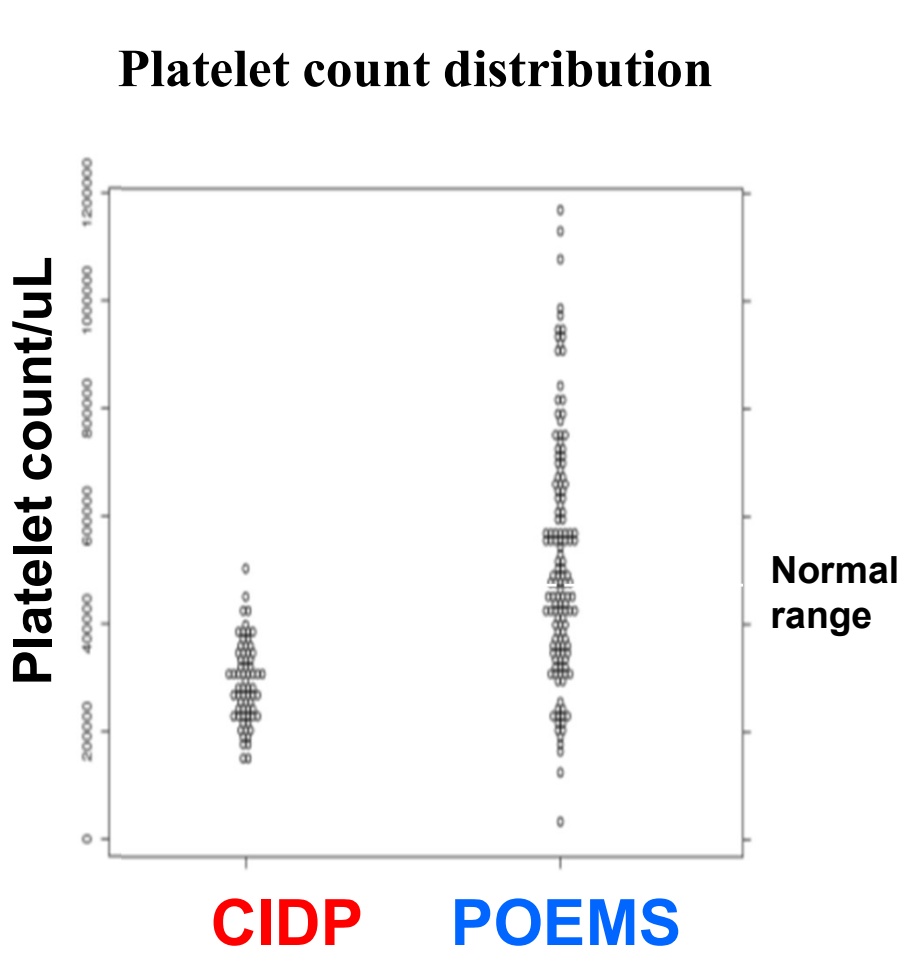


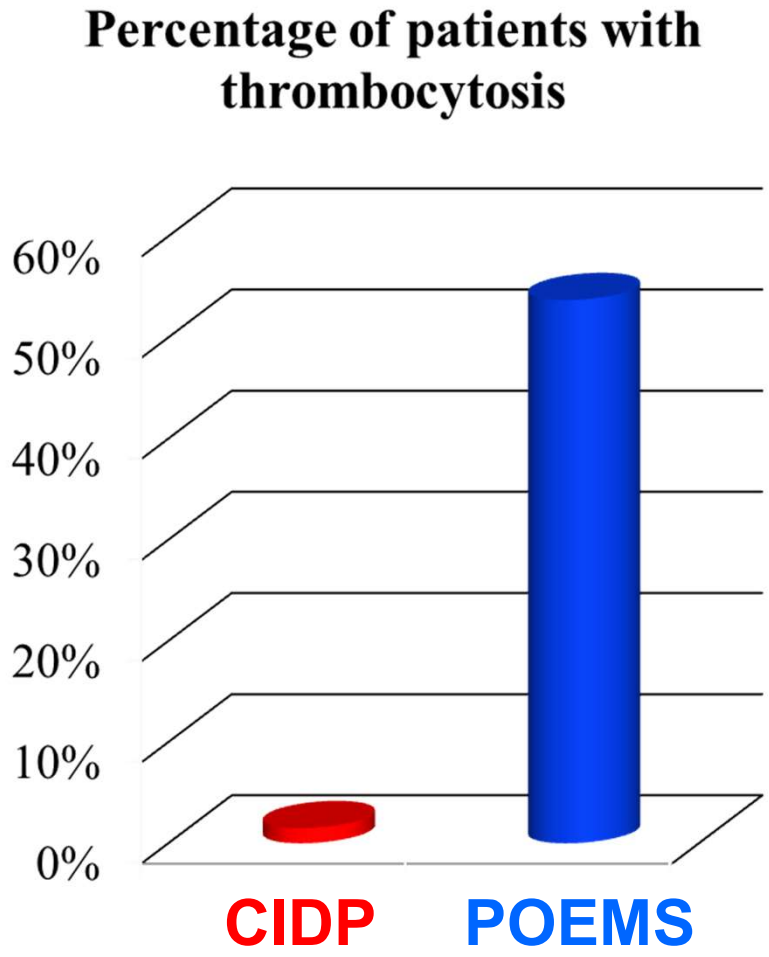
VEGF > 200 pg/mL
Sensitivity 68%
Specificity 95%

	AL *N=4*	MM *N=9*	PN *N=29*	CTD *N=9*	CD *N=9*	POEMS *N=29*
Median VEGF[a]	**38**	**68**	**50**	**142**	**412**	**342**
Range	**31-42**	**35-271**	**31-180**	**35-403**	**132-2030**	**48-2112**

D' Souza *Blood.* Oct 27 2011;118(17):4663-4665 Mayo study, CD = Castleman's Disease

Thrombocytosis is a Distinguishing Feature





Naddaf E. Muscle Nerve. 2015 Oct;52(4):658-9.

Nerve Pathological Findings: POEMS vs. CIDP

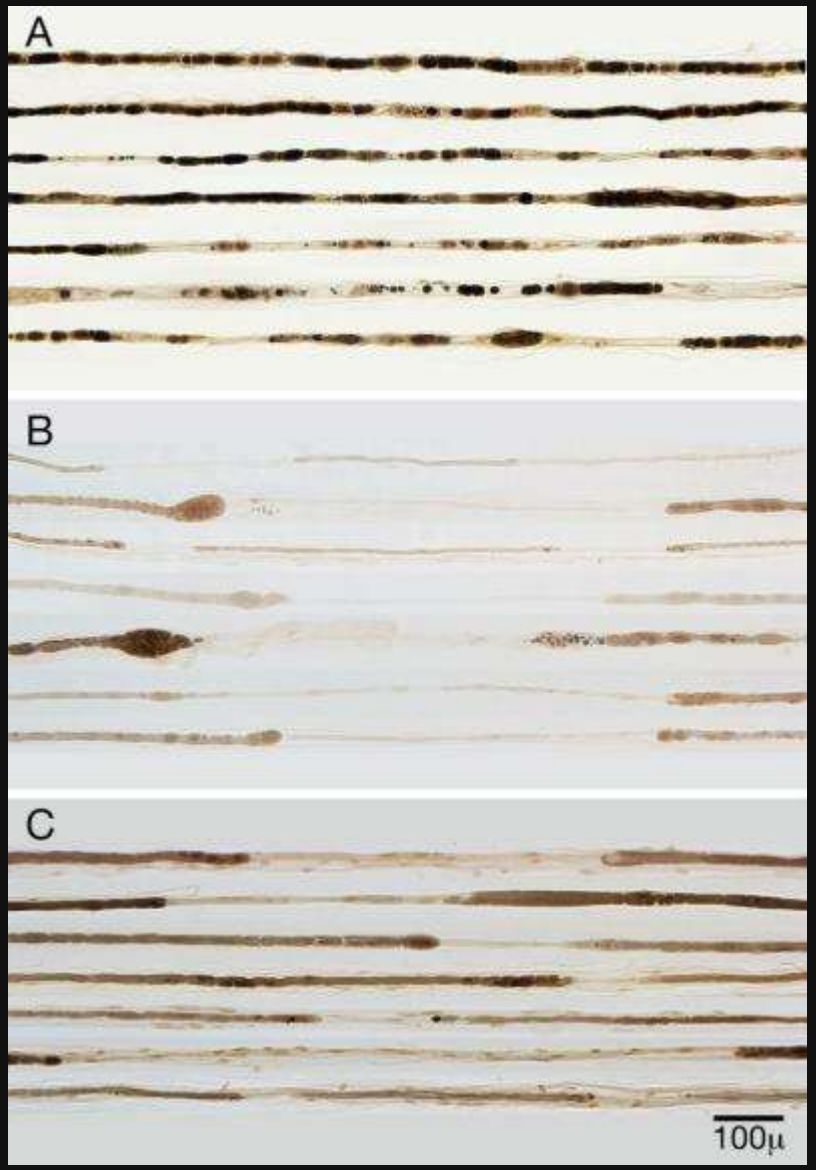
(Piccione et al. Acta Neuropathologica Communications 4:116, 2016)

Teased Fibers

POEMS
Axonal Degeneration

POEMS
Segmental Deyelination

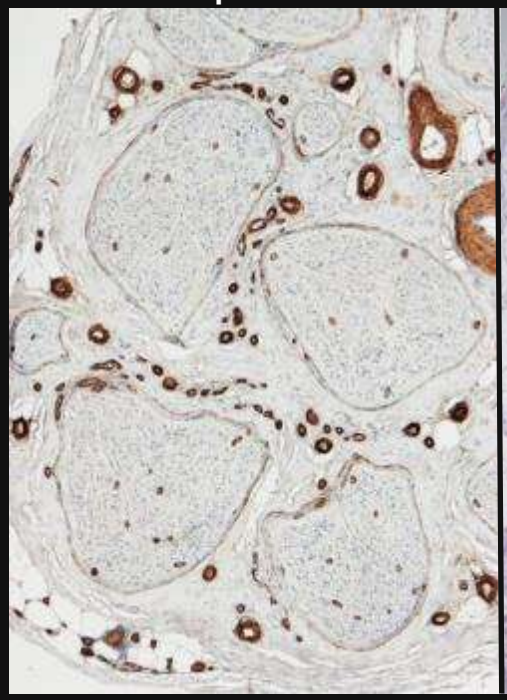
CIDP
Segmental Deyelination



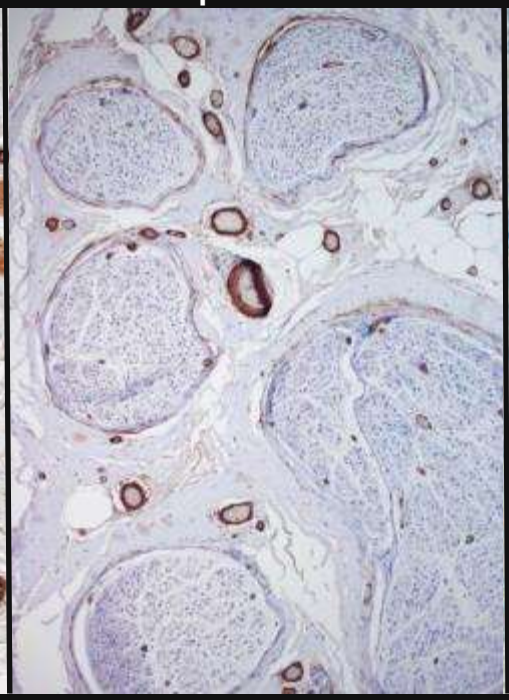
POEMS Syndrome – Pathology

- Comparison of 35 POEMS and 26 CIDP nerve biopsies.
- Pathological features of POEMS show paraneoplastic vasculopathy whereas CIDP shows inflammatory demyelination.
  - POEMS biopsies have significantly more epineurial neovascularization and axonal degeneration.
  - CIDP biopsies have more onion-bulbs and endoneurial inflammation

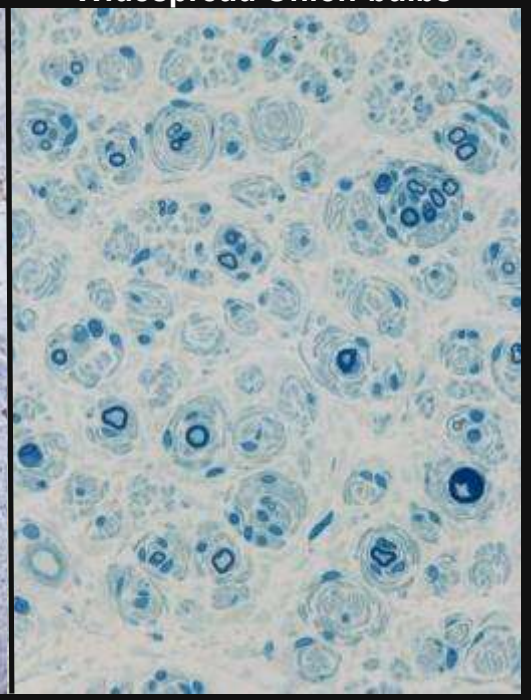
POEMS
Increased Epineurial Vessels



CIDP
Normal Epineurial Vessels



CIDP
Widespread Onion-bulbs



POEMS Syndrome – Treatment

- POEMS syndrome does not respond to conventional immunotherapy (IVIg, PE or steroids).
- So in a case of refractory CIDP, POEMS syndrome should be considered.
- Treatment is aimed at treating the underlying malignancy.
  - Radiation to the plasmacytoma.
  - Chemotherapy if not an isolated lesion.
  - Autologous stem cell transplant.

Management of POEMS Syndrome

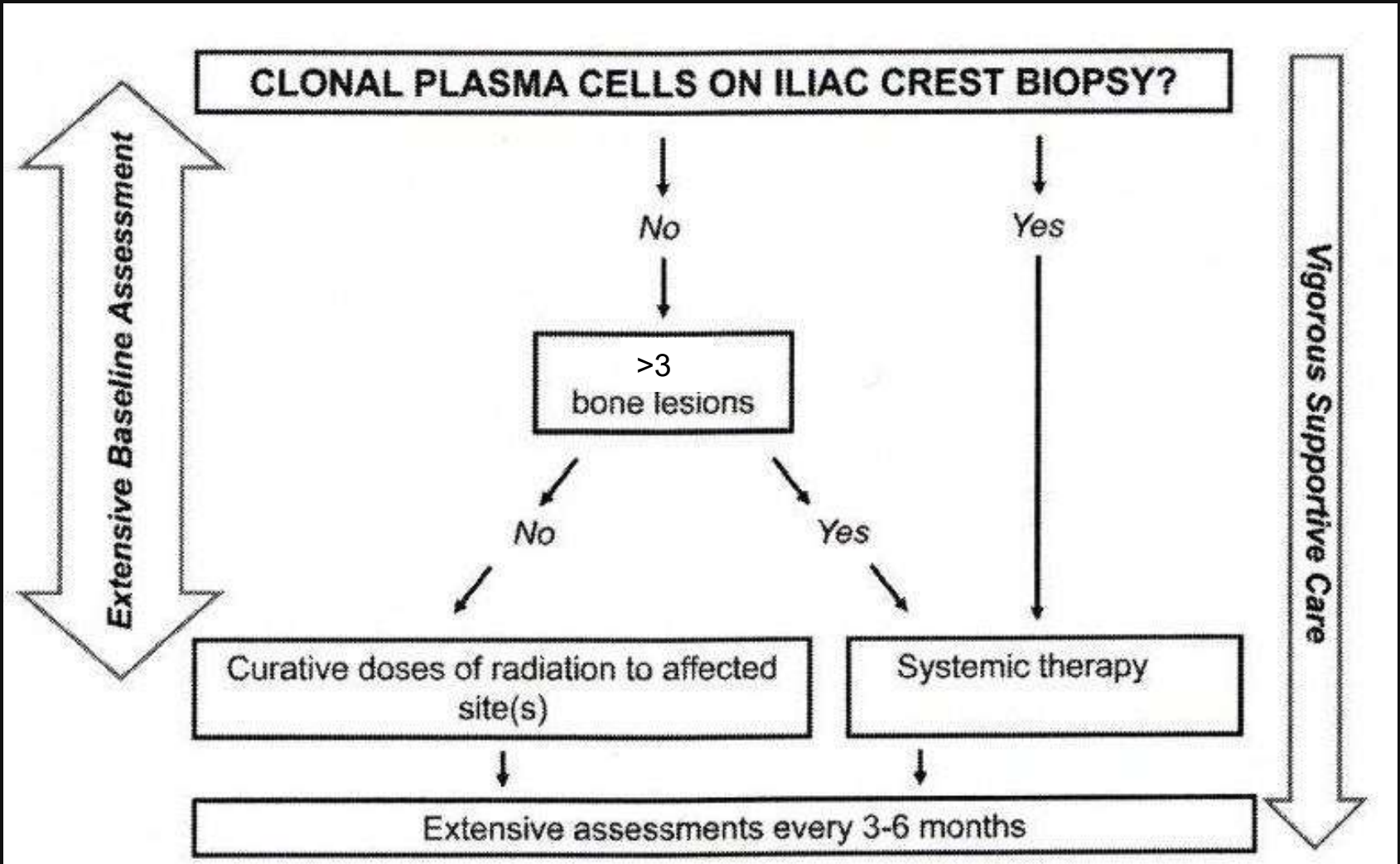


Figure 3. Algorithm for the treatment of POEMS syndrome.

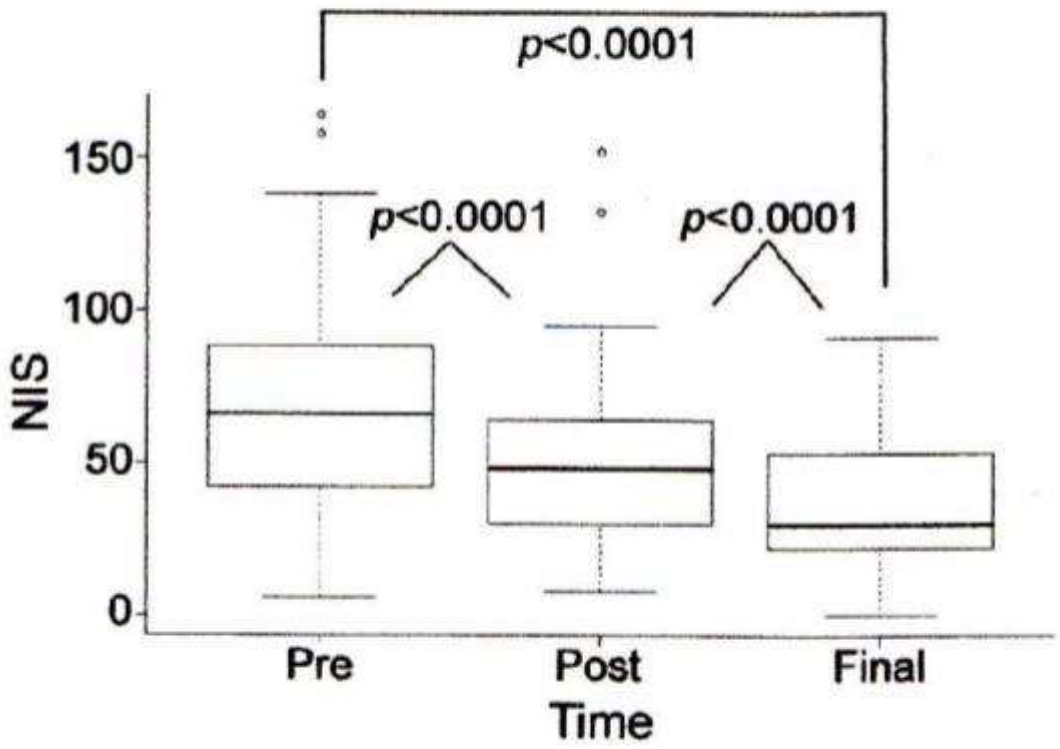
Dispenzieri, Angela. POEMS syndrome: Update on diagnosis, risk-stratification, and mangement, American Journal of Hematology, Vol 90, No. 10, October 2015, pages 952 – 962.

Polyneuropathy Improvement After ASCT in POEMS

(Karam et al. Neurology 2015;84:1981-1987)

- Retrospective study of 60 Mayo Clinic POEMS patients seen between 1999 and 2012 who had ASCT performed looking at neuropathy.
- All patients except one had improvement in neurological functional measures (NIS and mRS).
- The median NIS improved from 66 points (baseline) to 48 points (T1) to 30 points (T2) (meaningful recovery) ($p < 0.0001$).
- There was a significant correlation between improvement of NIS score and VEGF levels at T1 ($p < 0.0001$).

Figure 1 **Improvement in NIS following autologous stem cell transplantation**



Median NIS improved from 66 points at t0 to 48 points at t1 and 30 points at t2 ($p < 0.0001$). Box = 25th and 75th percentiles; bars = minimum and maximum values. NIS = Neuropathy Impairment Score.

Karam et al. Neurology 2015;84:1981-1987

POEMS Syndrome Conclusions

1) POEMS syndrome mimics CIDP and so in cases of "refractory CIDP" who are not responding to immunotherapy, POEMS neuropathy should be strongly considered.
2) VEGF and thrombocytosis are useful biomarker for POEMS syndrome.
3) NCS/EMG and nerve pathology show more uniform demyelination and axonal degeneration in POEMS than in CIDP.
4) Treatment of POEMS syndrome depends on the extent of the spread of the plasma cell disorder with isolated lesions being treated with radiation alone and disseminated disease being treated with chemotherapy and ASCT.

Overall CIDP Conclusions

1) CIDP is an inflammatory demyelinating neuropathy that is motor predominant with symmetrical weakness in proximal and distal segments.

2) There are different varieties of CIDP that present with different clinical phenotypes including classical, multifocal, CISP and others.

3) The first step in treatment of CIDP is the correct diagnosis and many patients are wrongly diagnosed with CIDP and so don't respond well to immunotherapy (thought to be refractory).

4) CISP is a form of CIDP confined to the sensory nerve roots and presents with sensory ataxia and normal nerve conduction studies and respond to immunotherapy.

Overall CIDP Conclusions

5) Multifocal CIDP (MADSAM) presents with asymmetrical motor and sensory neuropathy often in the upper limbs.

6) Multifocal motor neuropathy (MMN) is upper limb predominant and is pure motor. The conduction blocks are probably not due to inflammatory demyelination.

7) The three proven treatments for CIDP are steroids, plasma exchange and IVIG but many other agents can be used in refractory cases.

8) POEMS syndrome is a paraneoplastic demyelinating neuropathy that resembles CIDP but does not respond to traditional immunotherapy and so presents as “refractory CIDP”.

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