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Antibodies in PNS disease; does measurement aid diagnosis and treatment ?

Professor Bruce V Taylor

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- The simple answer is ”NO”, the specificity and sensitivity of all antibody tests in PN with a very few exceptions are too low.
- The tests are not routinely available.
- Associations with prognosis and treatment response have not been proven.

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- There has been significant interest in the role of pathogenic auto-antibodies in the aetio-pathogenesis of peripheral neuropathies.
- Most “immune” neuropathies have been associated with auto-antibodies.
- Therefore this remains an area of great interest.

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Strongest Associations

- GBS and various Abs.
- MMN and GM1 antibodies.
- DADS and anti MAG Abs.

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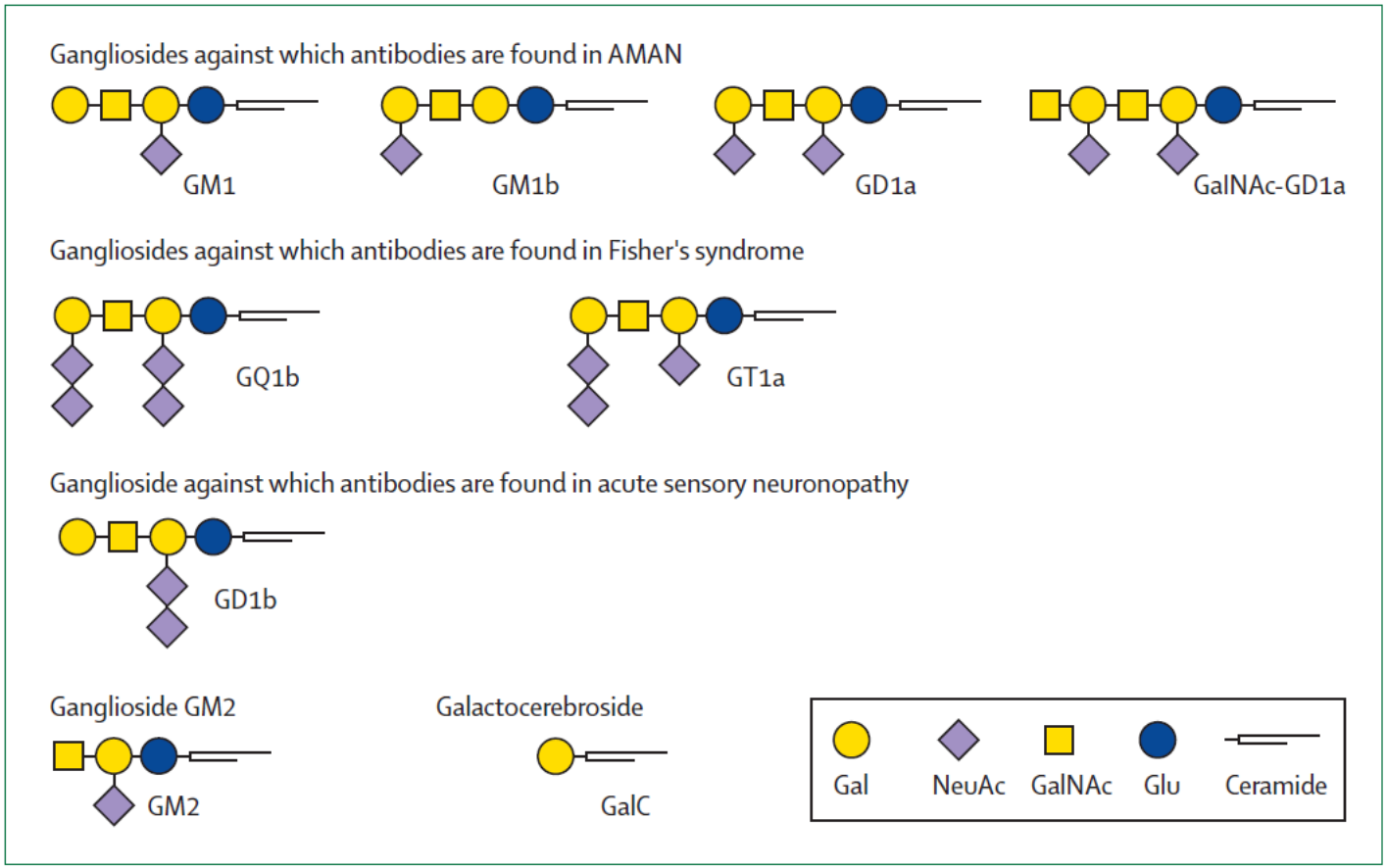
Ganglioside Structure



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GBS

- GBS is probably the proto-typical auto-immune neuropathy.
- Antibodies to a variety of different gangliosides and glycolipids have been described in GBS that vary by phenotype.

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AMAN

- IgG antibodies directed against gangliosides GM1, GD1a, GalNAc GD1a, and GM1b are seen in up to 83% of cases.
- In one study the presence of antibodies to any of these 4 gangliosides was associated with a significant increase in the chance of reclassification to AMAN from AIDP on follow-up NCS.

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AMAN

- Experimentally it has been shown that IgG GD1a and GD1b antibodies bind selectively to the nodes of Ranvier in motor and sensory nerves in AMAN.
- The continuing presence of GD1a antibodies has been associated with a poorer outcome in AMAN.

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AIDP

- In contrast to AMAN the presence of antibodies to any peripheral nerve antigen in AIDP is far less consistent and non-specific.
- Finding Abs to gangliosides may suggest that you have the classification wrong.

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MFS & BBE

- Associated with Anti GQ1b antibodies in >90% of cases.
- The propensity of the antibodies to breakdown the BBB may determine the phenotype.

J Neurol Neurosurg Psychiatry. 2013 Jul;84(7):756-65. doi: 10.1136/jnnp-2012-304306. Epub 2013 Apr 12.
Blood-brain barrier destruction determines Fisher/Bickerstaff clinical phenotypes: an in vitro study.
Saito K[1], Shimizu F, Koga M, Sano Y, Tasaki A, Abe M, Haruki H, Maeda T, Suzuki S, Kusunoki S, Mizusawa H, Kanda T.

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Uses in GBS variants

- Practically none except as research tools to help better understand the pathophysiology of the condition.
- Helpful to confirm MFS/BBE.
- Usually arrive back after the patient has been discharged!

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CIDP

- CIDP like MS has been the focus of research searching for auto-antibodies for many years.
- Sydney has been the driving force behind this for some time through the work of John Polllards lab.

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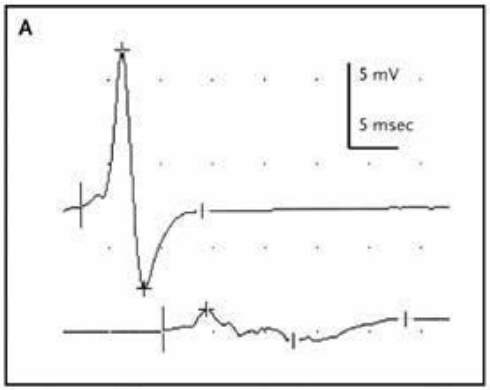
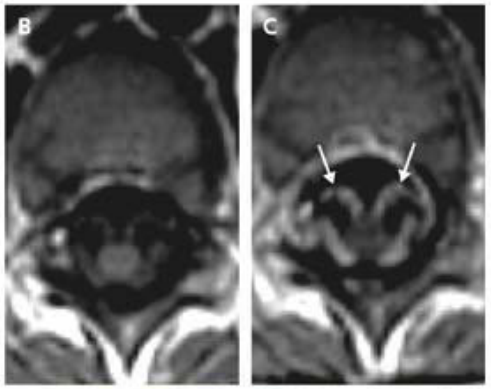
CIDP

- CIDP has been long thought to have a humeral mediated component as shown by the excellent response to plasma exchange.
- Initially there was much interest in antibodies directed at major myelin proteins PMP22 and P0.
- However this avenue of research has not proven fruitful.

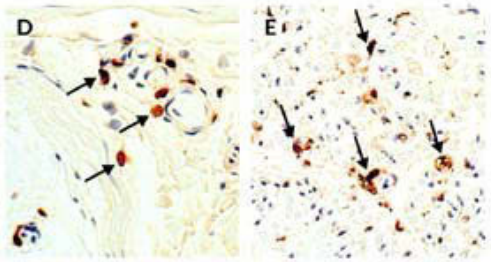
CIDP Pathology



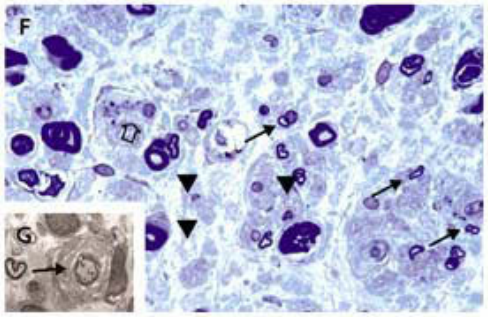
CB and dispersion in CIDP



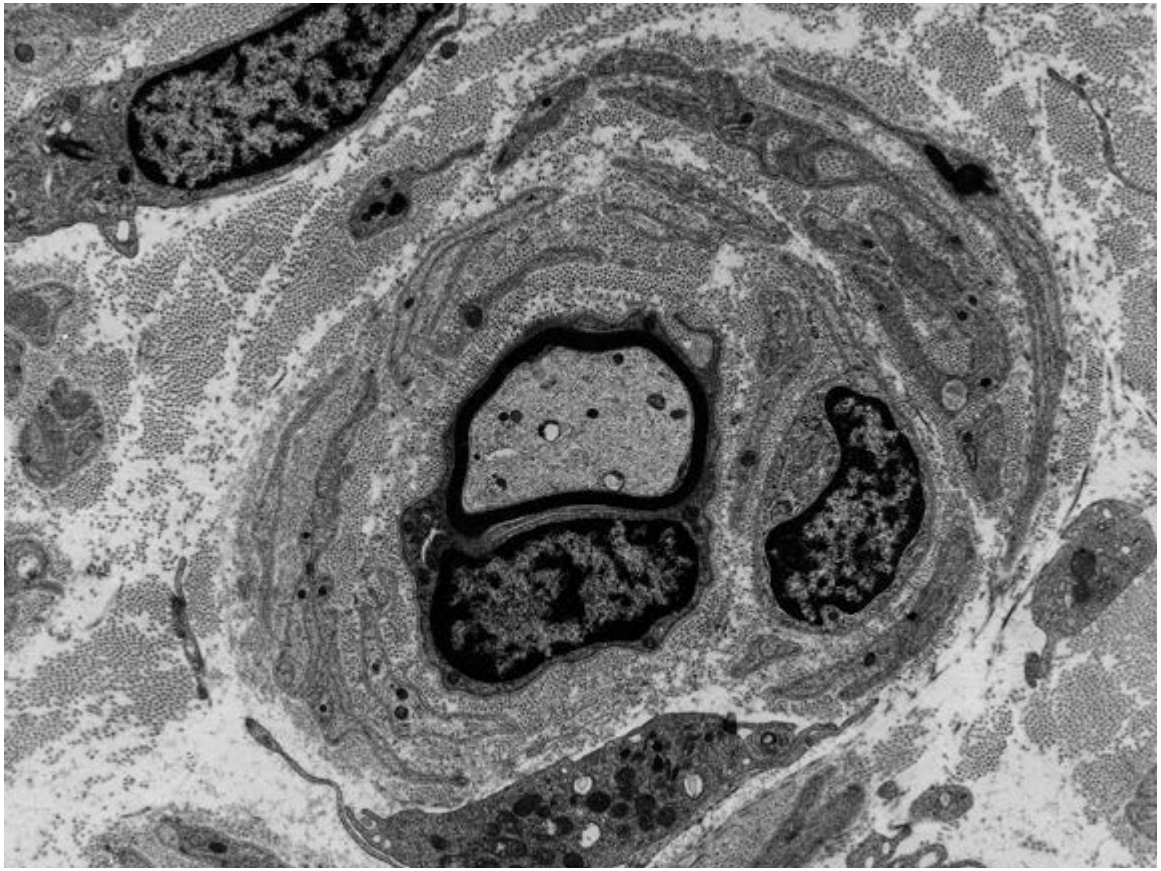
Enhancement of lumbar nerve roots



Inflammatory cells within endoneurium



De and remyelination and onion bulbs



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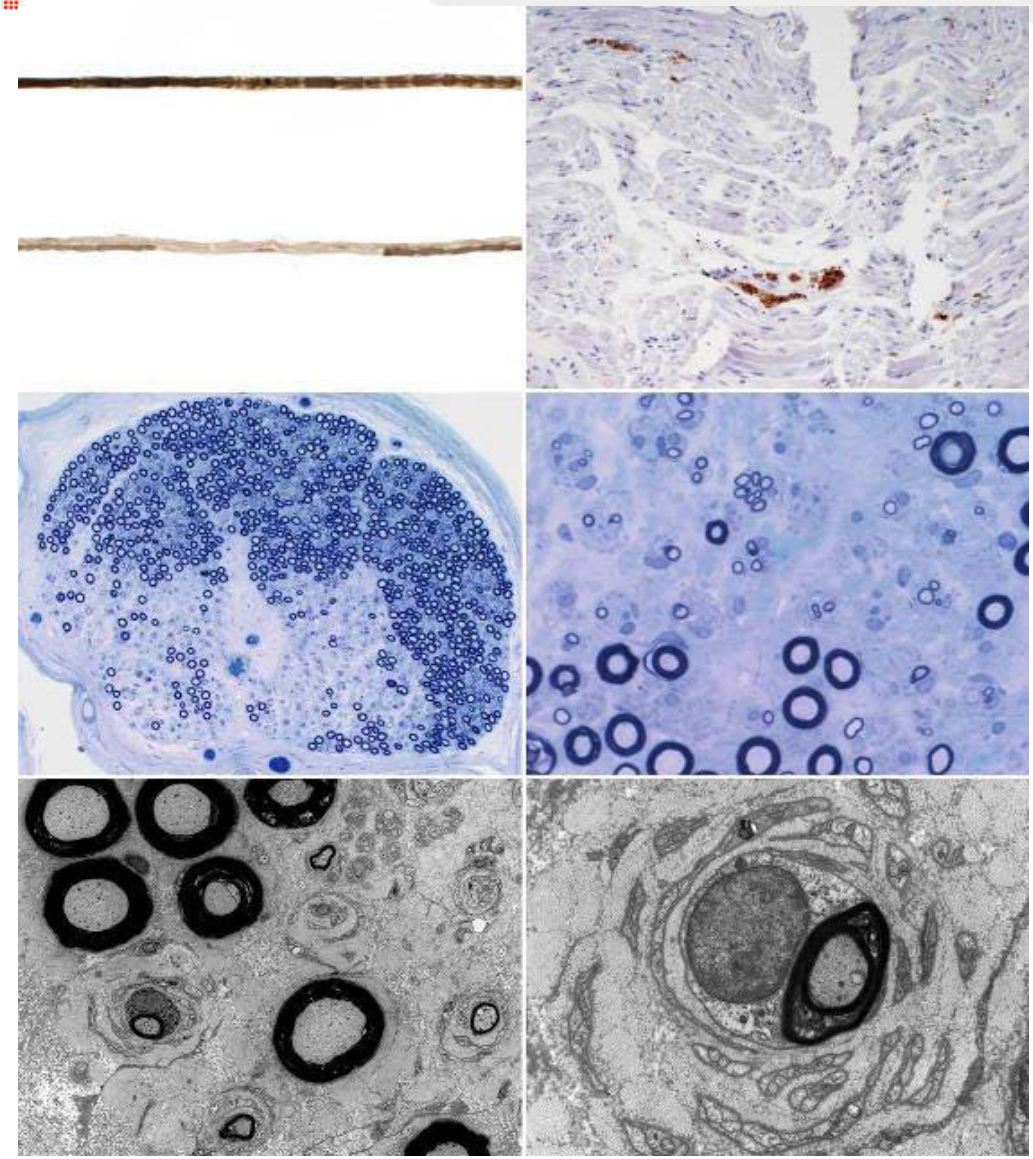
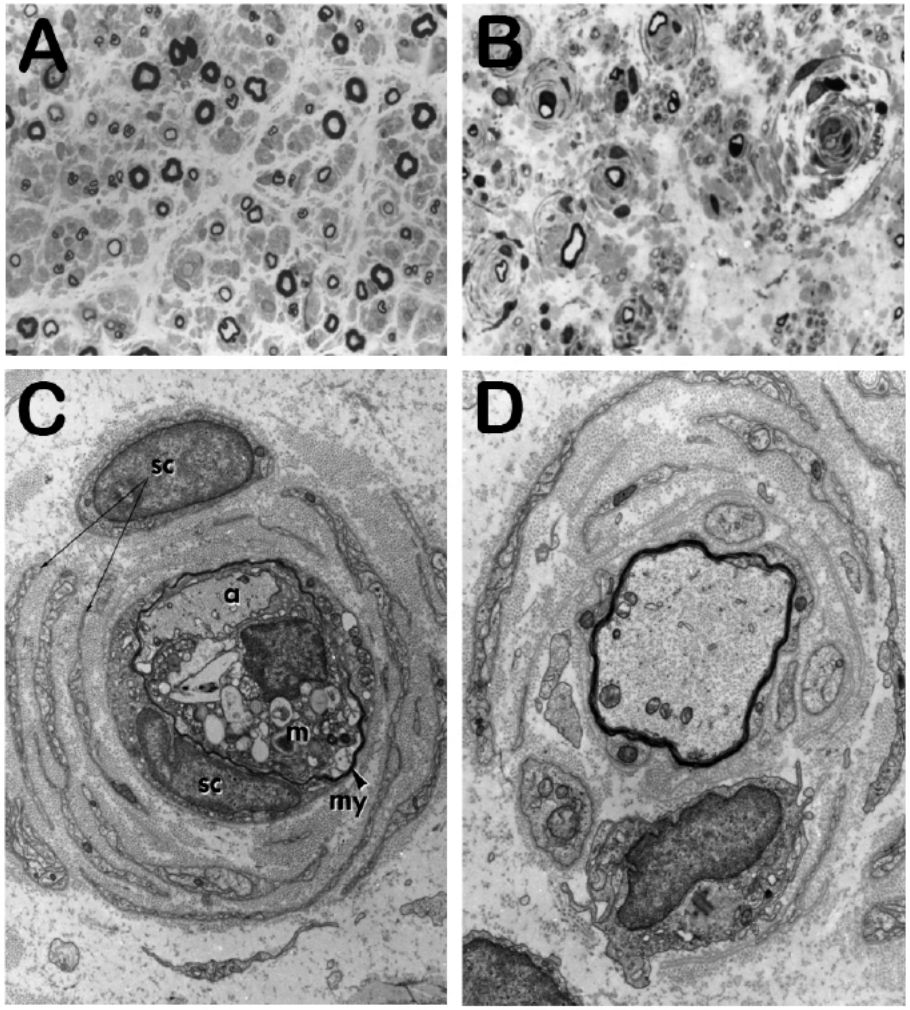
CIDP Pathology

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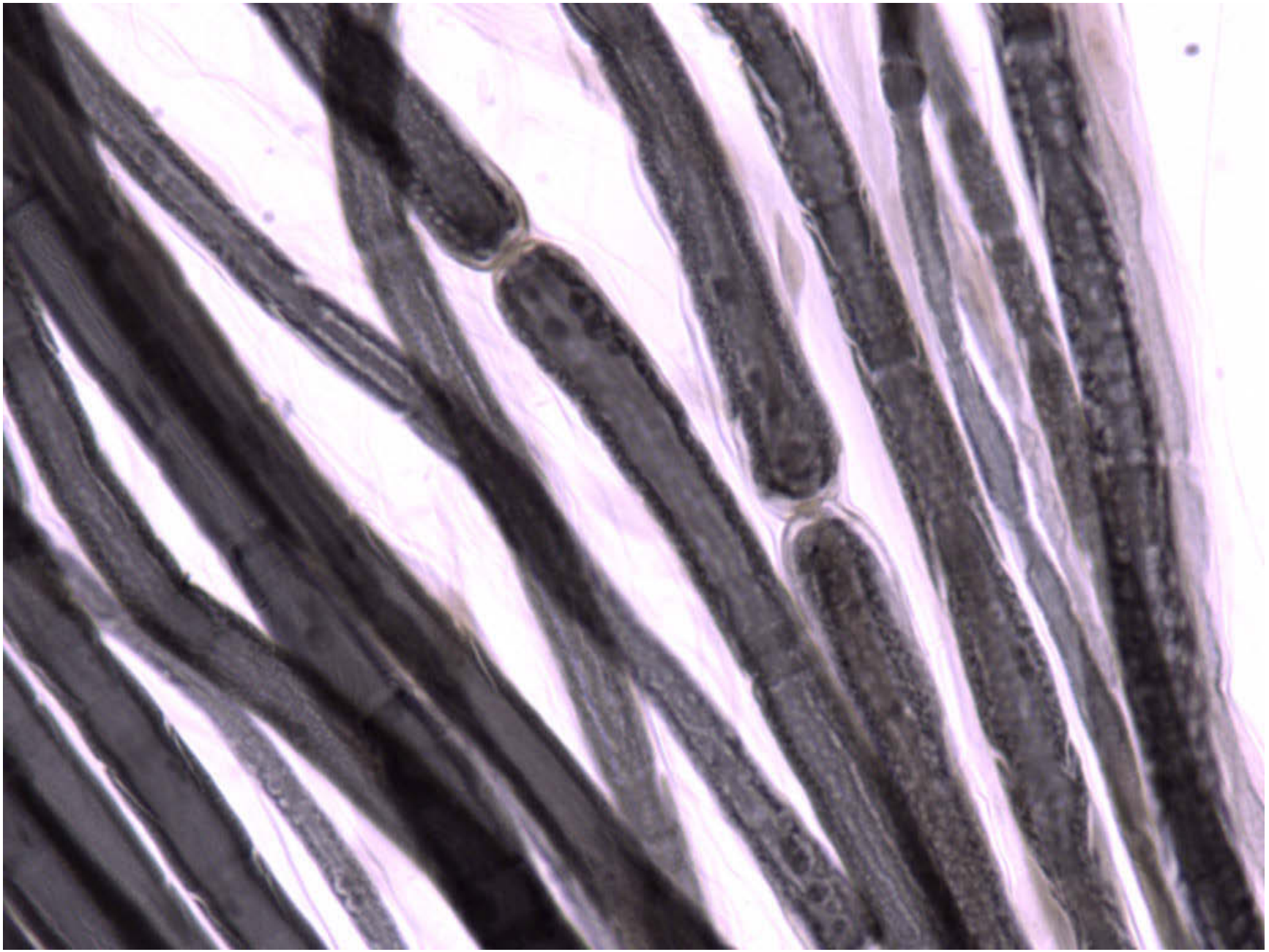
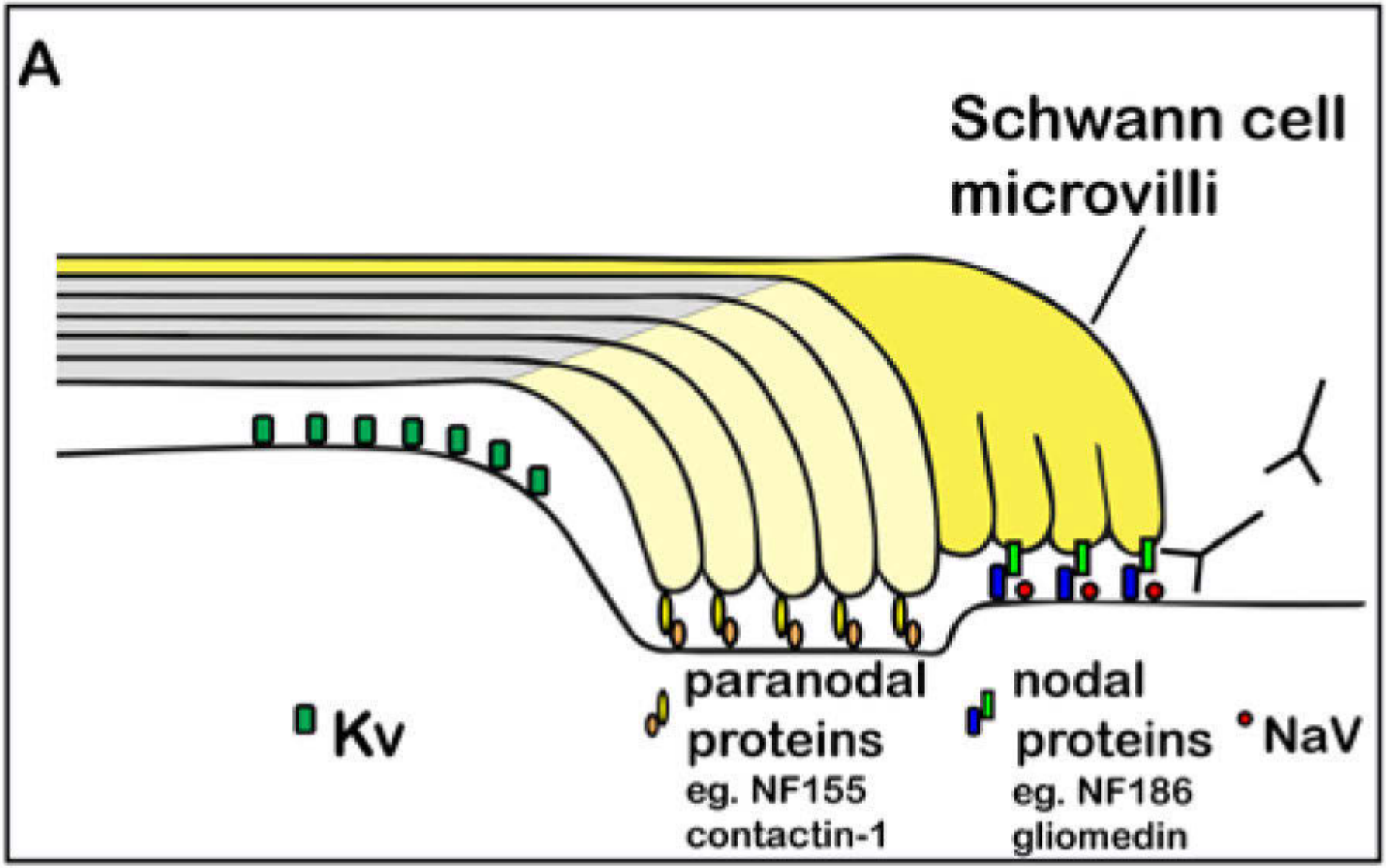
CIDP

- Current studies on autoantibody specificity, not only in CIDP but also in some forms of GBS, are shifting their focus from the major myelin proteins to those located in the non-compact myelin, the node of Ranvier and the regions surrounding it.
- That is the nodal and the paranodal area, also referred to as nodopathy or paranodopathy.

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Schwann cell microvilli
Kv
paranodal proteins
eg. NF155
contactin-1
nodal proteins
eg. NF186
gliomedin
NaV

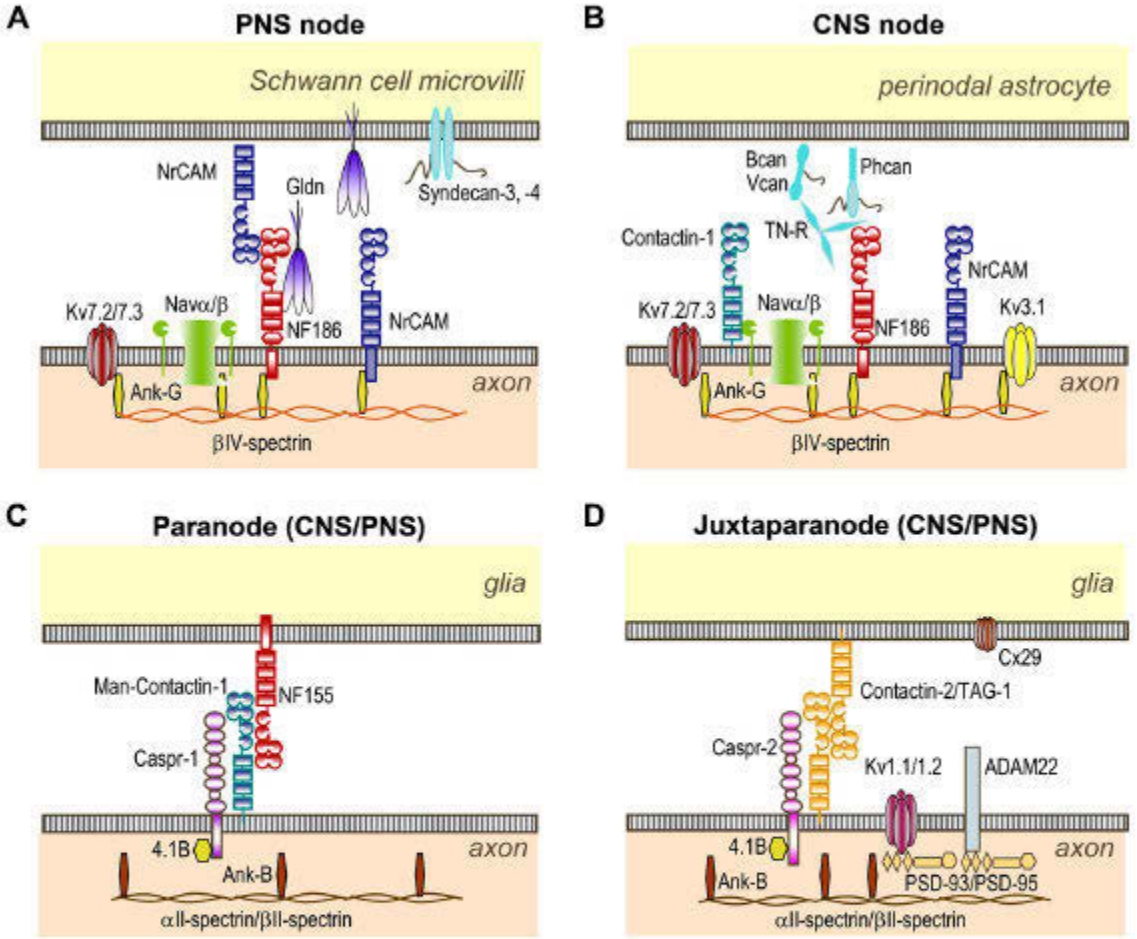

FIGURE 1 | Organization of CNS and PNS nodes of Ranvier. (A) At PNS nodes, NF186 binds Gliomedin (Gldn) and NrCAM which are secreted by Schwann cells in the nodal gap lumen. The cytoplasmic region of axonal NF186 and NrCAM bind ankyrin-G, which anchors the nodal complex to βIV-spectrin and to the actin cytoskeleton. Ankyrin-G enables the clustering of Nav and Kv7.2/7.3 channels at nodes. **(B)** In the CNS, Tenascin-R (TN-R), Brevican (Bcan), Versican (Vcan), and Phosphacan (Phcan) are enriched in the extracellular matrix surrounding the nodes, and stabilize the nodal complex. These molecules bind NF186, NrCAM, and Contactin-1 which are expressed at CNS nodes. **(C)** The complex Contactin-1/Caspr-1/NF155 forms the septate-like junctions at both PNS and CNS paranodes. This complex is stabilized by the cytosolic protein 4.1B which co-localizes with ankyrin-B, αII- and βII-spectrin at both paranodes and juxtaparanodes. **(D)** The complex Contactin-2/Caspr-2 enables the sequestration of Kv1.1/Kv1.2/Kv1.6 channels at juxtaparanodes, but also of PSD-93 and PSD-95. ADAM22 and Connexin-29 (Cx29) are also enriched at juxtaparanodes.

Front Cell Neurosci. 2013 Oct 29;7:196.. **Neuro-glial interactions at the nodes of Ranvier: implication in health and diseases.** Faivre-Sarrailh C[1], Devaux JJ.

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AXOGLIAL Proteins

- Axo-glial proteins are crucial to the formation and maintenance of the node of Ranvier and paranodal regions of myelinated axons.
- The nodal cell adhesion molecules (CAMs) gliomedin, neuron glia-related CAM (NrCAM) and neurofascin 186 (NF186) are vital for the initial clustering of Na^+ channels during development

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Paranodal Proteins

- The adjacent paranode consists of axoglial junctions between paranodal loops and axonal membrane composed of Contactin-1/Caspr-1 complexes which bind to glial neurofascin 155 (NF155).
- These proteins form and maintain the paranodal septate junctions. NF155 is essential for ion channel segregation, paranodal structure and efficient nerve conduction.

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Paranodal auto-antibodies

- Autoantibodies to a number of proteins located in the nodal regions have recently been described in a small minority of patients with AIDP and CIDP, these include: gliomedin, neurofascin, contactin-1, caspr1 and moesin.

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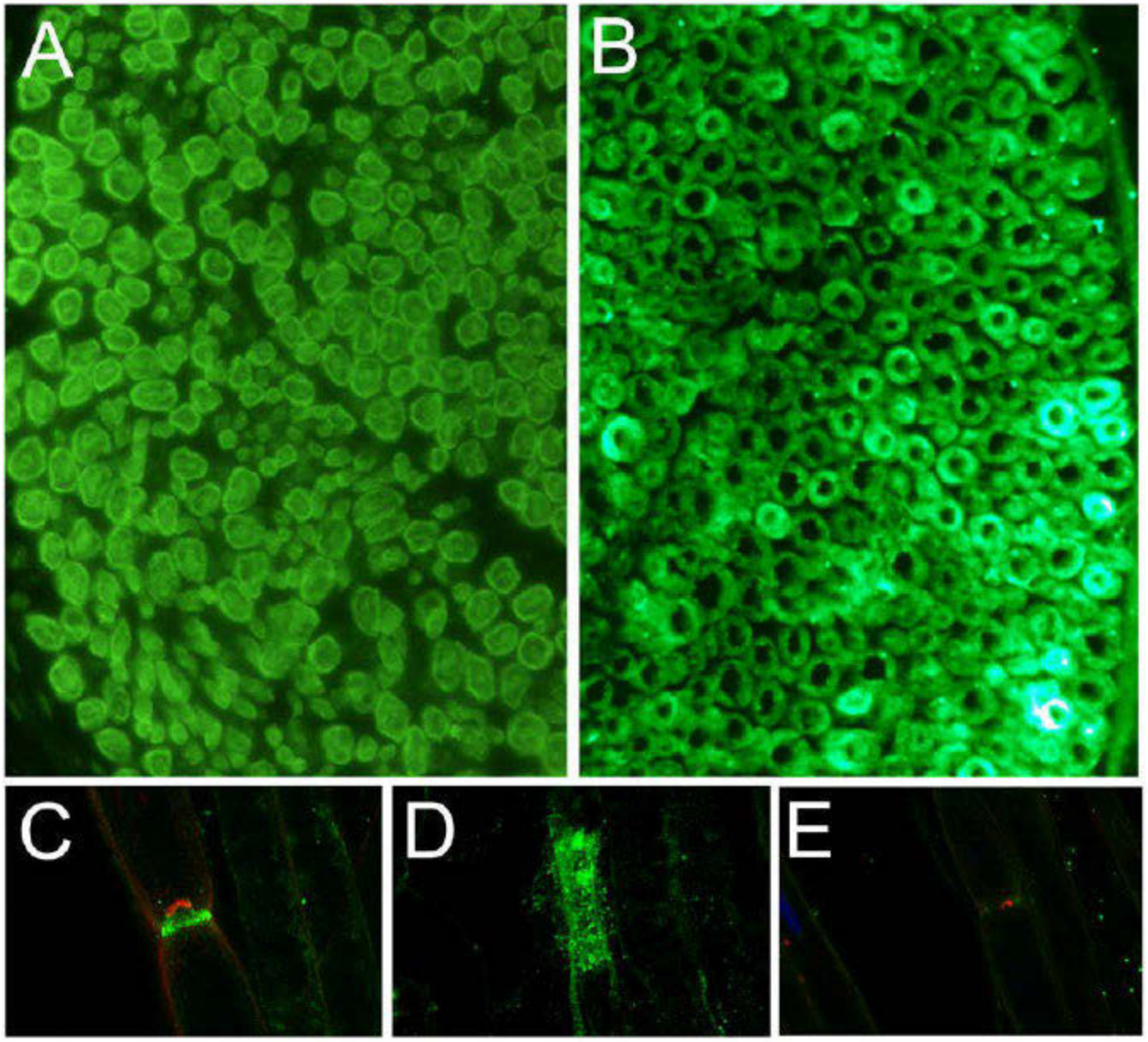
- Devaux and colleagues found that 30% of patients with CIDP have serum IgG that binds to either the nodes of Ranvier or the pananodes in teased nerve fibres and in some cases identified the target antigens as neurofascin, gliomedin or contactin.

Devaux JJ, Odaka M, Yuki N. Nodal proteins are target antigens in Guillain-Barré syndrome. *J Peripher Nerv Syst* 2012;**17**:62-71.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CIDP

- We can show binding to nodes of Ranvier in CIDP and low levels of auto-antibodies to key axoglial proteins in CIDP.
- E.g. Antibodies to neurofascin have been found in 4% of CIDP patients.
- Interestingly anti-NF155 antibodies have also been identified in 5/7 patients with combined central and peripheral demyelination.

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CIDP

- Antibodies reactive to contactin-1/caspr complex in the paranode were reported in a subset (8.6%) of CIDP cases with an atypical clinical and neurophysiological profile, they had an aggressive onset of disease, predominantly motor symptoms, early axonal involvement and were partially or not at all responsive to IVIg requiring further treatment with corticosteroids.

Querol L, Nogales-Gadea G, Rojas-Garcia R et al. Antibodies to contactin-1 in chronic inflammatory demyelinating polyneuropathy. *Ann Neurol* 2013;**73**:370-80.

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CIDP

- Therefore there is still considerable interest in auto antibodies in CIDP pathogenesis.
- However the low levels of sero-positivity 4-10% willl make it very unlikely that these antibodies will be useful at any time in the immediate future for clinical management.

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DADS

- D***istal acquired demyelinating symmetric neuropathy*** DADS is symmetrical with predominantly distal sensory symptoms, although there is often electrophysiological evidence of motor involvement.
- 50-70% are associated with an IgM paraprotein having anti-myelin associated glycoprotein (anti-MAG) antibody.

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DADS

- However, MAG-ve DADS patients are considered to have a phenotypic variant of CIDP, with considerable overlap with sensory and sensory ataxic CIDP phenotypes.
- Treatment responses may be vastly different with MAG associated DADS having minimal or no treatment response.

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CANOMAD

- ***CANOMAD (Chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins and disialosyl antibodies)*** is a rare disorder with specific clinical features consisting of severe sensory ataxia and cranial nerve involvement including ophthalmoplegia, dysphagia or dysarthria and only minimal weakness. It occurs in around 2% of patients with IgM associated peripheral neuropathy. CANOMAD is associated with antibodies to ganglioside disialosyl moieties.

Willison HJ, O'Leary CP, Veitch J, et al. The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies. *Brain* 2001; **124**:1968–77

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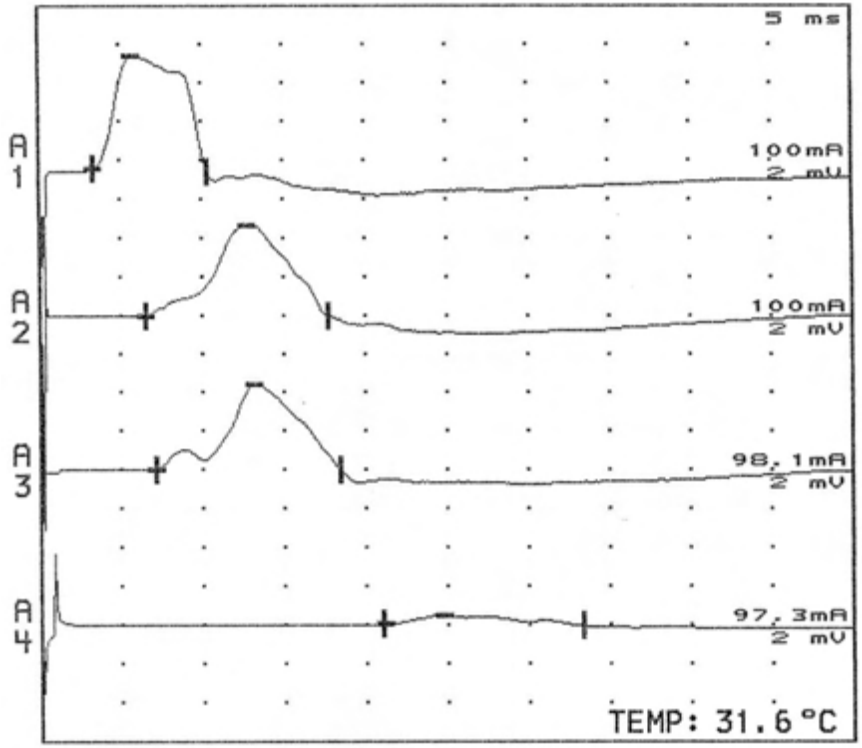
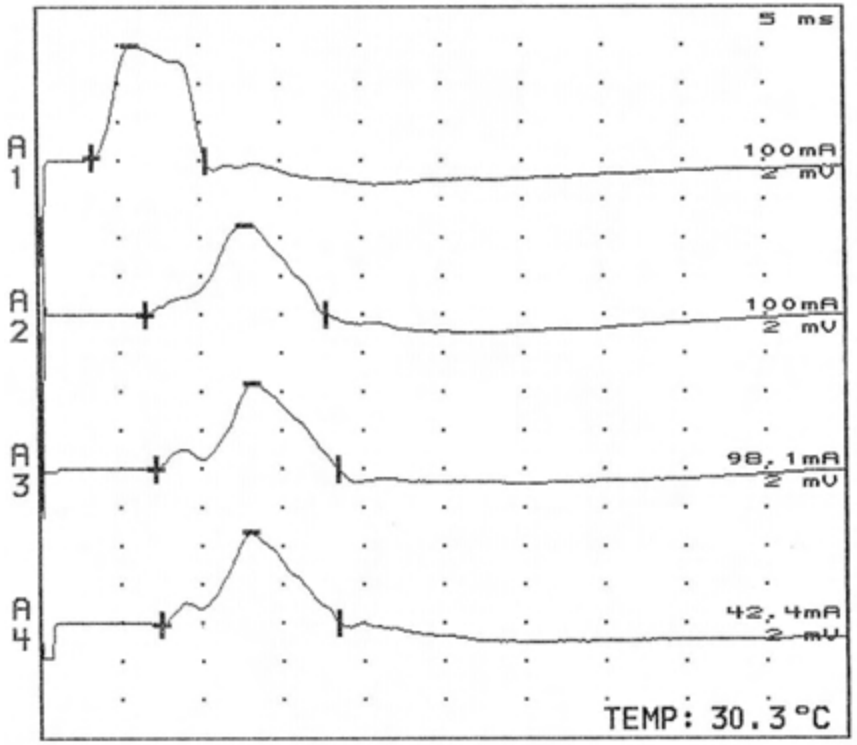
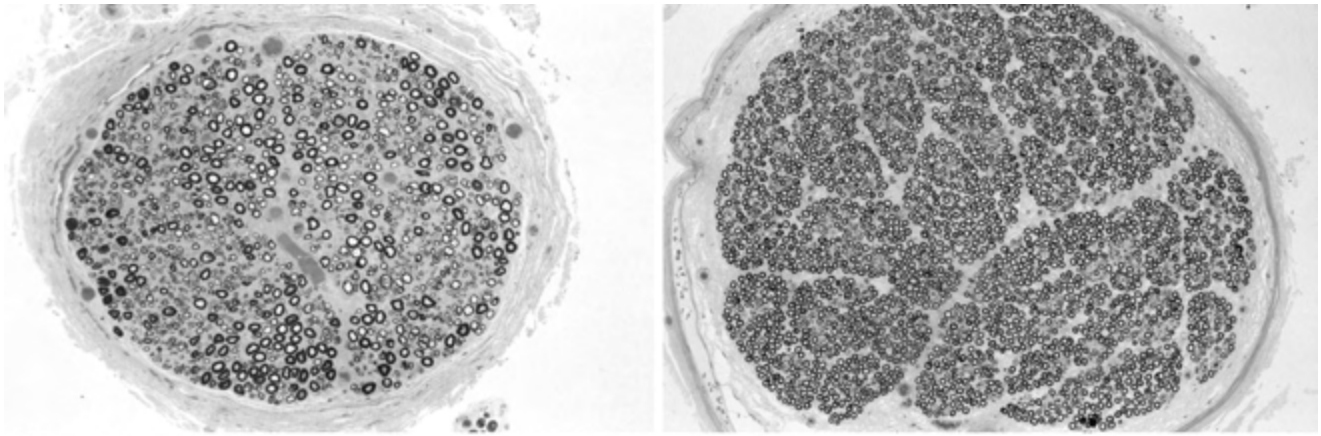
MMN

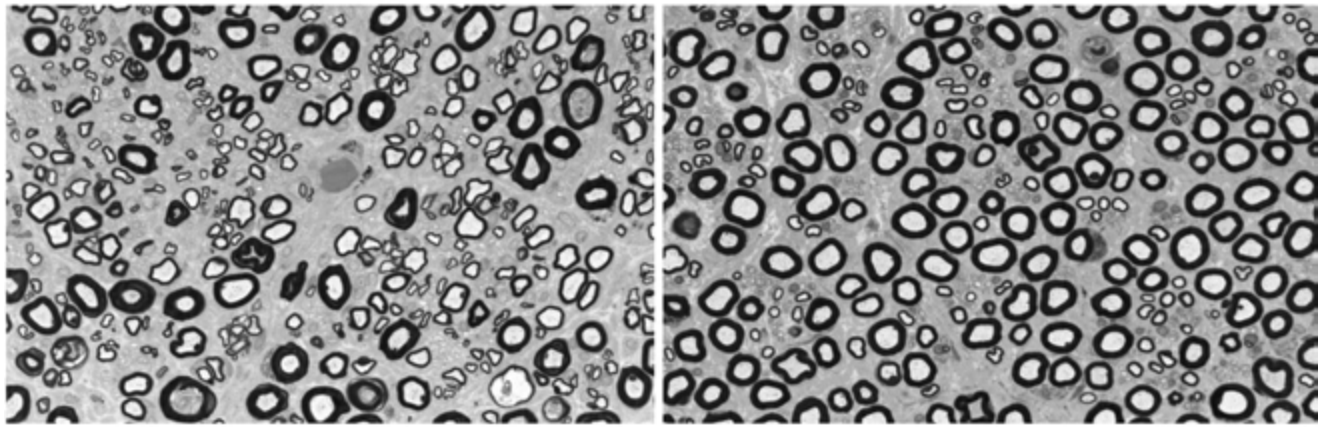
- Multifocal motor neuropathy is a unique axonal probably autoimmune neuropathy/ Characterised by the prescence of focal motor conduction block in motor fibres of mixed nerves with normal sensory conduction through the same region.
- At least initially CB may be functional at the nodes of Ranvier.

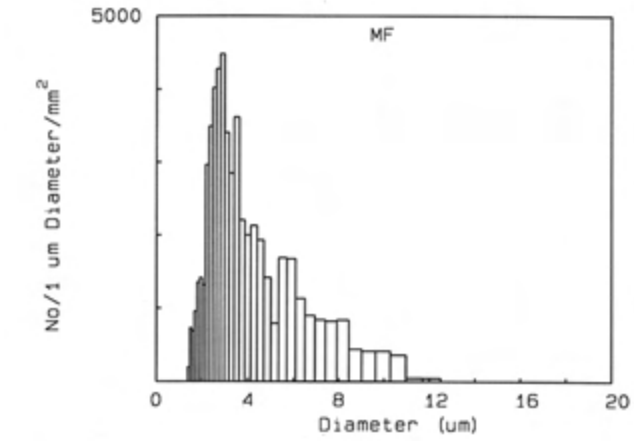




MMN Definite CB Right radial nerve, normal study left radial nerve.



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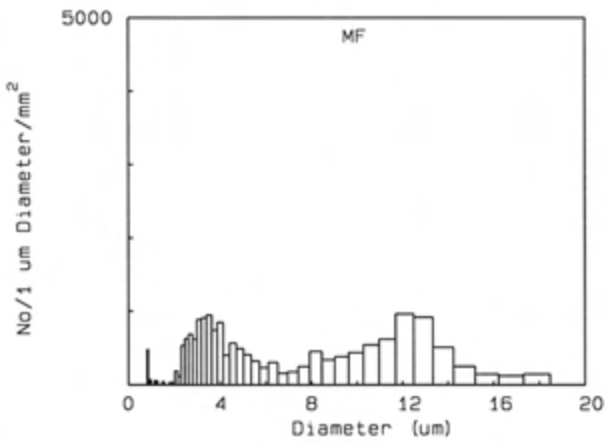
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MMN

- In 20-80% of MMN cases high titre IgM anti GM1 monoclonal or polyclonal antibodies can be detected.
- Smaller numbers <10% have IgM antibodies to GM2 and GD1b.
- Some studies have shown that GM1 antibodies can bind at the nodes of Ranvier and activate complement.

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MMN

- Passive transfer of IgM GM1 antibodies into rat phrenic nerve preparations have induced conduction failure.
- There has recently been some interest in ganglioside antibody complexes with increased sensitivity and specificity. Although this is still highly controversial.

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MMN

- Measuring GM1 antibodies in MMN may have some limited clinical application where the differential diagnosis is SMA/ motor neuronopathy where the presence of high titre Abs may suggest a trial of therapy.
- This is a very difficult area that requires considerable caution.

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Conclusions

- Antibody testing for peripheral neuropathy is still in its infancy.
- With the exception of anti MAG IgM And GQ1b Abs antibodies no antibody predicts clinical response or clinical course reliably.
- At this stage there is no clear indication to measure other antibodies outside of research situations.