# A personal journey through conduction blocks, nodes and surroundings

**Antonino Uncini**


Chair of Neurology
Department of Neuroscience, Imaging and Clinical Sciences
University "G. d'Annunzio"
Chieti-Pescara, Italy

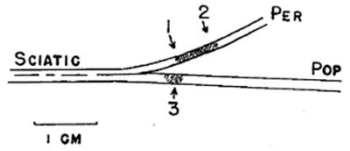
# Conduction block: the origins

Archives of Neurology and Psychiatry
VOLUME 51 JANUARY 1944 NUMBER 1


PARALYSIS OF NERVE INDUCED BY DIRECT PRESSURE AND BY TOURNIQUET

D. DENNY-BROWN, M.B., F.R.C.P.
AND
CHARLES BRENNER, M.D.
BOSTON

| Nerve | Motor Response: Above Lesion | Below Lesion |
|---|---|---|
| Peroneal | None | Good (90%) |



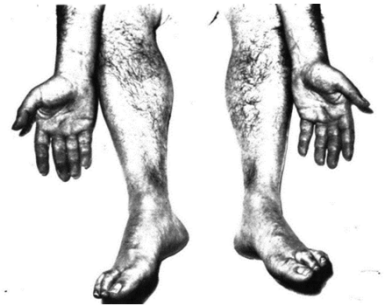

JUNE 1958
BRAIN
VOL. 81, PART 2.

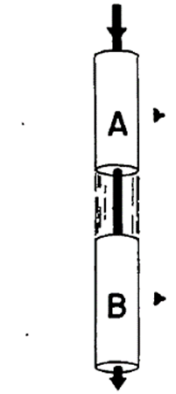
RECURRENT POLYNEUROPATHIES AND THEIR CORTICOSTEROID TREATMENT

WITH FIVE-YEAR OBSERVATIONS OF A PLACEBO-CONTROLLED CASE TREATED WITH CORTICOTROPHIN, CORTISONE, AND PREDNISONE

BY
JAMES H. AUSTIN[1]

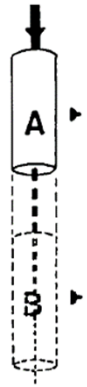
20 relapses without atrophy






CONDUCTION BLOCK

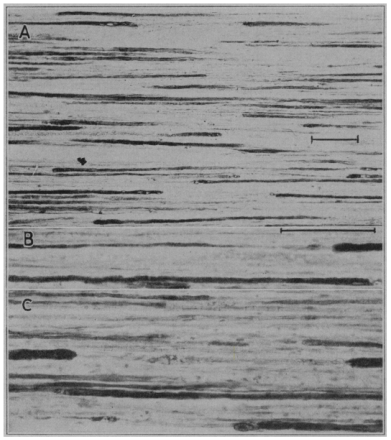
EXAMPLE Tourniquet paralysis
Segmental neuropathies
Myelin altered segmentally — Stimulation A - No response
Axone anatomically preserved — Stimulation B - Response
Muscle preserved — EMG - No fibrillation




WALLERIAN DEGENERATION

EXAMPLE : Peripheral nerve section
Myelin degenerates distally — Stimulation A - No response
Axone degenerates distally — Stimulation B - No response
Muscle atrophies — EMG - Fibrillation

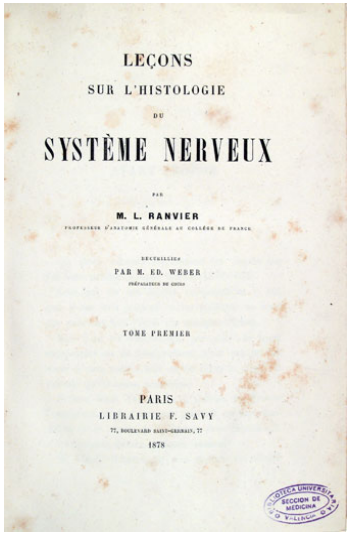
- CB was associated with demyelination across the compressed nerve segment
- Return of conductivity was associated with reappearance of thin myelin coat
- No muscle atrophy

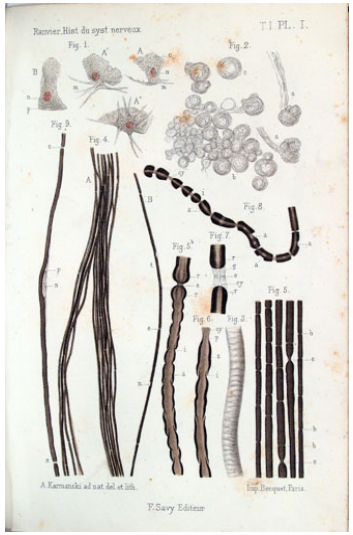


# The node of Ranvier

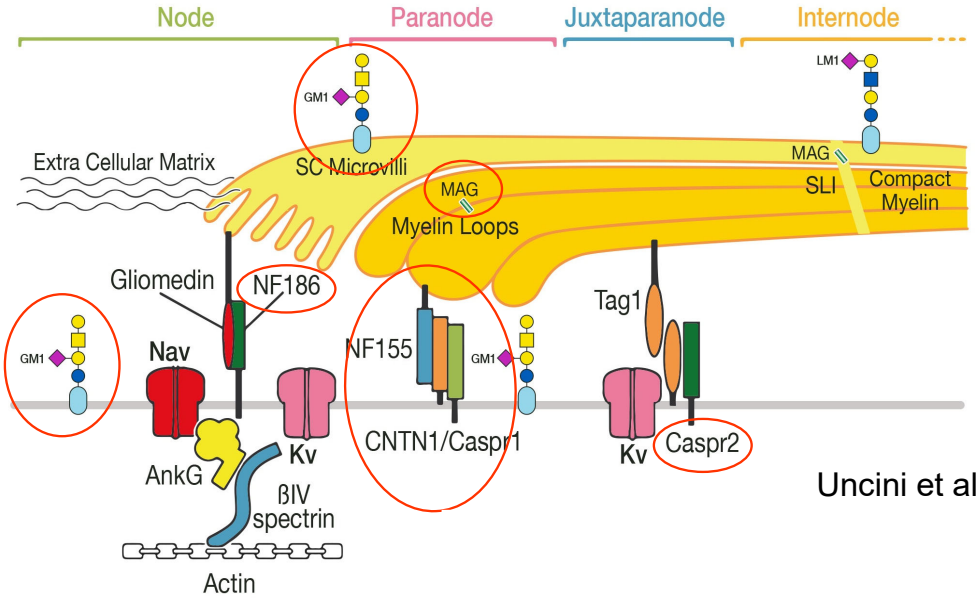
Louis-Antoine Ranvier
(1835-1922)

"Les étranglements annulaires",1871



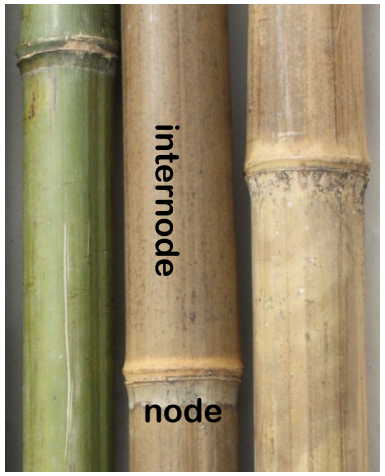



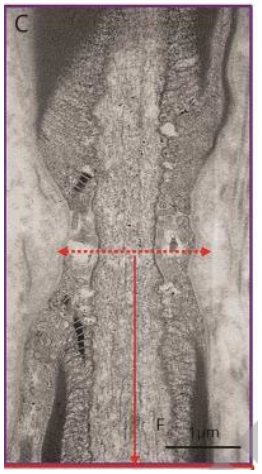
# The domains of the myelinated fibre




Uncini et al. 2022

**Nodes and internodes**:
when botany meets anatomy and misleading terms are coined




…. are constrictions not knots…
(Ranvier)

# The beginning of the my journey

- 1984: Congress of the Italian Socity of EEG and Clinical Neurophysiology, Lipari
- 1985: Peripheral Nerve Laboratory of Pennsylvania University, Philadelphia
- 1986: Neurological Institute of Columbia University, New York

Austin J. Sumner

Lewis P. Rowland
(1925-2017)

Norman Latov

NEUROLOGY (Ny) 1982;32:958-64

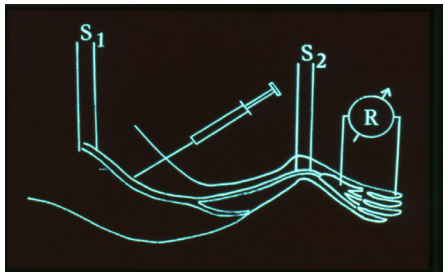
**Multifocal demyelinating neuropathy with persistent conduction block**

Richard A. Lewis, Austin J. Sumner, Mark J. Brown, and Arthur K. Asbury

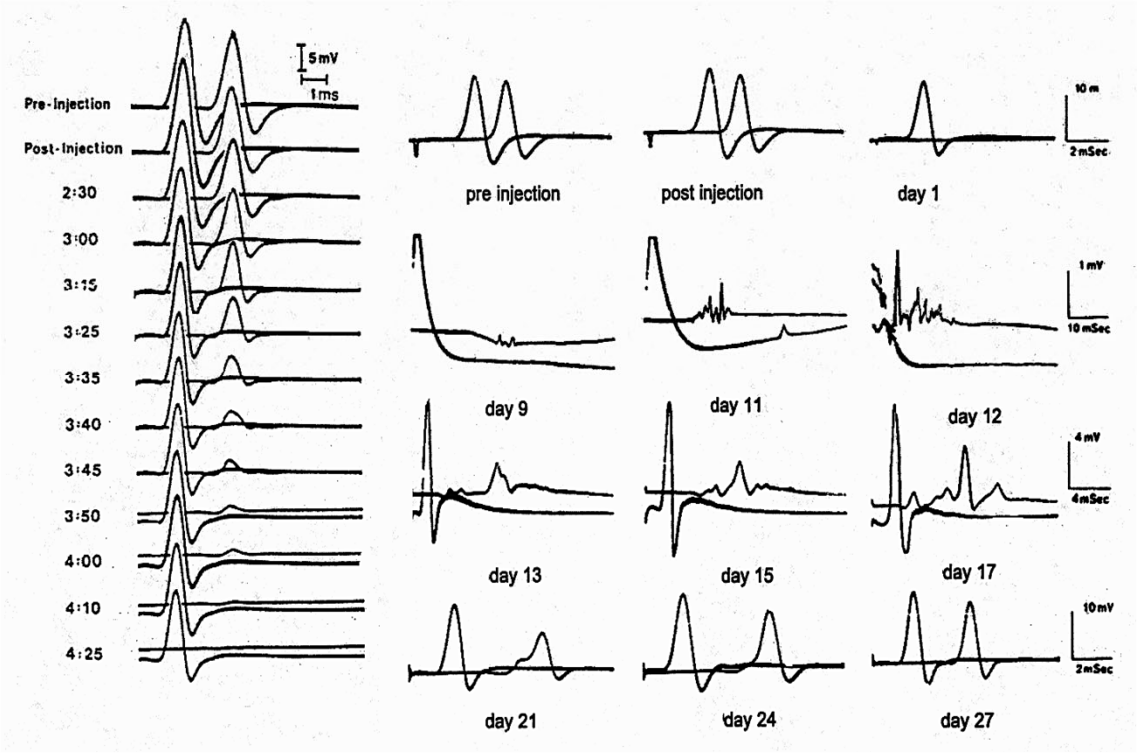
Acute Conduction Block Associated with Experimental Antiserum-Mediated Demyelination of Peripheral Nerve

Austin J. Sumner, MD,* Kyoko Saida, MD,† Takahiko Saida, MD,† Donald H. Silberberg, MD,* and Arthur K. Asbury, MD*

The intraneural injection model



# Conduction block and temporal dispersion in acute demyelination




CB is the correlate of acute paranodal demyelination

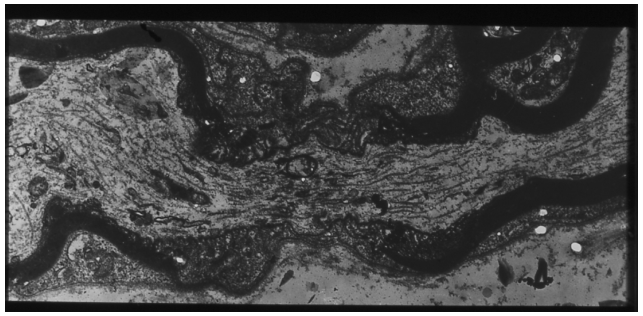
TD and very slow CV are the correlates of remyelination

MUSCLE & NERVE 11:871–879 1988

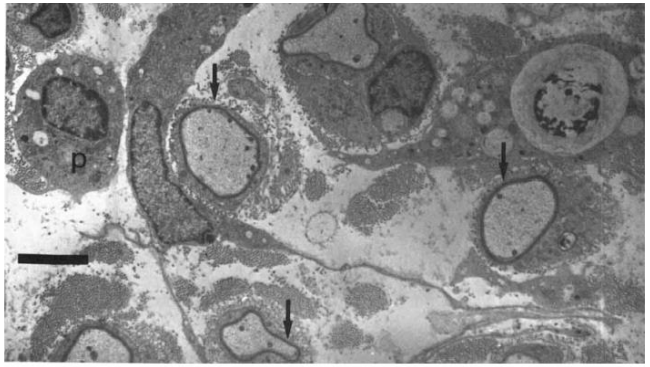
## TELLURIUM-INDUCED DEMYELINATION: AN ELECTROPHYSIOLOGICAL AND MORPHOLOGICAL STUDY

ANTONINO UNCINI, MD, JOHN D. ENGLAND, MD, EDWARD K. RHEE, BA, SERGE W. DUCKETT, MD, PhD, and AUSTIN J. SUMNER, MD

EM at 6 hours



EM at 11 days



*Brain* (1984), **107**, 219-239

# CONDUCTION BLOCK AND DENERVATION IN GUILLAIN-BARRÉ POLYNEUROPATHY

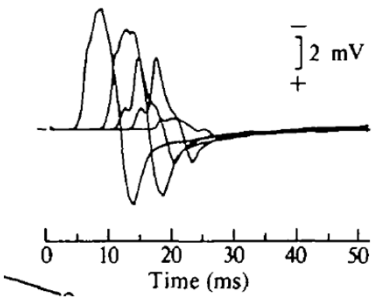
*by* W. F. BROWN *and* T. E. FEASBY

*Journal of Neurology, Neurosurgery, and Psychiatry* 1985;**48**:239–244

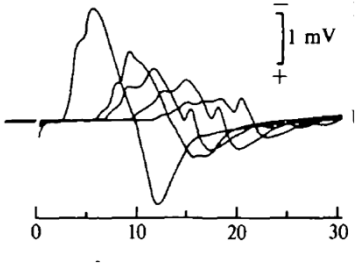
# The pathological basis of conduction block in human neuropathies

TE FEASBY,* WF BROWN,* JJ GILBERT,† AF HAHN*

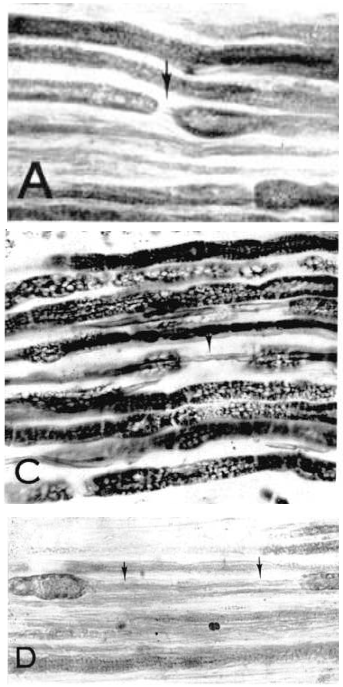
## Conduction Block



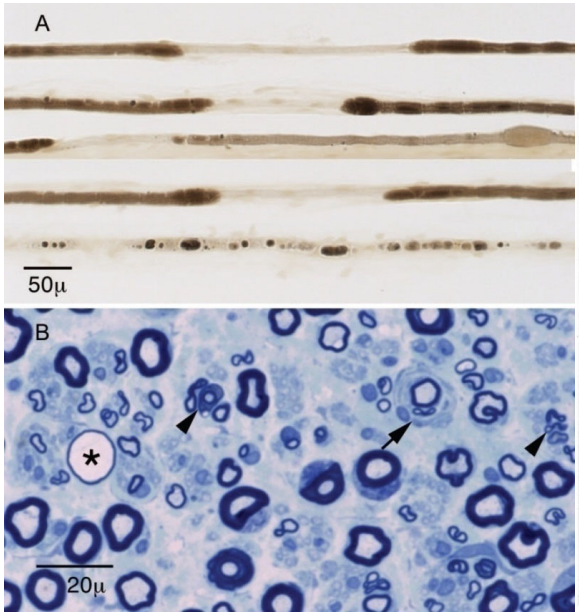

## Abnormal Temporal Dispersion



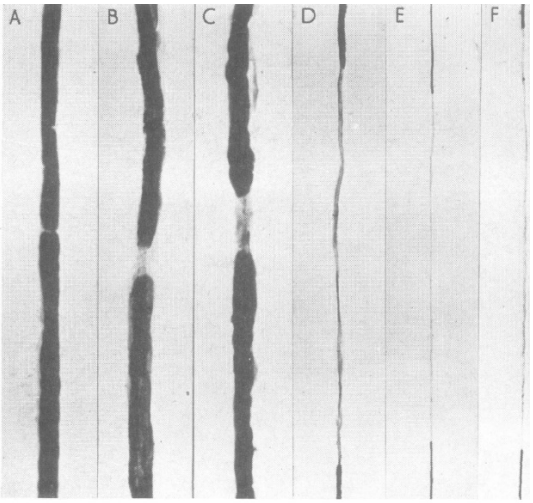

## AIDP




## CIDP




## EAN

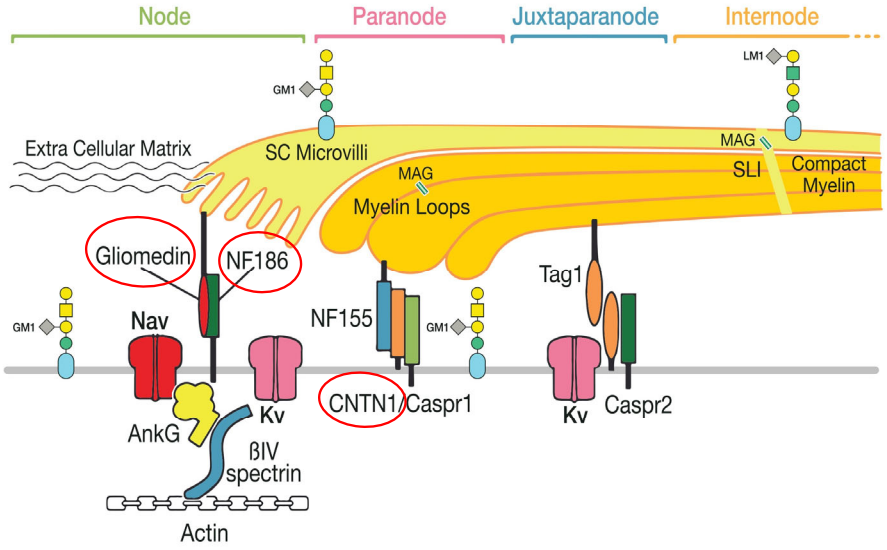



**Demyelination is the pathological basis of CB**

# Nodal targets in GBS and CIDP

100 GBS and 50 CIDP sera (Devaux et al. 2012):

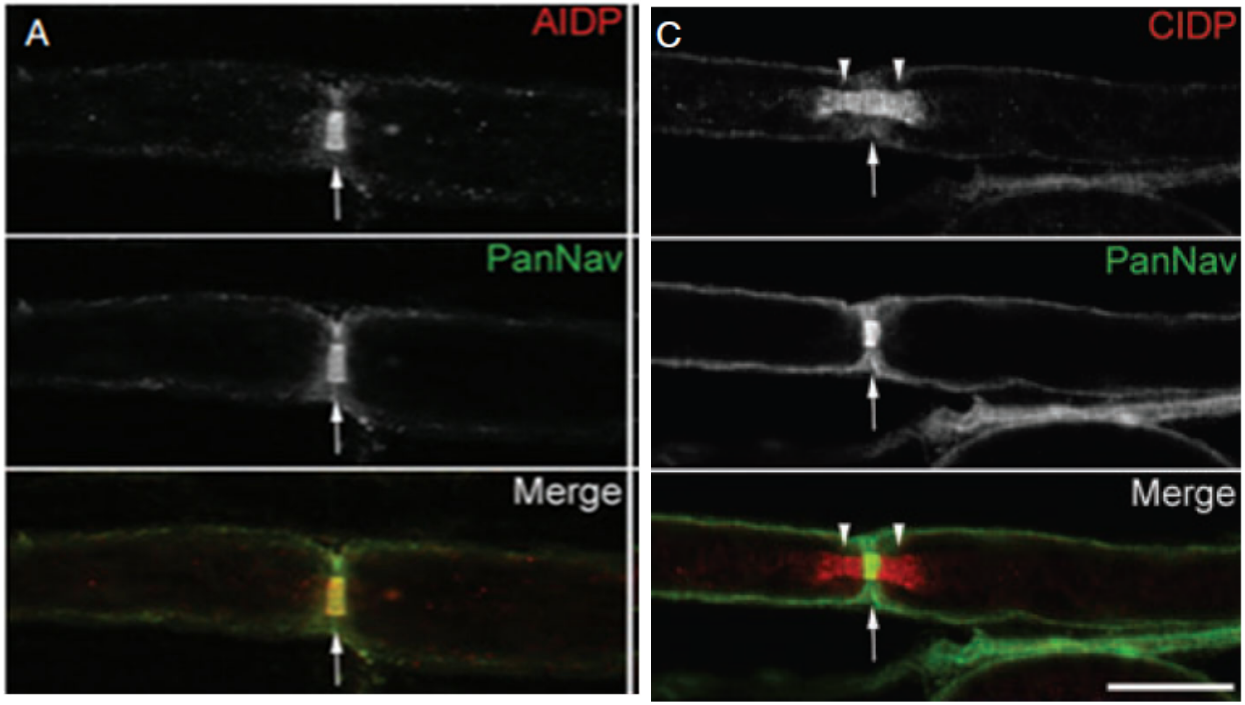
- IgG from sera of 43% of GBS and 30% of CIDP pts bound at the node and/or paranode of rat sciatic nerve
- NF186, gliomedin, and contactin were identified as targets of autoantibodies in some pts




Uncini et al. 2022

Nodal binding

Paranodal binding




Devaux et al. 2012

# Neuropathy with Ab anti-Neurofascin 186 and 140

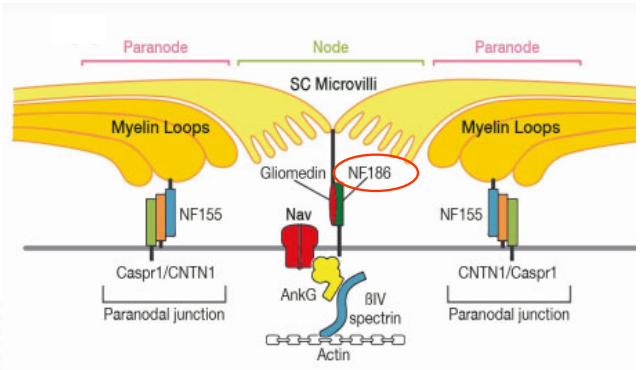
**Clinical features**:
5 pts reported (Delmond et al. 2017)
1 other pt showed (Vallat et al. 2018):

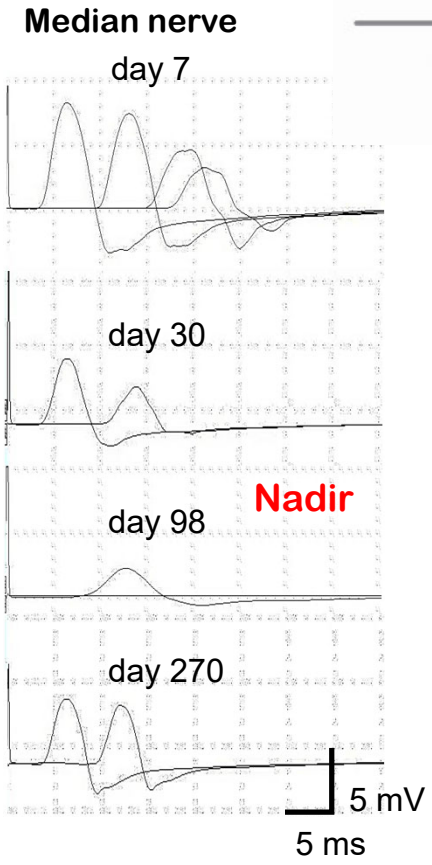
- acute onset
- sensorimotor neuropathy evolving to tetraplegia
- respiratory insufficiency requiring invasive ventilation
- chronic course with no response to IVIg, PE, IV steroids
- at 4 months started improvement
- at 9 months almost complete recovery

**Eletrophysiology**:

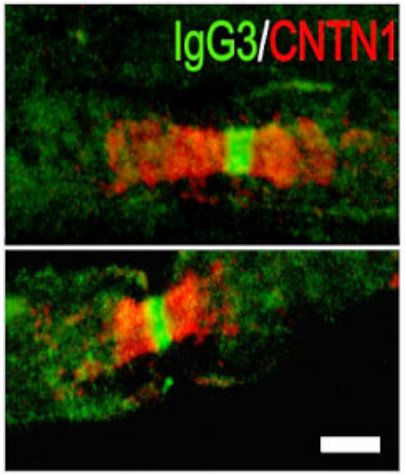
- long lasting CB without TD
- DMLs: 142-146% ULN
- CVs: 47-50% LLN
- long lasting CB without TD

**Serology**
IgG3 Ab anti-NF186 and -NF140
activating complement



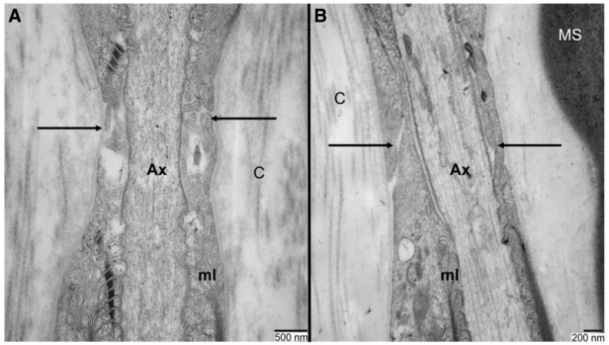

Patient's IgG3 bind to the node of mouse sciatic nerve fibers




Vallat et al. 2018

Normal

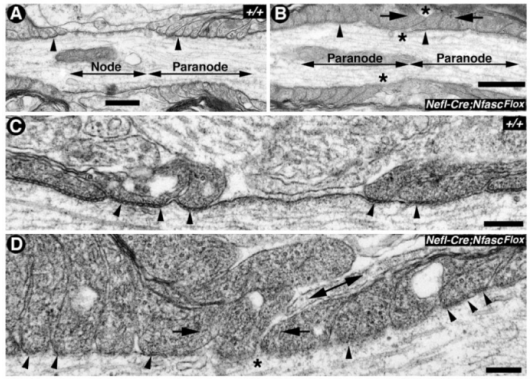
Patient with ab to NF186/140



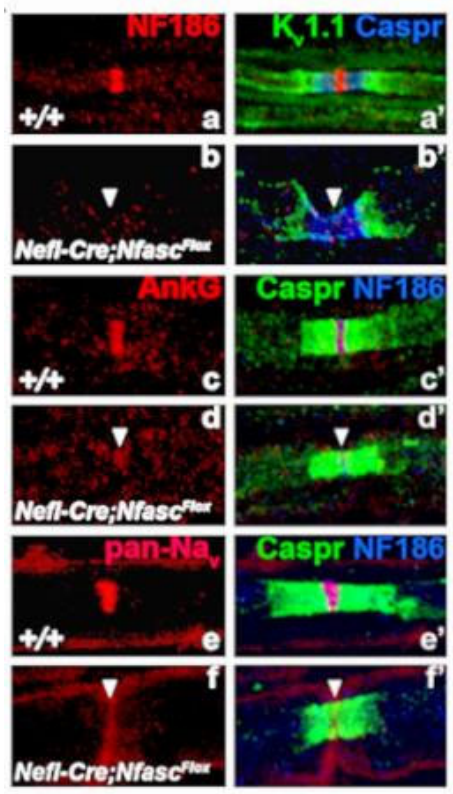

Vallat et al. 2018

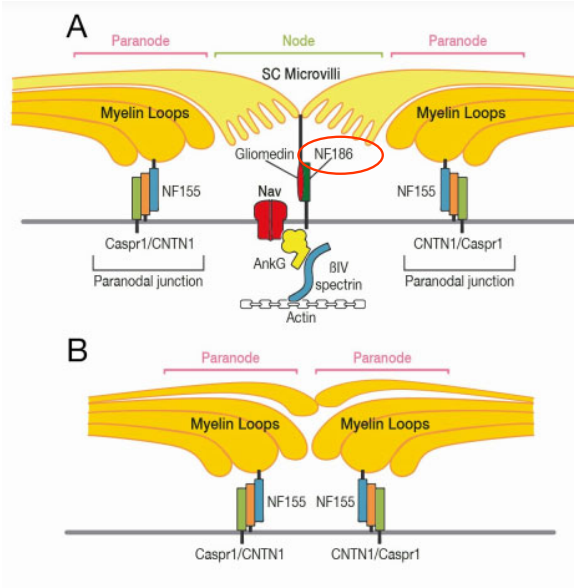
Normal mouse

NF186 mutant mouse




Thaxton et al. 2011



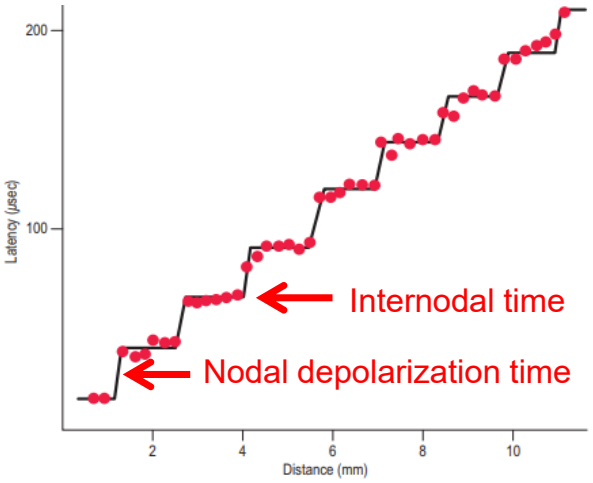

Uncini et al. 2022

- Loss of SC microvilli
- Decreased nodal length till to complete occlusion by extension of SC cytoplasm
- No evidence of demyelination
- No inflammatory infiltrates
- In mutant mouse: nodal disorganization with loss of Nav channels and Ankirin

**How to explain slow CV in neuropathies without demyelination?**

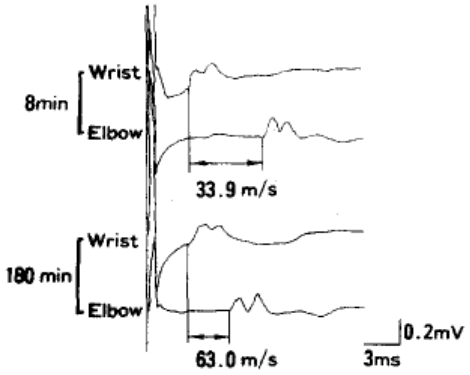
# Can Nav channel loss explain slow conductions?

**CV is mainly due to nodal depolarization time**

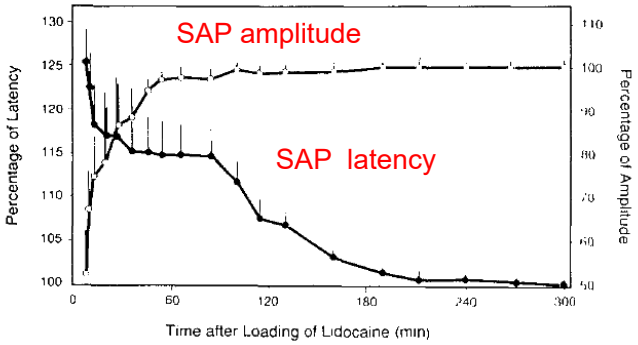



Modified from Rasminsky and Sears 1972

Single MUP recording




- 4 healthy volunteers
- 20 ml 0.5% lidocaine i.v.
- Rapid decrease CMAPs and SAPs
- Increased latencies and decreased CVs (by 20-30 m/s) in the fibers not blocked

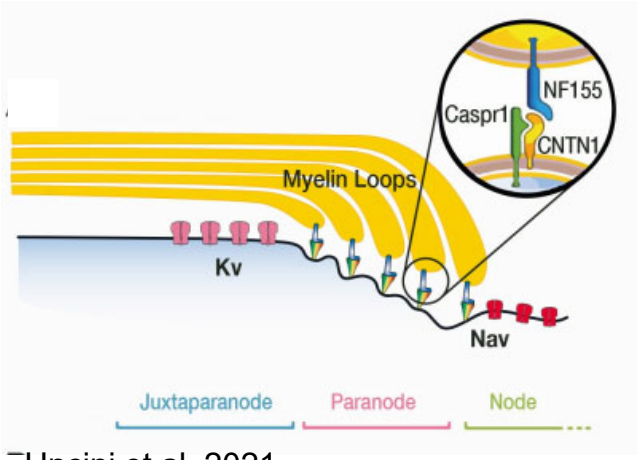



Yokota et al. 1994

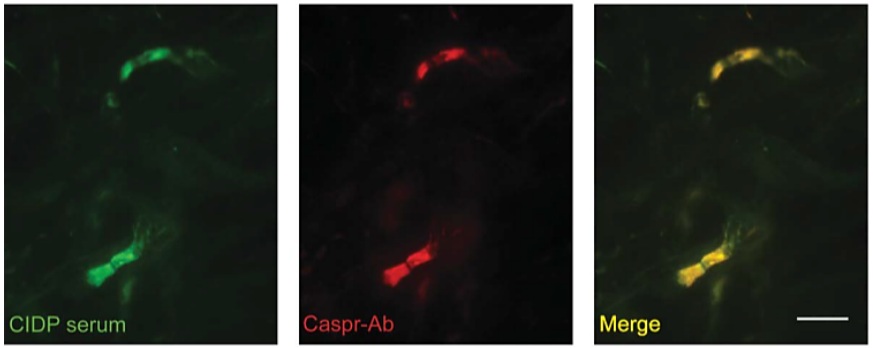
**Nav loss (or inactivation) increases the nodal delay and, if occurring in many sequential nodes, can induce conduction slowing even in the «demyelinating» range**

# Ab anti-Contactin1 and -NF155 in CIDP (Querol et al. 2013, 2014)

- ~10% patients diagnosed as CIDP
- Ab are predominatly or exclusively IgG4

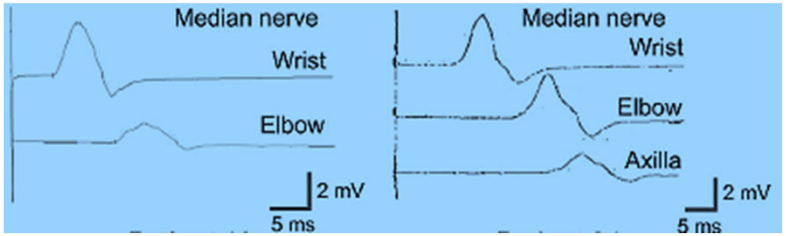



Uncini et al. 2021



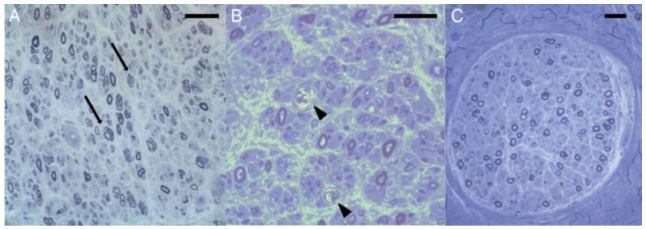

**Electrophysiology**:

- DML= 161-423% ULN
- CV= 26-62% LLN
- F latency= 146-321% ULN
- Infrequent CB and TD
- ↓ CMAP amplitudes




Devaux et al. 2016

**Sural biopsy** (Doppler et al. 2015)



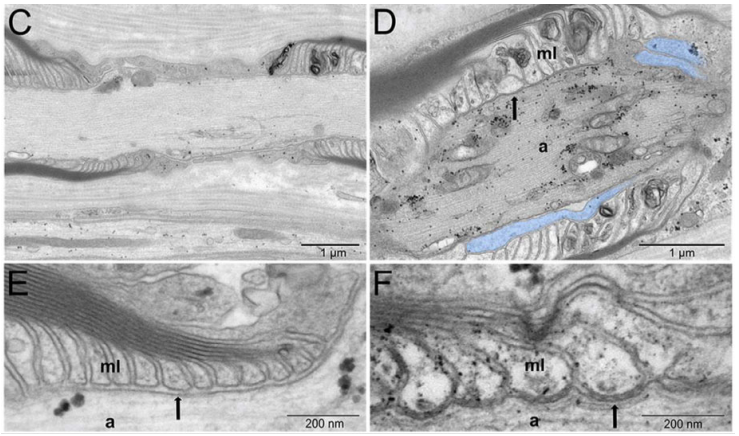

- axonal loss and degeneration
- regenerating fibers
- only few thinly myelinated fibers
- no onion bulbs
- no inflammatory infiltrates

Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders 27 (2017) 290–293
www.elsevier.com/locate/nmd

Short communication

# Paranodal lesions in chronic inflammatory demyelinating polyneuropathy associated with anti-Neurofascin 155 antibodies

Jean-Michel Vallat [a,*], Nobuhiro Yuki [b], Kenji Sekiguchi [c], Norito Kokubun [d], Nobuyuki Oka [e], Stéphane Mathis [f], Laurent Magy [a], Diane L. Sherman [g], Peter J. Brophy [g], Jérôme J. Devaux [h]




Anti-NF155 ab  Normal

- lack of tranverse bands
- detachment of terminal myelin loops
- lengthening of nodes
- widening of periaxonal space
- cellular processes interposed between myelin loops and axon

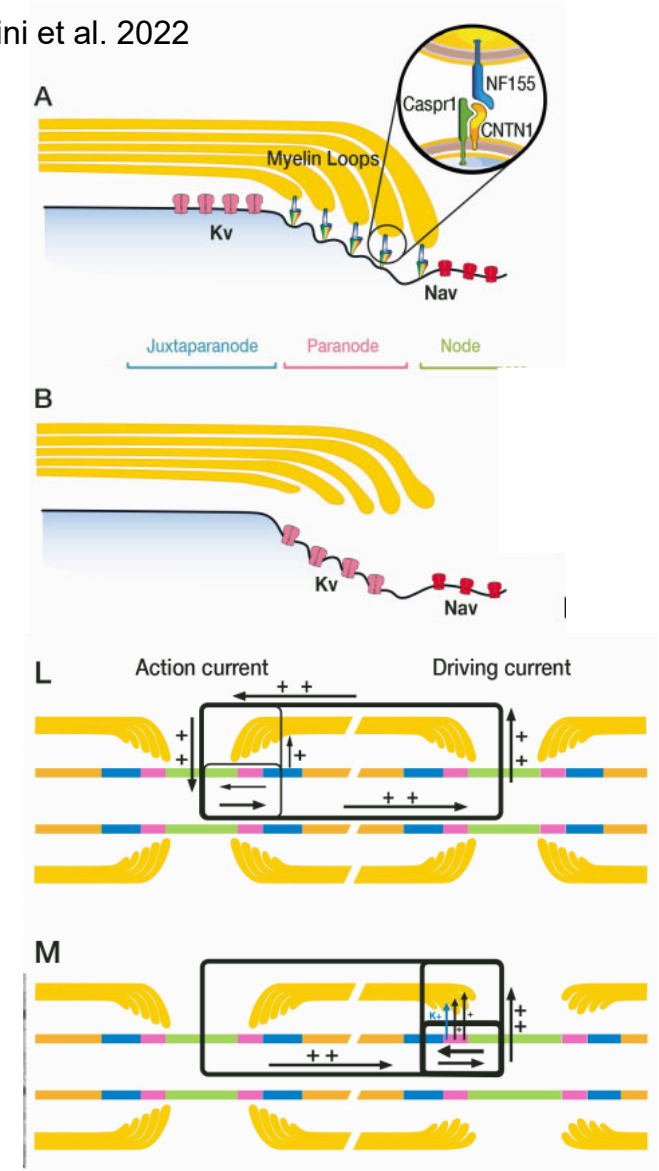
## Koike et al. 2017

| | 1. Antineurofascin-155 antibody-positive patients n=9 | 2. Antibody-negative patients n=13 | 3. Normal controls* n=10 | Probability 1 vs 2 | 1 vs 3 | 2 vs 3 |
|---|---|---|---|---|---|---|
| Nerve fibre density (number/mm$^2$) | | | | | | |
| Myelinated fibres | 6594±985 | 5948±1516 | 8887±1330 | NS | <0.01 | <0.0001 |
| Unmyelinated fibres | 30 298±4794 | 26 881±5221 | 30 586±4376 | NS | NS | NS |
| Teased-fibre study (%) | | | | | | |
| Demyelination | 1.3±3.0 | 4.1±4.6 | 0 | NS | NS | <0.05 |
| Remyelination | 3.6±2.6 | 13.7±12.3 | 4.3±4.5 | <0.01 | NS | <0.05 |
| Axonal degeneration | 3.6±4.2 | 1.4±1.9 | 0.6±0.7 | NS | <0.05 | NS |
| Axo–glial detachment (%) | 53.5±25.5 | 3.4±3.7 | | <0.001 | | |

Patients with anti-NF155 ab have paranodal disruption but not segmental de-remyelination

# Biophysical effects of paranodal junction dismantling

Uncini et al. 2022




**Terminal myelin loop detachment induces**:

- nodal lengthening ↑ nodal capacitance with dilution of the driving current over a larger surface
- ↑ periaxonal space ↓ paranodal transverse resistance, with ↑ leakage, radial shunting, and backflow of current
- extension of Kv channels at paranode shifts membrane polarization to more negative values

↓

↑ **nodal time to generate AP**

↓

**conduction slowing**

↓

**if the safety factor is <1**

↓

**conduction failure**

**These effects are similar to true paranodal demyelination**

# Autoimmune neuropathies are classified in demyelinating and axonal

**How should we classify:**

1) neuropathies with Ab to NF186 showing: ?

- CB and conduction slowing in the «demyelinating range»
- nodal disorganization with loss Nav channels and no demyelination

2) neuropathies with Ab to paranodal junction components:

- with «demyelinating electrophysiology» ?
- paranodal dismantling/disruption but no segmental demyelination
- with small or no inflammatory infiltrates and with IgG4 antibodies that do not activate complement or machrophages by Fc receptor

These neuropathies could be better characterised as nodopathies and paranodopathies with specific antibodies

*J Neurol Neurosurg Psychiatry* 2018;**89**:627–635

Neuromuscular

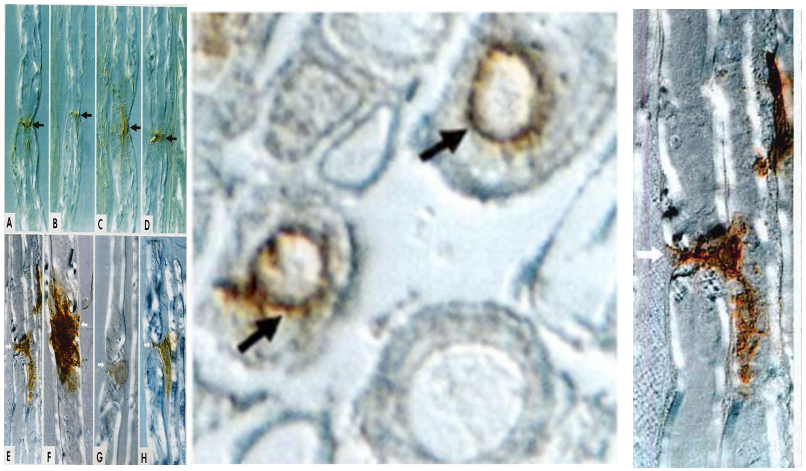
REVIEW

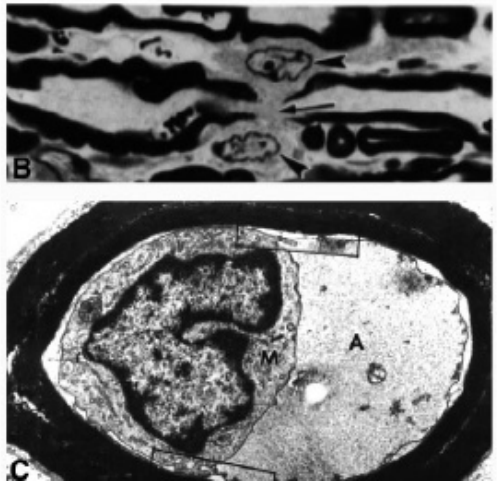
Autoimmune nodo-paranodopathies of peripheral nerve: the concept is gaining ground

Antonino Uncini,[1] Jean-Michel Vallat[2]

# Acute motor axonal neuropathy (AMAN)

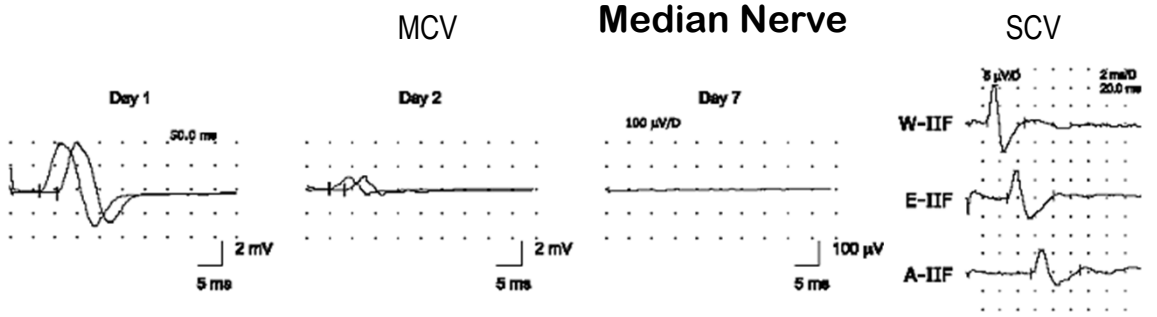
Target antigens:
GM1, GD1a





Hafer-Macko et al.1996, Griffin et al. 1996

Pathology:
- axonal degeneration
- little or no demyelination

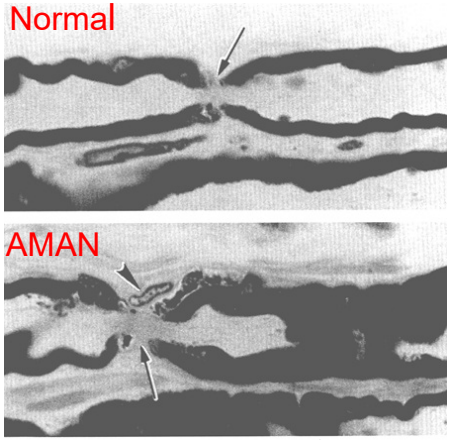



Lugaresi et al. 1997

**AMAN electrodiagnostic criteria** (Ho et al. 1995, Hadden et al. 1998)
- no evidence of demyelinating fatures
- distal CMAP amplitude < 80% LLN in at least 2 nerves

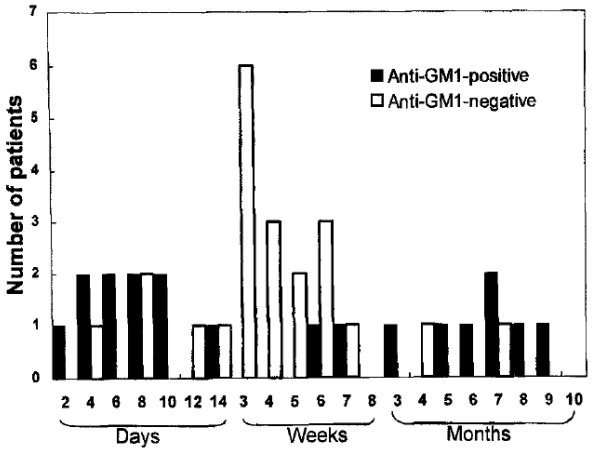
# Paradoxes in AMAN

**Severely paralyzed fatal cases show few degenerating fibers and lengthened nodes**



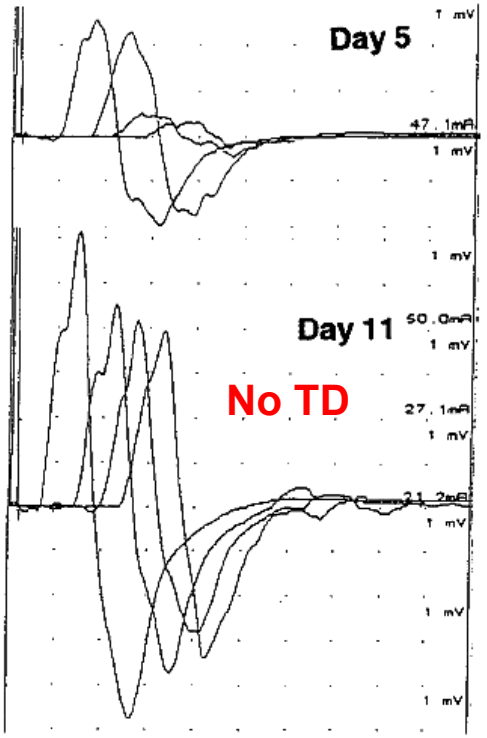

Griffin et al. et al.1996

**Some pts wit anti-GM1 ab improve and recover much faster than expected in axonal degeneration**



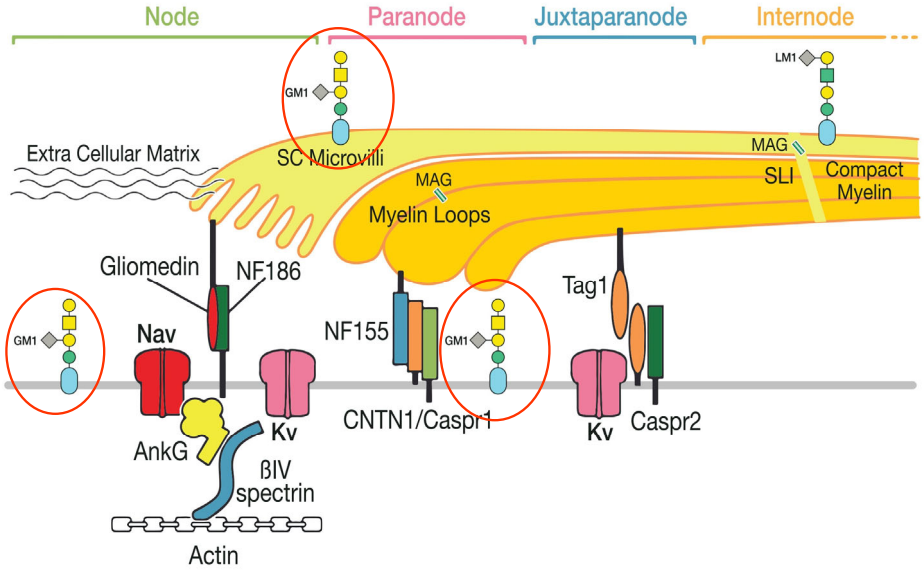

Kuwabara et al.1998

**CB promptly resolves without TD**

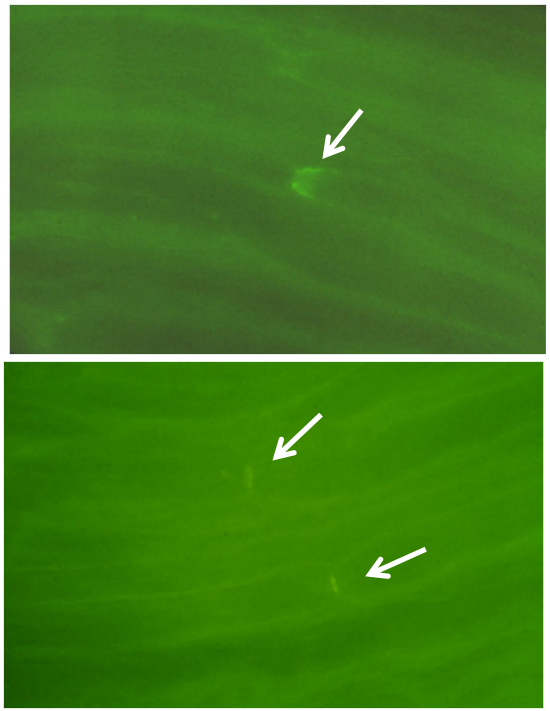


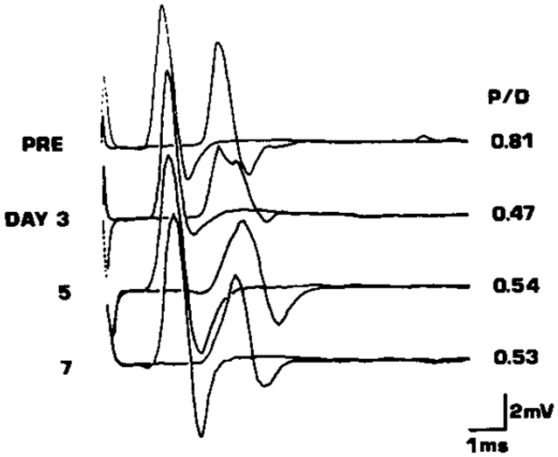

Besides axonal degeneration AMAN is characterized by a transient impared impulse conduction at the node, possibly due to anti-ganglioside antibodies, named Reversible Conduction Failure

# GM1 is enriched at the axolemma of nodal region and abaxonal paranodal myelin




Uncini et al. 2022

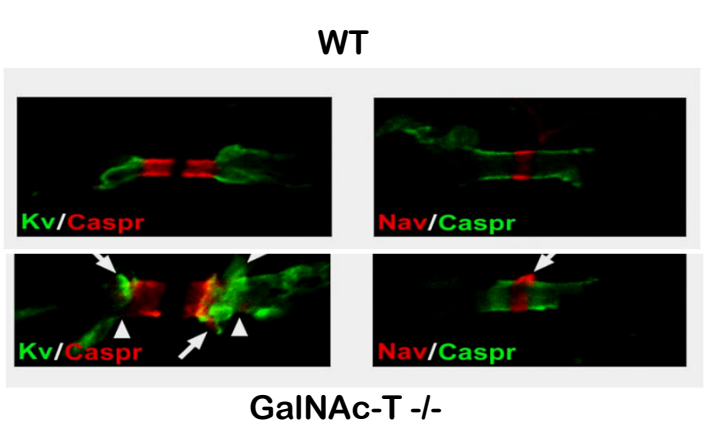


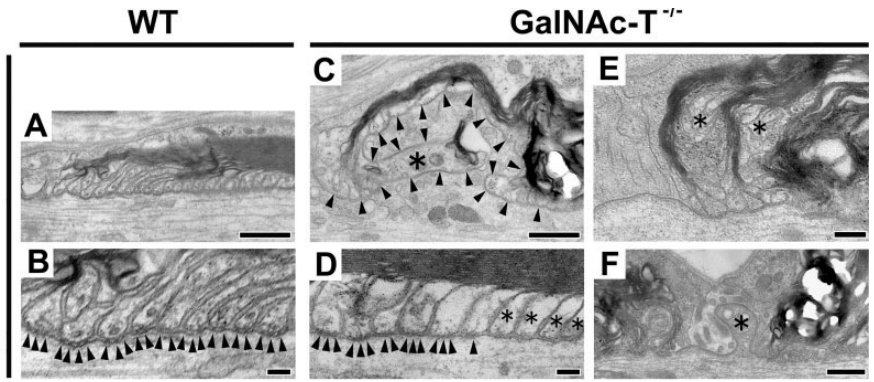


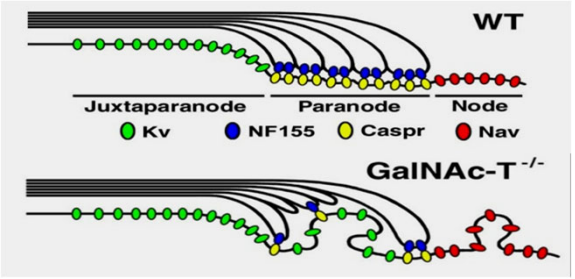

Uncini et al. 1993

Patients' sera containing anti-GM1Ab bind to the node and paranode of rat sciatic nerve and when addition with fresh complement induce a transient conduction block

# Effects of GM1 and GD1a ablation in mice



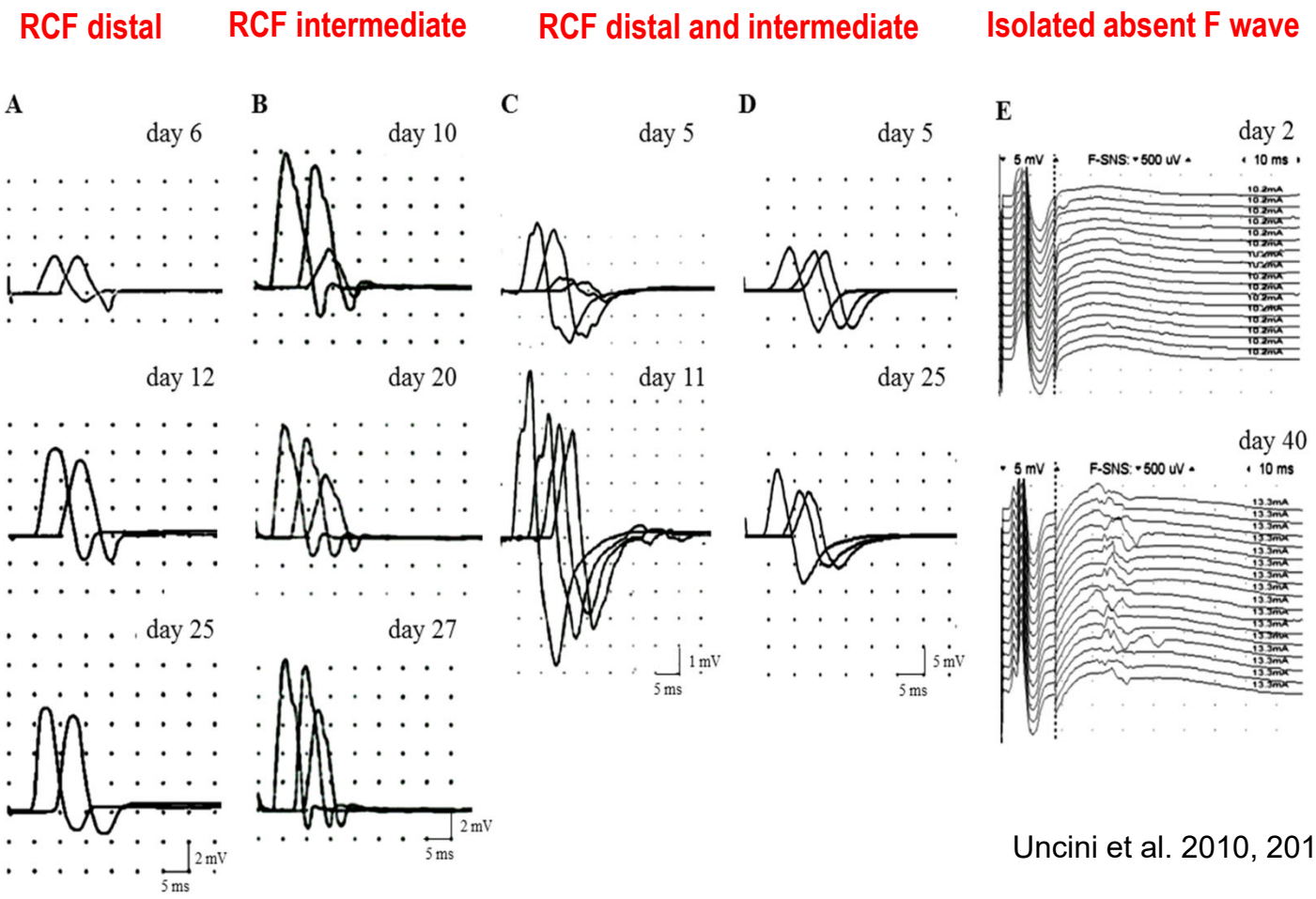

Susuki et al 2007

- Immunostaining of Caspr and NF155 are attenuated
- Transverse bands are lacking and paranodal loops fail to attach to the axolemma
- Nav channels clusters are broadened
- Kv channels are mislocated in the paranode

**Gangliosides contribute to the stability of paranodal junction and ion channel clusters**

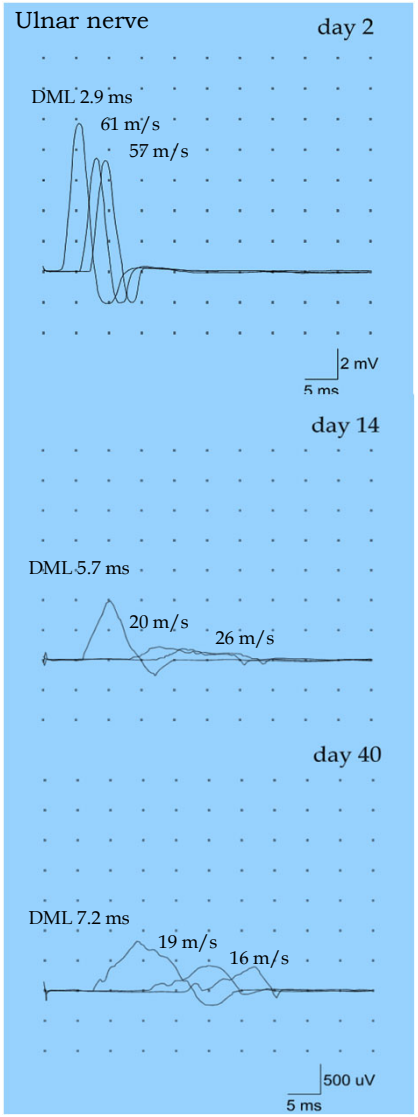
# Reversible conduction failure in axonal GBS

- 47% of pts with axonal GBS show RCF in at least two nerves
- RCF is an «a posteriori» diagnosis that can be made only by serial studies




Uncini et al. 2010, 2017

## AIDP

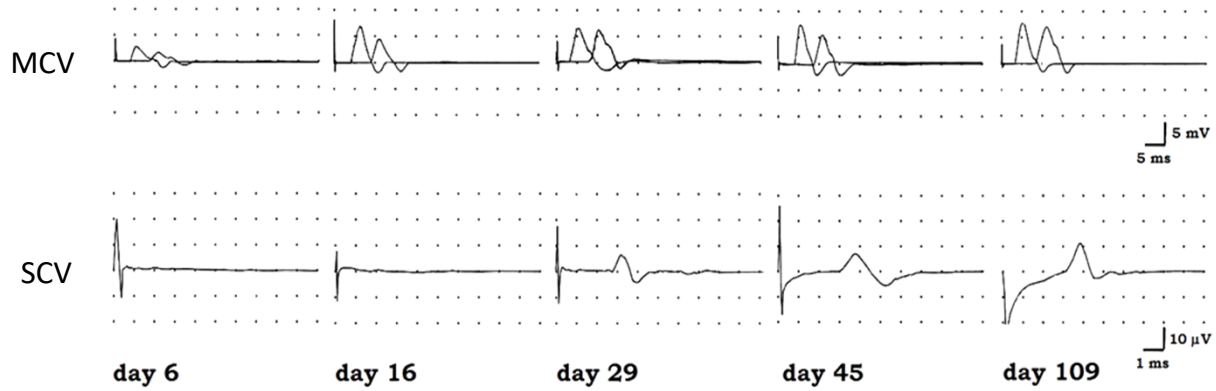


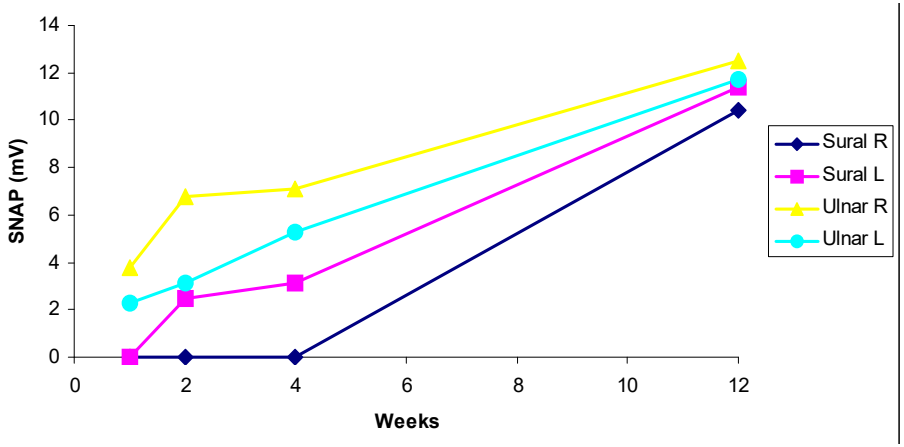
# REVERSIBLE CONDUCTION FAILURE IN PHARYNGEAL-CERVICAL-BRACHIAL VARIANT OF GUILLAIN-BARRÉ SYNDROME

MARGHERITA CAPASSO, MD, PhD,[1] FRANCESCA NOTTURNO, MD,[1,2] CLAUDIA MANZOLI, MD,[1] NOBUHIRO YUKI, MD, PhD,[3] and ANTONINO UNCINI, MD[1]

*Muscle Nerve* 42: 608–612, 2010

## RCF in median nerve motor and sensory fibres



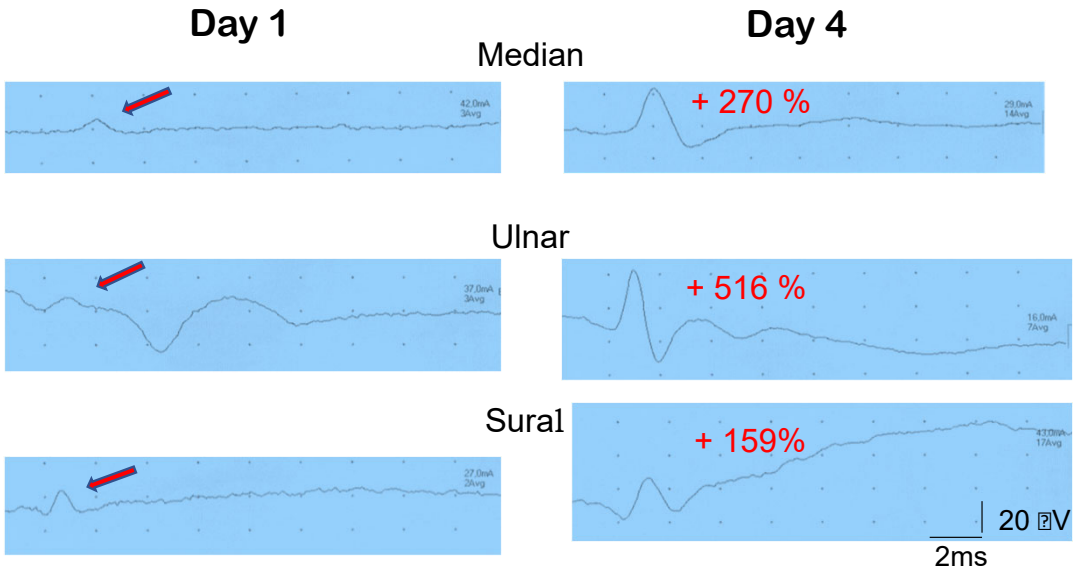



*Muscle Nerve* **37:** 265–268, 2008

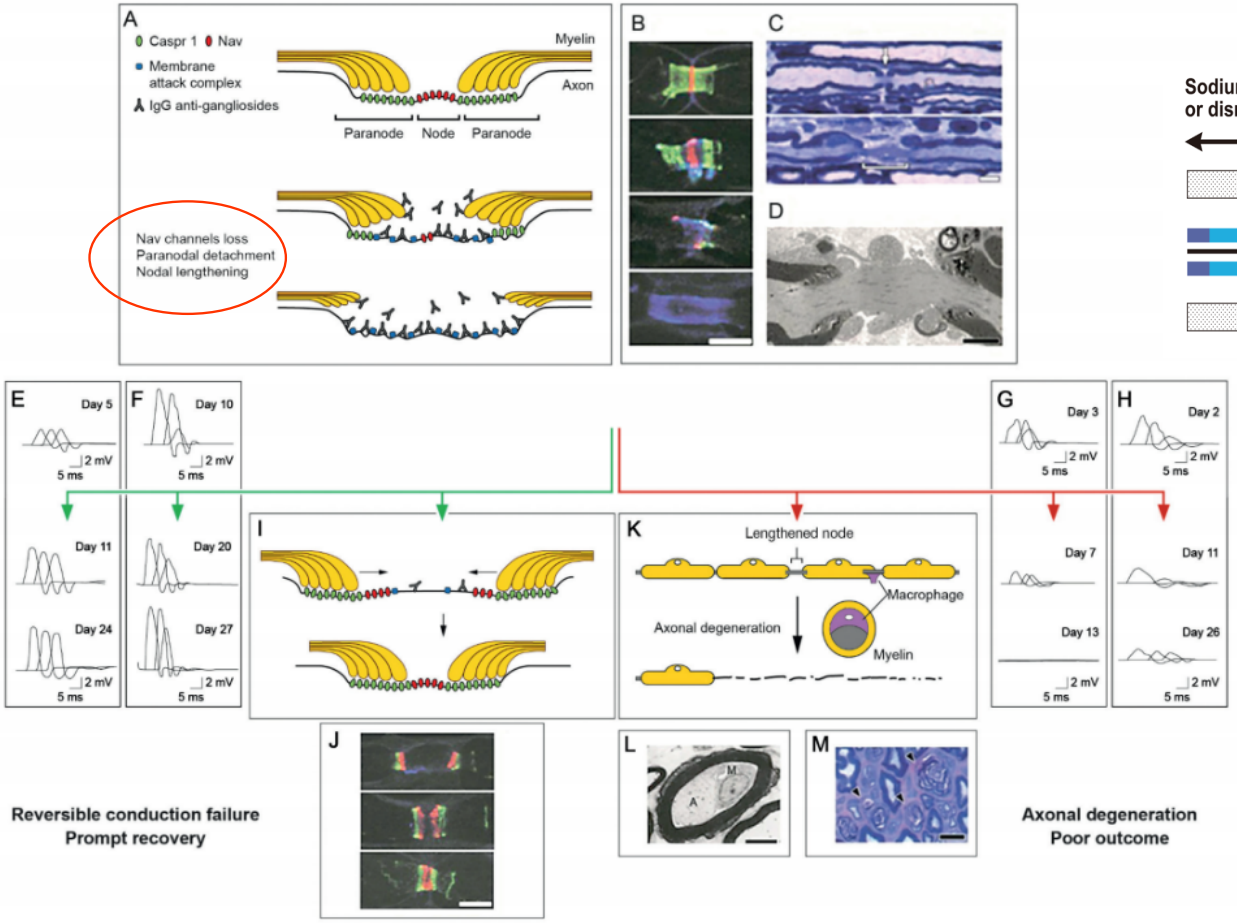
# ACUTE SENSORY ATAXIC NEUROPATHY WITH ANTIBODIES TO GD1b AND GQ1b GANGLIOSIDES AND PROMPT RECOVERY

FRANCESCA NOTTURNO, MD, CHRISTINA M. CAPORALE, MD, and ANTONINO UNCINI, MD

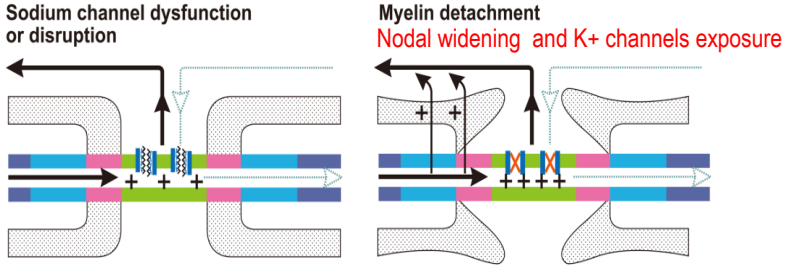
**RCF restricted to sensory fibres**



# Immunopathological and electrophysiological correlates in AMAN

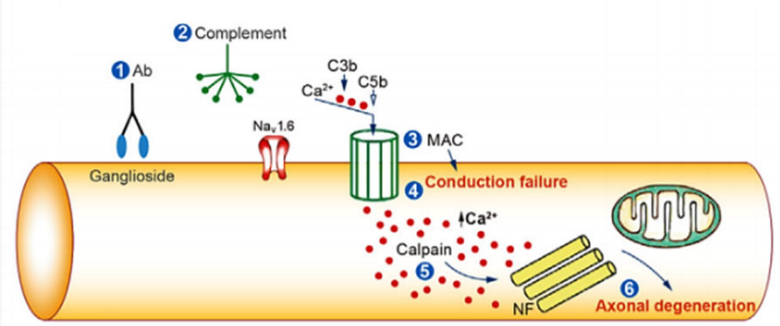



## Causes of conduction failure




Uncini and Kuwabara 2015

## Cascade leading to axonal degeneration




Uncini and Santoro 2020

Research paper

# Pitfalls in electrodiagnosis of Guillain—Barré syndrome subtypes

Antonino Uncini,[1,2] Claudia Manzoli,[1] Francesca Notturno,[1,2] Margherita Capasso[1]

*J Neurol Neurosurg Psychiatry* 2010;**81**:1157—1163.

Clinical Neurophysiology 124 (2013) 1456–1459

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

# Two sets of nerve conduction studies may suffice in reaching a reliable electrodiagnosis in Guillain–Barré syndrome

Nortina Shahrizaila[a,*], Khean Jin Goh[a], Suhailah Abdullah[a], Rishikesan Kuppusamy[a], Nobuhiro Yuki[b]

doi:10.1093/brain/awq260 Brain 2010: 133; 2897–2908 | 2897

BRAIN
A JOURNAL OF NEUROLOGY

# Conduction block in acute motor axonal neuropathy

Norito Kokubun,[1] Momoka Nishibayashi,[1] Antonino Uncini,[2,3] Masaaki Odaka,[1] Koichi Hirata[1] and Nobuhiro Yuki[4,5]

## The electrophysiology of GBS is dynamic

- 120 pts with serial conduction studies
- Because of recognition of RCF 22-38% pts changed classification after serial conduction studies mainly from AIDP and Equivocal diagnosis to AMAN

Practical implications are:

- Electrodiagnostic criteria sets based on a single test are inadequate
- The lack of distinction between RCF and demyelinating CB leads to fallaciously classify AMAN patients with RCF as AIDP
- The lack of documentation of distal RFC may lead, on the basis of a single test showing reduced distal CMAP amplitudes, to erroneously formulate a bad prognosis

# Autoimmune neuropathies are classified in demyelinating and axonal

**How should we classify** acute axonal neuropathies with Ab to gangliosides and:

- RCF and some «demyelinating-like» electrophysiological features
- dysfunction/disruption of the node and paranode without segmental demyelintion
- prompter clinical and electrophysiological recovery than expected from axonal degeneration

?

These neuropathies could be better characterised as nodo-paranodopathies with specific antibodies

Clinical Neurophysiology 124 (2013) 1928–1934

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Review

Nodo-paranodopathy: Beyond the demyelinating and axonal classification in anti-ganglioside antibody-mediated neuropathies

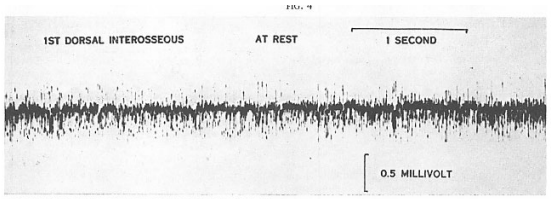
Antonino Uncini [a,*], Keiichiro Susuki [b], Nobuhiro Yuki [c]

*J. Neurol. Neurosurg. Psychiat.*, 1961, **24**, 319.

# A SYNDROME OF CONTINUOUS MUSCLE-FIBRE ACTIVITY

BY

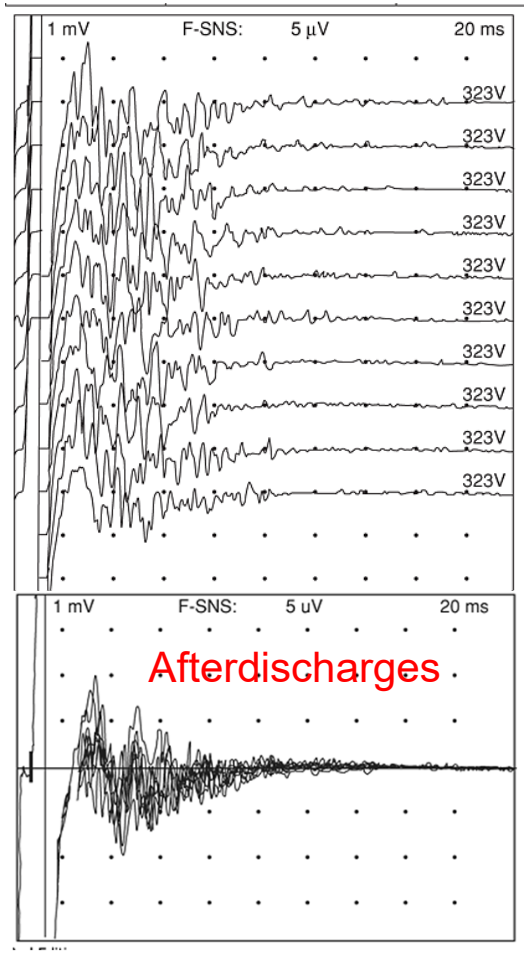
HYAM ISAACS*




- "Isaacs syndrome" or Neuromyotonia (NMT) is the result of motor nerve hyperexcitability
- NMT is characterized by fasciculations, muscle stiffness, cramps and pseudomyotonia
- Pain and paraesthesias are frequent and, in some pts, distal sensory loss is found
- ENMG shows: fasciculations, myokymic and NMT discharges and repetitive firing of potentials after electrical nerve stimulation.
- Some patients have reduced CMAP and SNAP amplitudes and EMG shows high amplitude, complex, MUPs and reduced recruitment indicating axonal loss

IgG1 or IgG4 anti-Caspr2 have been reported in NMT

Tibial ankle



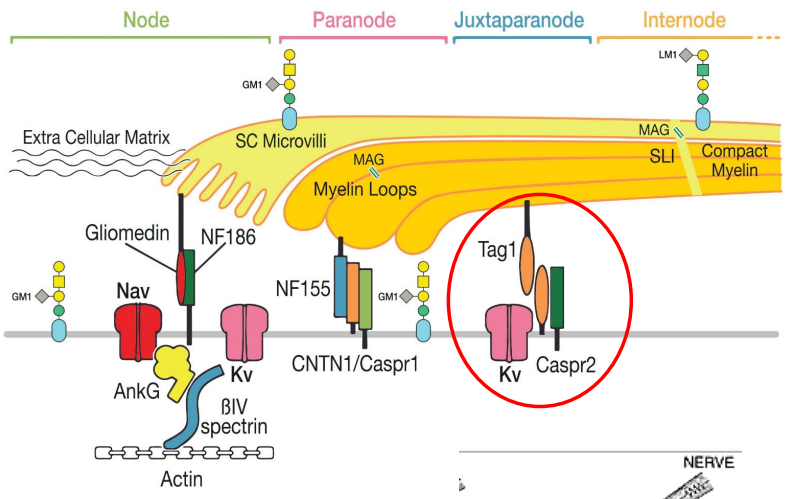
# Kv channels

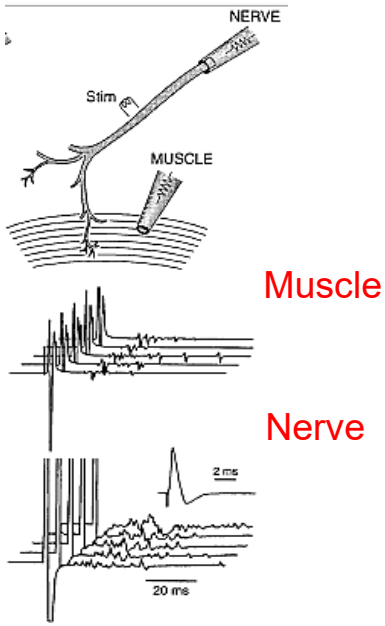
Juxtaparanodal Kv1.1/Kv1.2 channels:

- are concealed under the myelin sheath
- are anchored to axolemma and clustered by Caspr2 and TAG1
- act as current stabilizer mantaining the resting potential along the entire axon (Chiu and Ritchie 1984) and as current damper impeding the re-excitation of node (Vabnick et al. 1999)
- in K1.1 knockout mice the stimulated axon backfires after stimulation (Chiu et al. 1999)
- backfiring occurs in the myelinated segment just proximal to the transition zone with the unmyelinated nerve terminal

Malfunction of Kv channels well explains peripheral nerve hyperexcitability

NMT can be classified as an juxtaparanodopathy with anti-Caspr2 ab



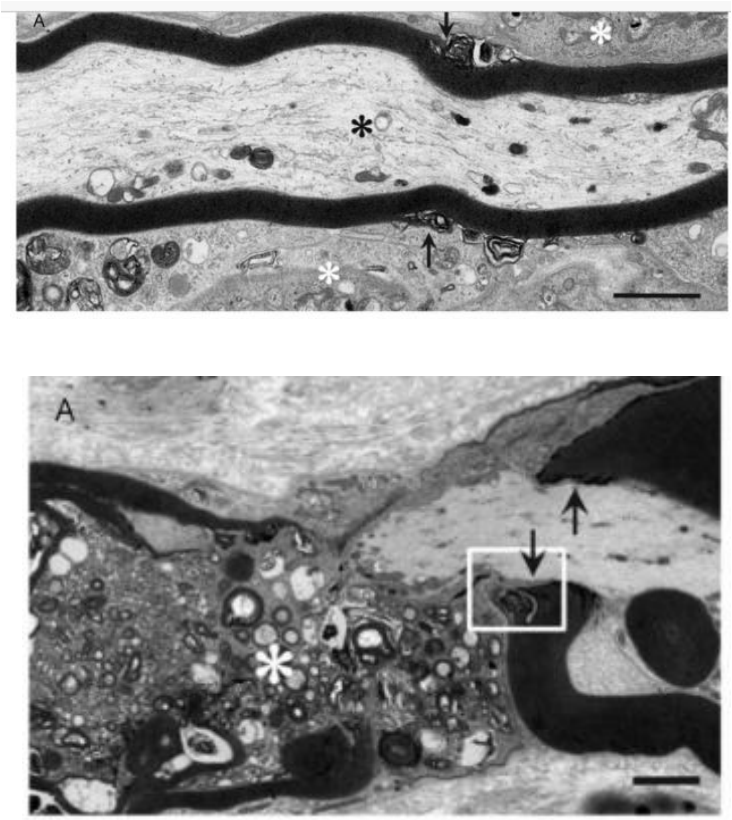




Chiu et al. 1999

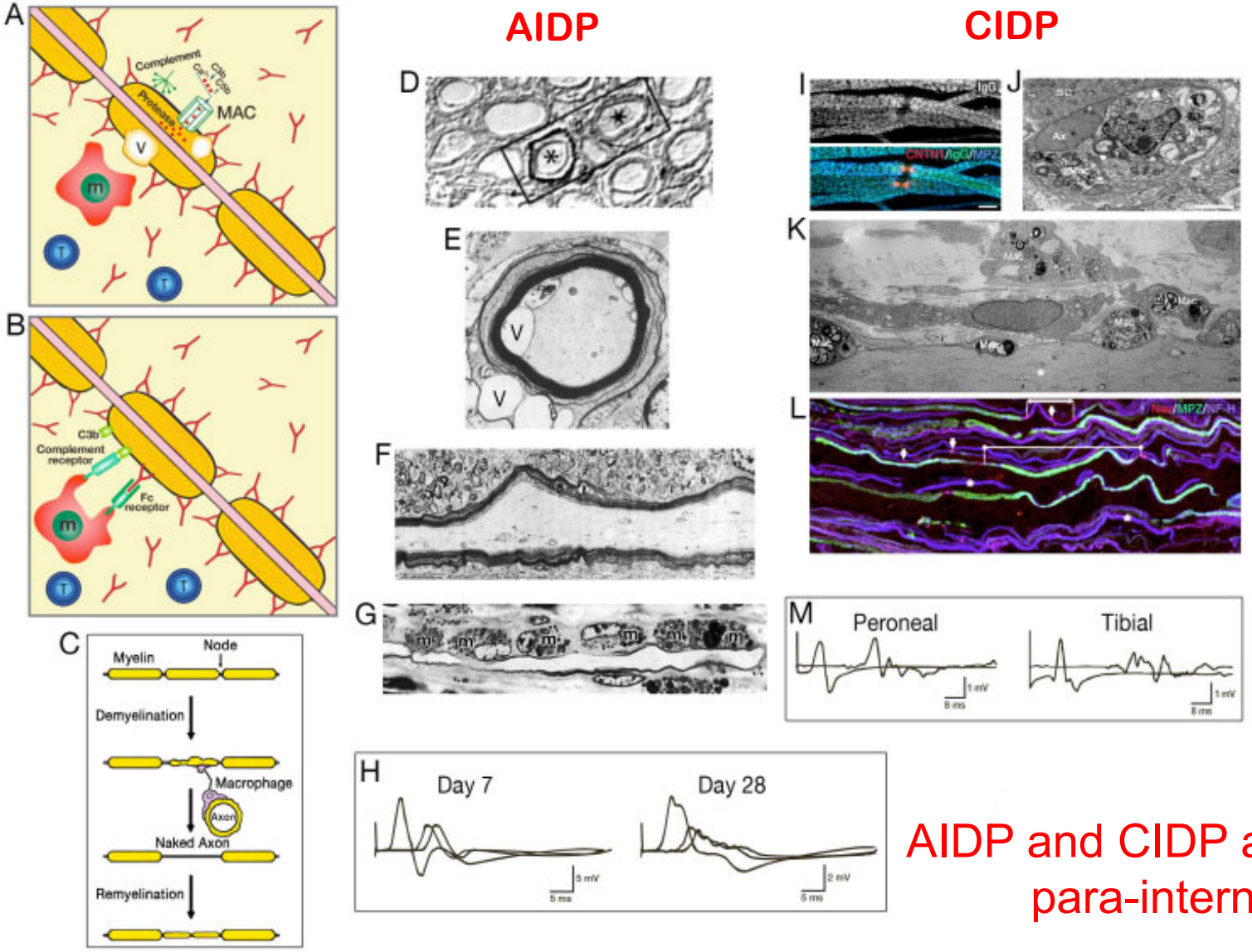
# What about AIDP and CIDP?

AIDP, CIDP and its subtypes (LSS, DADS….):

- Target antigens are still unidentified
- AIDP and CIDP show, during the disease course, similar electrophysiological features (CV slowing, CB, abnormal TD)
- AIDP and CIDP share common pathologic features such as segmental de-remyelination and infiltrates of T-cells and macrophages
- In AIDP and CIDP macrophage-mediated demyelination may involve the internode or the paranode. These two modalities usually coexist, although in some patients one appears predominant (Koike et al. 2018, 2020)



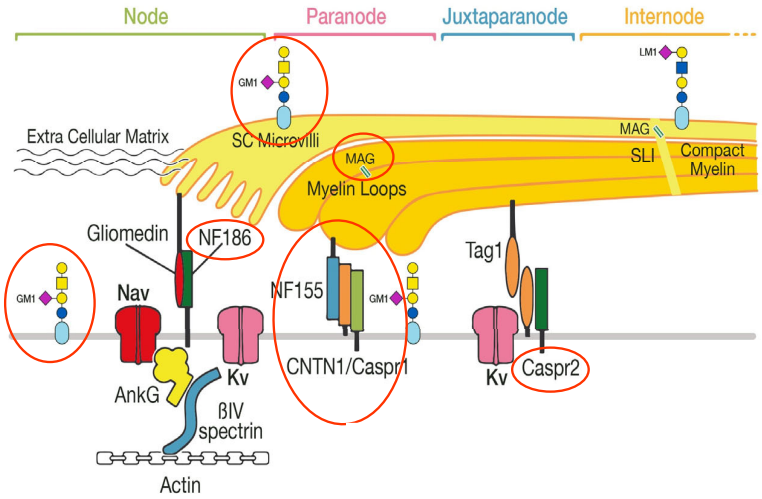

(Koike et al. 2018)




Uncini et al. 2022

AIDP and CIDP are demyelinating para-internodopathies

# The sectorial/antigenic classification of autoimmune neuropathies




Uncini et al. 2022