LE PATOLOGIE DELLA MIELINA: GLI STRUMENTI PER LA DIAGNOSI DIFFERENZIALE

Cremona 9 giugno 2017

DIAGNOSI DIFFERENZIALE DELLE MALATTIE DEL SISTEMA NERVOSO PERIFERICO

Il ruolo della diagnostica di laboratorio

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No conflicts of interest

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Table 2: Autoantibodies to gangliosides and their association with GBS.

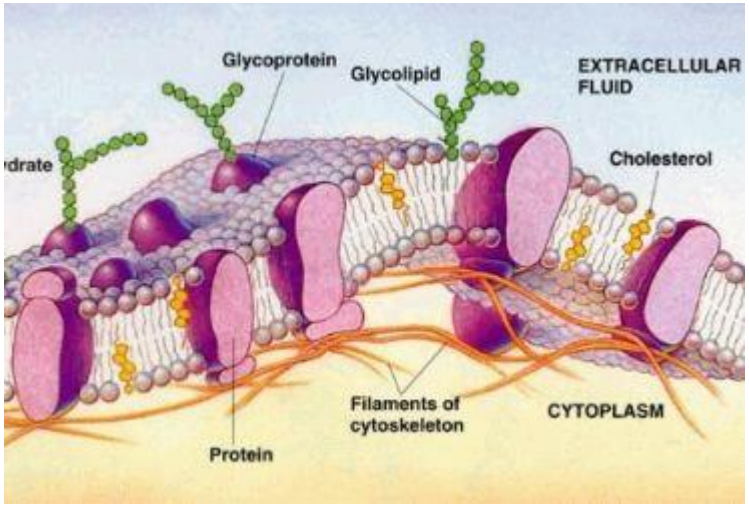
Antigen	Infection	Subtype	Association with GBS	Reference
GA1		AMAN		[96]
GD1a			Younger, predominantly male, facial nerve involvement	[97]
GD1b			Reversible conduction failure, ataxia	[96, 96]
GalNAc-GD1a	G[a]	Axonal dysfunction	Distal weakness, low amplitudes for the compound muscle action potentials, facial palsy	[98]
9-O-Acetyl GD1b			Potential target	[99]
GD3			Ophthalmoparesis	[100]
GM1	G	AMAN	Reversible conduction failure, rapidly progressive stage, distal distribution of weakness, not sensitive to plasma change treatment	[96, 97]
GT1a			Ophthalmoplegia	[97]
GT1b			Ataxia	[101]
GT3			Ophthalmoparesis	[100]
O-Acetyl GT3			Ophthalmoparesis	[100]
GQ1b			Ataxia, ophthalmoparesis	[101, 102]
LM-1			Potential target	[103]
GD1a/GD1b			Severe disability, mechanical ventilation	[104, 105]
GD1b/GT1b			Severe disability, mechanical ventilation	[104, 105]
GM1/GalNac-GD1a	R[b]		Pure motor GBS, conduction blocks at intermediate nerve	[106]
GM1/PA			Potential target	[107, 108]
GM1/GD1a			Potential target	[107]
GM1/GT1b			Potential target	[105]
LM1/GA1		AMAN	Reversible conduction failure	[96]

[a]Gastrointestinal infection.
[b]Respiratory infection.

Wang Y et al. Mediators of Inflammatory 2015

Gangliosides & GBS

- Gangliosides are glycosphingolipids predominantly distributed on the cell-surface membrane and anchored in the external leaflet of the lipid bilayer by a ceramide moiety.
- Gangliosides composed of a ceramid attached to one or more sugar, contain sialic acid linked to the oligosaccaride core that is exposed extracellulary.
- **Gangliosedes are abundant in the peripheral nerve (nodes and paranodes)**



- Anti-ganglioside antibodies firstly described in GBS in 1988 *(Ilyas et al, Ann Neurol)*
- Anti-GM1 and anti-GD1a antibodies in AMAN with Campylobacter enteritis. *(Yuki et al Neurology 1990 & Muscle & Nerve 1992)*

Antibodies against single ganglioside

Table 1. Well established and emerging phenotypic association of antiganglioside antibodies

Antiganglioside antibody specificity	Phenotype	
	Well established	Putative associations
Anti-GD1a	AMAN	GBS with CN involvement, PCB, polyneuritis cranialis
Anti-GM1	AMAN	Pure motor GBS, GBS without CN involvement
Anti-GQ1b	MFS, BBE	MFS-PCB, MFS-GBS, MFS-BBE, polyneuritis cranialis, acute bulbar palsy, extraocular muscle weakness
Anti-GT1a	PCB	GBS with bulbar weakness, acute bulbar palsy, AMAN
Anti-GM2[a]	AIDP	limited CN palsies
Anti-GD1b	Sensory GBS, GBS with bulbar weakness	
Anti-GalNAc-GD1a	Pure motor GBS	

AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; BBE, Bickerstaff's brainstem encephalitis; CN, cranial nerve; GBS, Guillain–Barré syndrome; MFS, Miller Fisher syndrome; PCB, pharyngeal–cervical–brachial variant GBS.
[a]Anti-GM2 antibodies can be IgG or IgM; all others are IgG.

Goodfellow JA & Wilison HJ Current Opinion 2016

useful in routine clinical practice:

- ✓ when positive in patients with a compatible clinical syndrome, they are strongly supportive of the diagnosis
- ✓ may identify a regional or pathological variant.

Antiganglioside-complex antibodies

multiple glycolipid and lipid components can associate to form neoantigens not present in any single molecule

Ganglioside complexes as new target antigens in Guillain-Barre syndrome. *Kaida K et al. Ann Neurol 2004; 56:567 – 571.*

Table 2. Emerging antibody–phenotype associations for antigangliosides complexes antibodies

Anti-GCS antibody specificity	Emerging phenotype associations
Anti-GD1a/GD1b	Mechanical ventilation
Anti-LM1 complexes	AIDP or AMAN[a]
Anti-GM1/GalNAc-GD1a	Pure motor GBS, AMCBN
Anti-GM1b/GA1	Pure motor GBS
Anti-GQ1b complex	Various variant features
Anti-glycolipid complex	Table 3

Table 3. Clinical features statistically significantly associated with specific antigens in Guillain–Barré syndrome patients

Clinical feature	Associated antigens
Axonal electrophysiology	CTH/GM1, GD2/GM1, globoside/GM1, GalC/GM1, GA1/GM1, GM1, GM1/GD1b, SM/GM1, GM3/GM1, GM1/GD3, SGPG/GM1, GM2/GM1, PS/GM1, sulfatide/GM1, GA1/GalC, GM1/GQ1b, GA1, GA1/globoside
Greater disease severity	CTH/GA1, globoside/GA1, PS/GalC, GA1/GalC, globoside/GD3, GD2/GD3, GA1, GD3/GT1b, GalC/GQ1b
Need for mechanical ventilation	CTH/GA1, globoside/GA1
Preceding *Campylobacter jejuni* infection	GD1a/GT1b, GD3/GD1a, sulfatide/GD1a, GalC/GD1a, GM2/GD1a, GD1a, GD1a/GQ1b, GD2/GD1a, CTH/GD1a
No cranial nerve deficit	Sulfatide/GM1, sulfatide/GT1a

Antibodies against GCS may be useful in identifying specific clinical subtypes or predicting clinical progression.

Goodfellow JA & Wilison HJ Current Opinion 2016

Pathogenetic mechanism in acute immune-mediated neuropathies

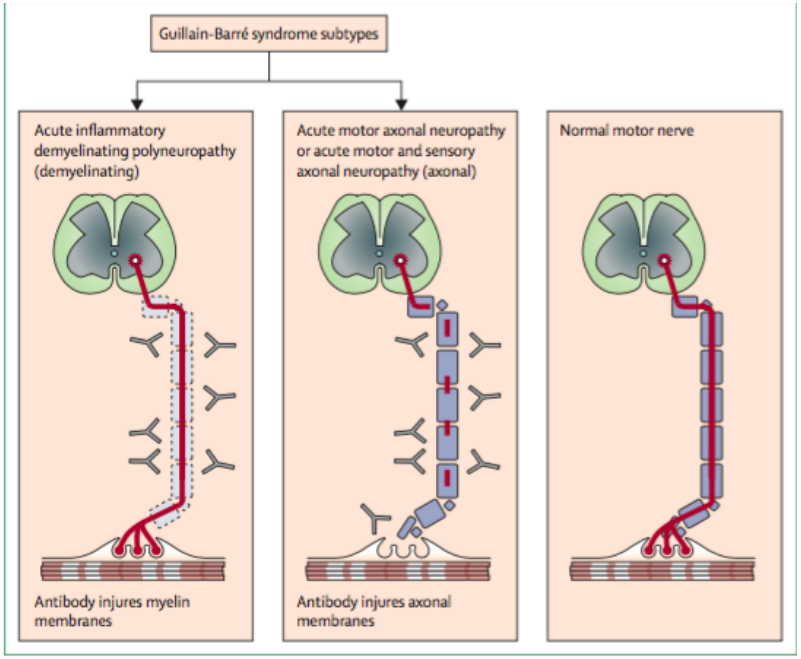


Figure 2: **Major Guillain-Barré syndrome subtypes in which antibody-mediated effector pathways, including complement activation, cause glial or axonal membrane injury with consequent conduction failure**

- the main phenotypes: acute inflammatory demyelinating polyneuropathy (**AIDP**) and acute motor axonal neuropathy (**AMAN**)
- **IMMUNE INJURY** specifically takes place at the myelin sheath and related Schwann-cell components in AIDP, whereas membranes on the nerve axon in AMAN
- Distinct phenotypes supported by the identification of **specific antibody biomarkers (anti-GM1 & GD1a IgG)** for AMAN

Willison Jacobs & van Doorn, Lancet 2016

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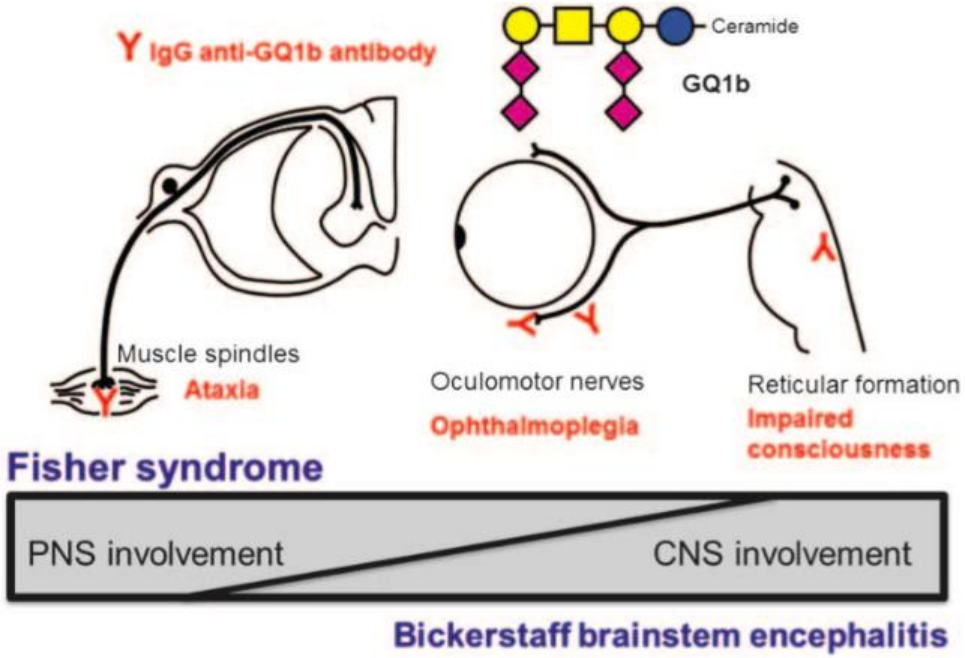
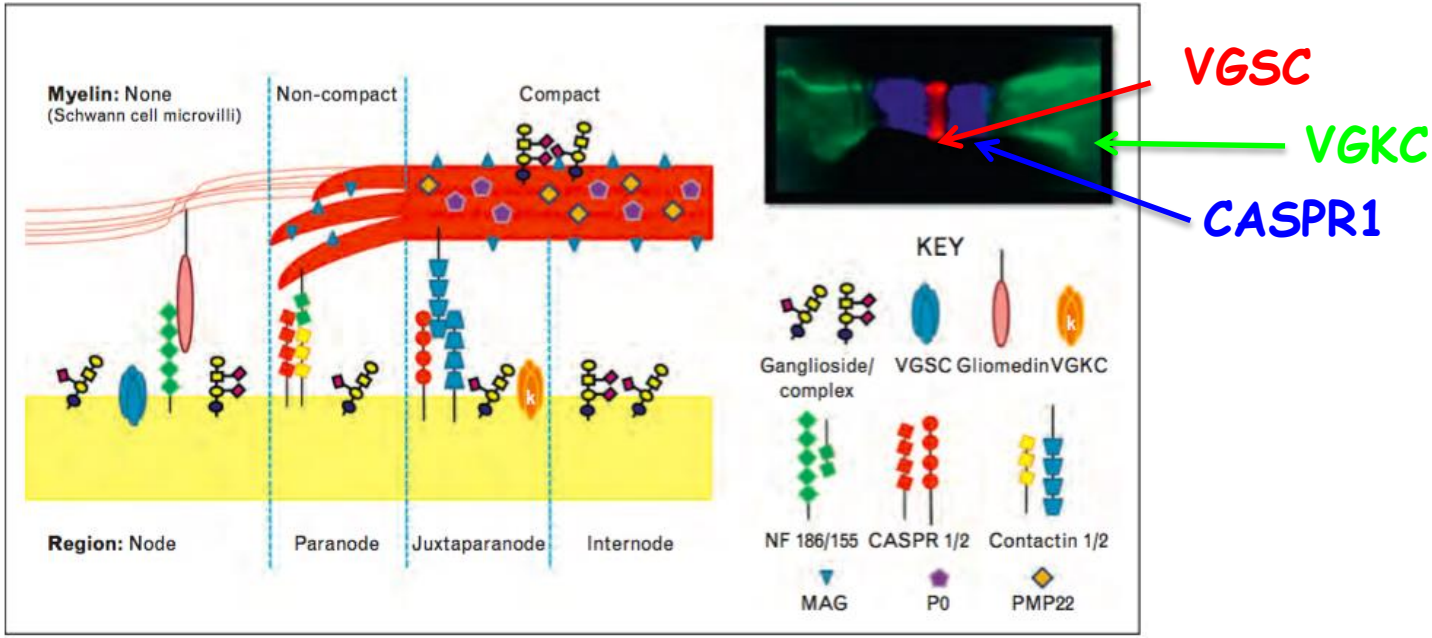
Pathogenetic mechanism in acute immune-mediated neuropathies



- **GQ1b**: paranodes of III, IV and VI nerves, muscle spindles in the limbs, and probably reticular formation in the brainstem.
- **Anti-GQ1b antibodies** against oculomotor nerves and muscle spindles induce **Fisher syndrome.**
- anti-GQ1b antibodies to brainstem induce **Bickerstaff brainstem encephalitis**

Shahrizaila N, et al. J Neurol Neurosurg Psychiatry 2013;84:576–583.

THE NODAL COMPLEX



NODE

cell adhesion molecules (CAMs): gliomedin, NF186 and other neuron glia-related CAM (NrCAM)

Functions:

- initial clustering of Na+ channels during development
- long-term maintainence of VGSC clustering at the node of Ranvier.

PARANODE

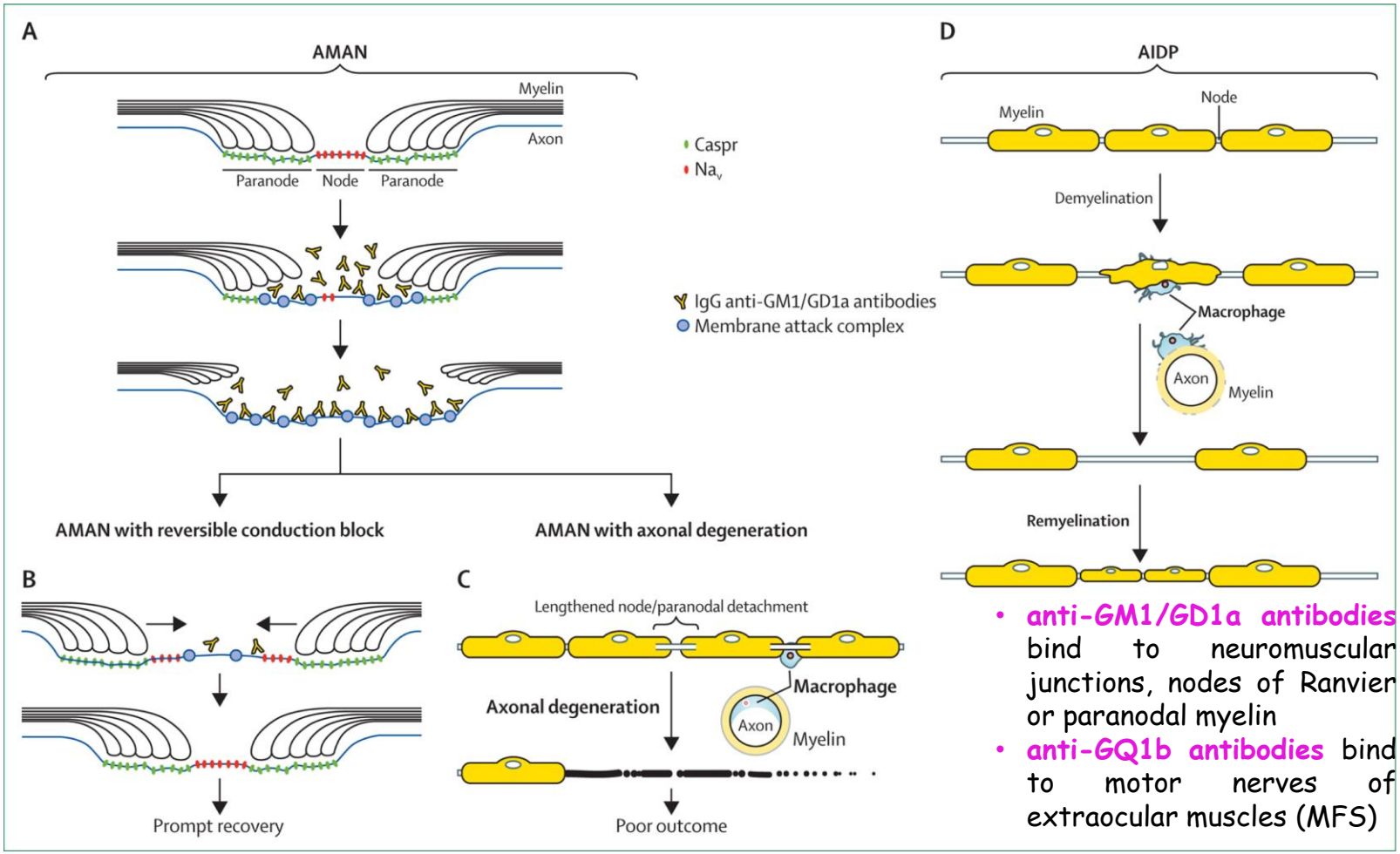
axoglial junctions (paranodal loops and axonal membrane): contactin-1/caspr-1 complexes which bind to NF155 of Schwann cell

Functions:

- form and maintain the paranodal septate junctions.
- effective saltatory conduction
- membrane barrier to limit lateral diffusion of ion channels, ensuring that Na+ is concentrated at the node and K+ at the juxtaparanode.

Rinaldi S & Bennet DLH Neurology 2014

Mechanism of action of anti-ganglioside antibodies in AMAN

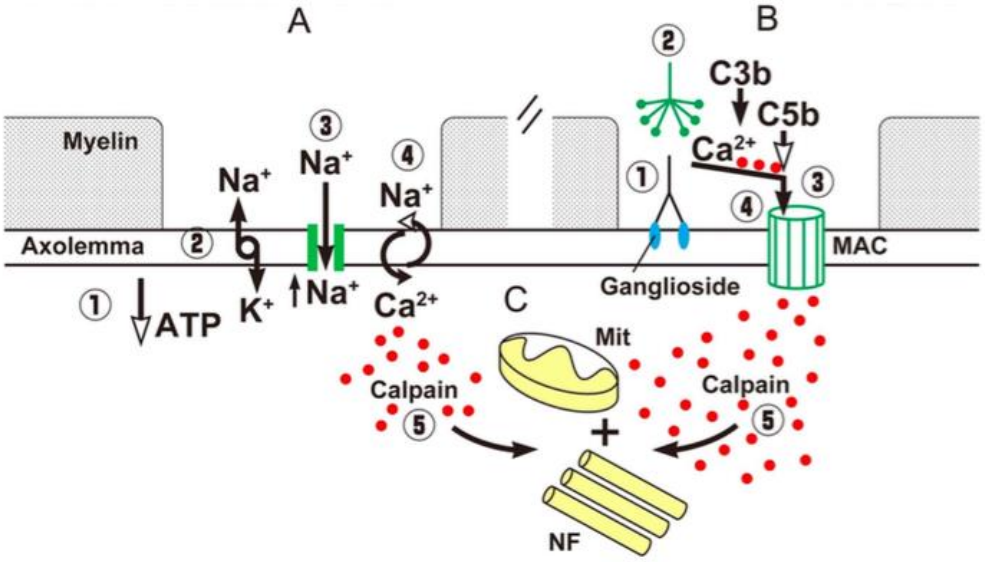


- **anti-GM1/GD1a antibodies** bind to neuromuscular junctions, nodes of Ranvier or paranodal myelin
- **anti-GQ1b antibodies** bind to motor nerves of extraocular muscles (MFS)

Some AMAN patients with anti-ganglioside antibodies recovered promptly and completely; early neurophysiological studies show rapidly reversible CB (RCB) that later disappear suggesting a transient impaired conduction at the node of Ranvier due to anti-ganglioside antibodies.

Uncini Revue Neurologique 2016, Uncini & Kuwabara J Neurol Neurosurg Psychiatry 2015

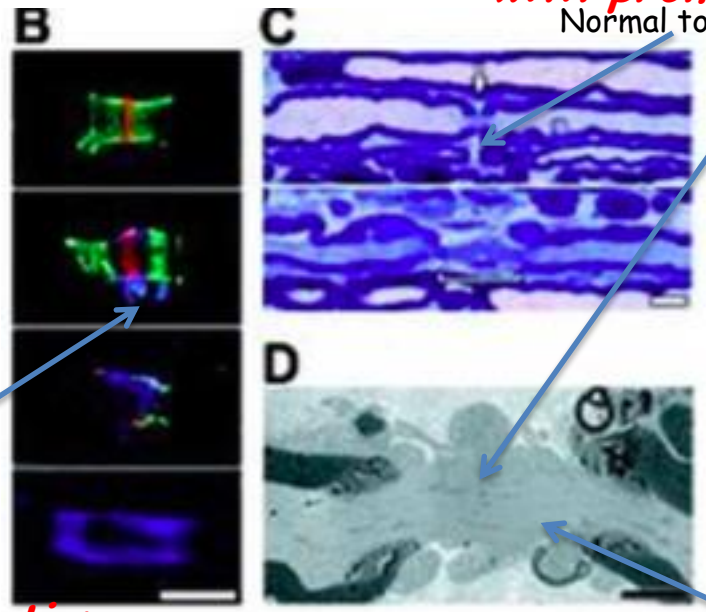
Possible events leading to axonal degeneration



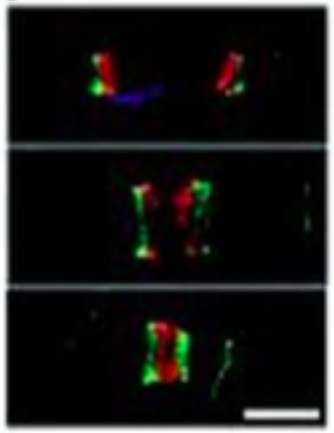
1. Antibodies bind to gangliosides in the axolemma
2. Classical pathway of complement is activated
3. The terminal component of complement form the membrane attack complex (MAC) pore
4. Ca^{2+} enters through the MAC pores and accumulates in the axoplasma
5. Activation of Ca^{2+} -dependent calpain causing proteolytic cleavage of neurofilaments, damage of mitochondria and finally Wallerian degeneration

Uncini Revue Neurologique 2016,

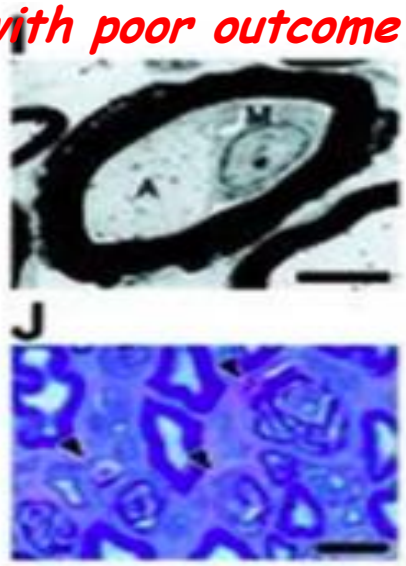
Acute nodal disruption + RCB with prompt recovery



Recovery phase



Axonal degeneration with poor outcome



NODOPATHY: acute neuropathy with anti-ganglioside antibodies

Nodo-paranodopathy: beyond the demyelinating and axonal classification in anti-ganglioside antibody-mediated neuropathies. Uncini A, Susuki K, Yuki N. Clin Neurophysiol 2013;124:1928-34.

Uncini Revue Neurologique 2016, Uncini & Kuwabara J Neurol Neurosurg Psychiatry 2015

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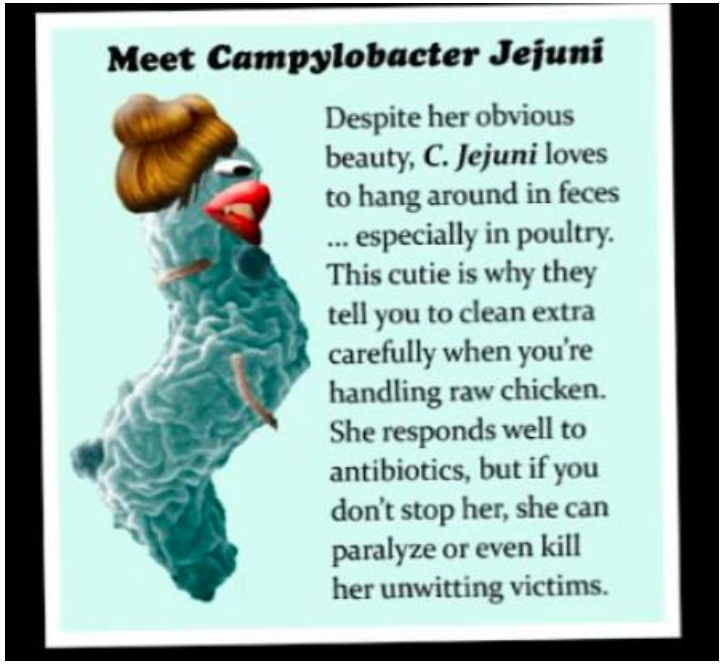
CJ & GBS



- Diarrhoeal illness can precede GBS
- CJ is one of the most common cause of acute gastroenteritis worldwide
- GBS associated with antecedent CJ infection was in 1982 *(Rhodes et al. Br Med J)*
- 1995 a case-control study established an epidemiological association between CJ infection and GBS *(Rees et al. N Eng J Med)*

CJ & gangliosides & GBS

…the lipo-oligosaccharides of the CJ strains have structural similarity with various gangliosides present on peripheral nerve membranes, indicating that molecular mimicry of gangliosides could contribute to GBS.

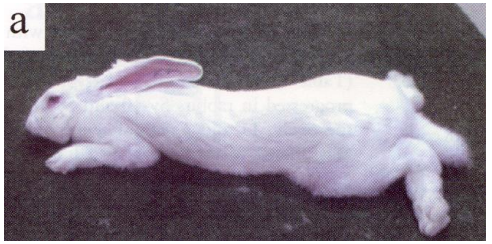
Yuki, N. et al. A bacterium lipopolysaccharide that elicits Guillain–Barré syndrome has a GM1 ganglioside-like structure. J. Exp. Med. 178, 1771–1775 (1993)

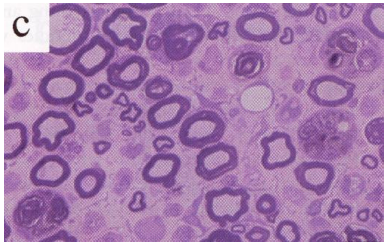
…lipo-oligosaccharides from the CJ strains associated with MFS were shown to have identical structures to ganglioside GQ1b.

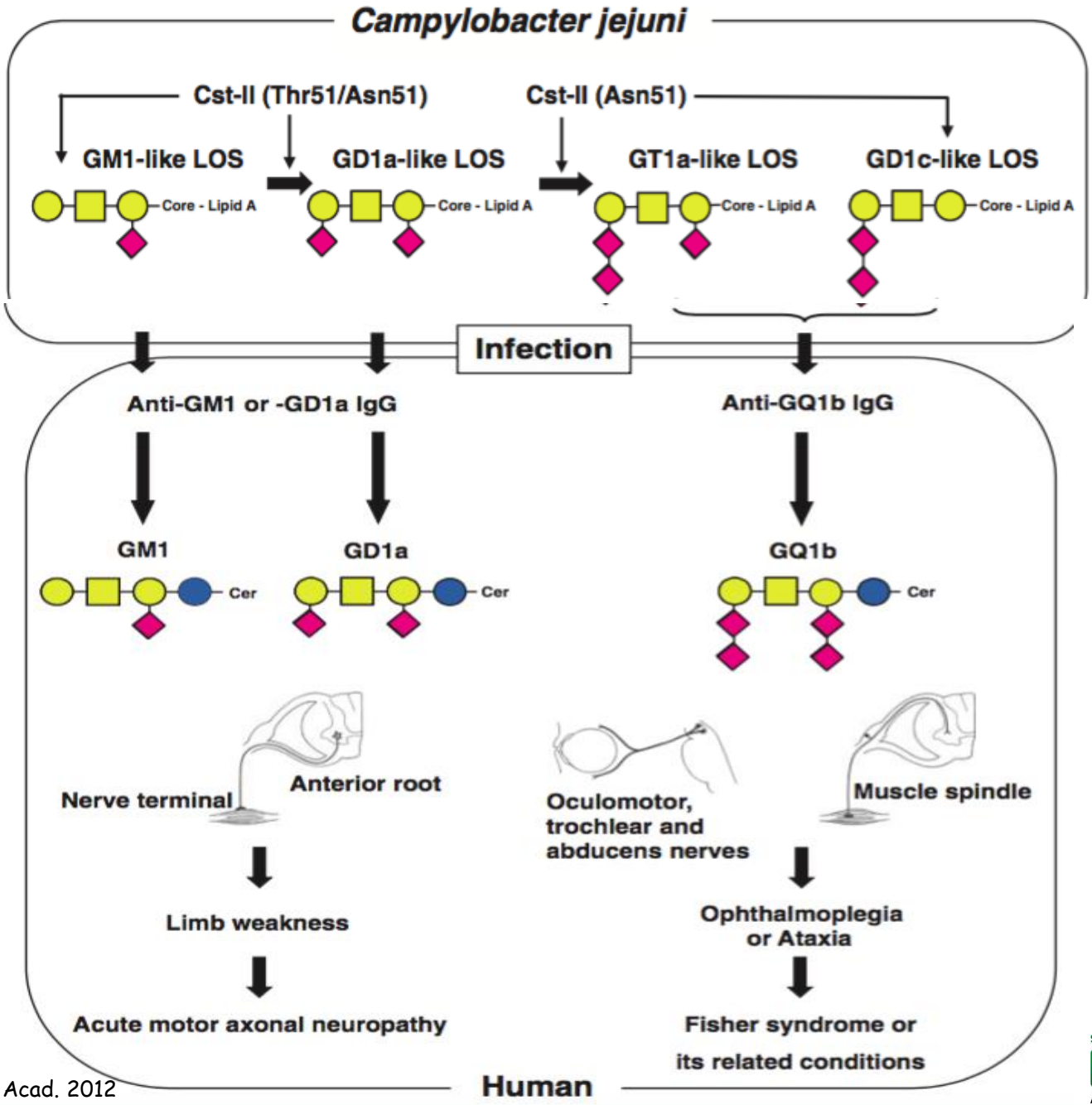
Yuki, N. et al. Molecular mimicry between GQ1b ganglioside and lipopolysaccharides of Campylobacter jejuni isolated from patients with Fisher's syndrome. Ann. Neurol. 36, 791–793 (1994).

….immunization of rabbits with the ganglioside-like lipo-oligosaccharides from GBS-associated CJ strains resulted in a subacute flaccid tetraplegia and pathological changes similar to AMAN.

Yuki, N. et al. Carbohydrate mimicry between human ganglioside GM1 and Campylobacter jejuni lipooligosaccharide causes Guillain–Barré syndrome. Proc. Natl Acad. Sci. USA 101, 11404–11409 (2004).

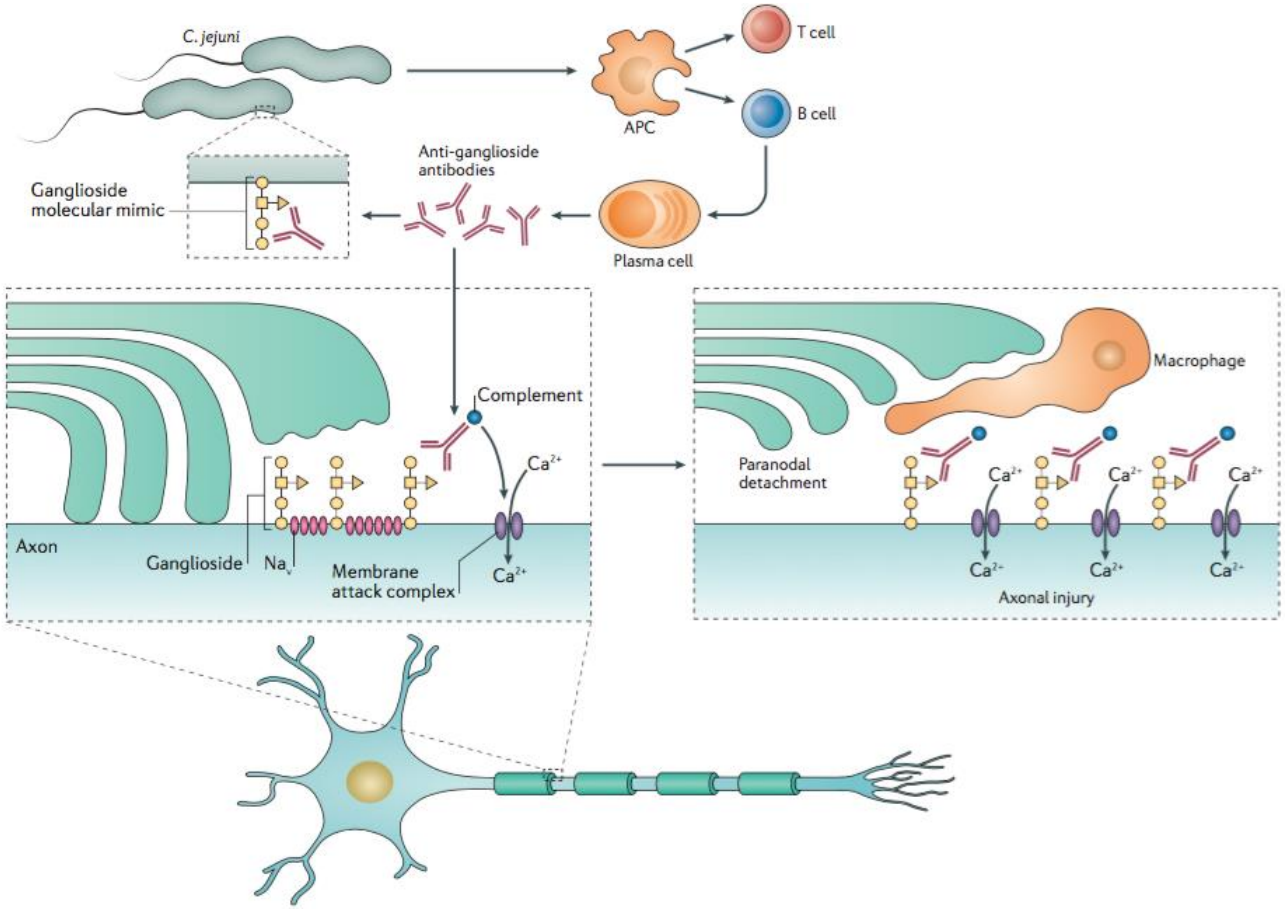






Yuki N. Proc. Jpn. Acad. 2012

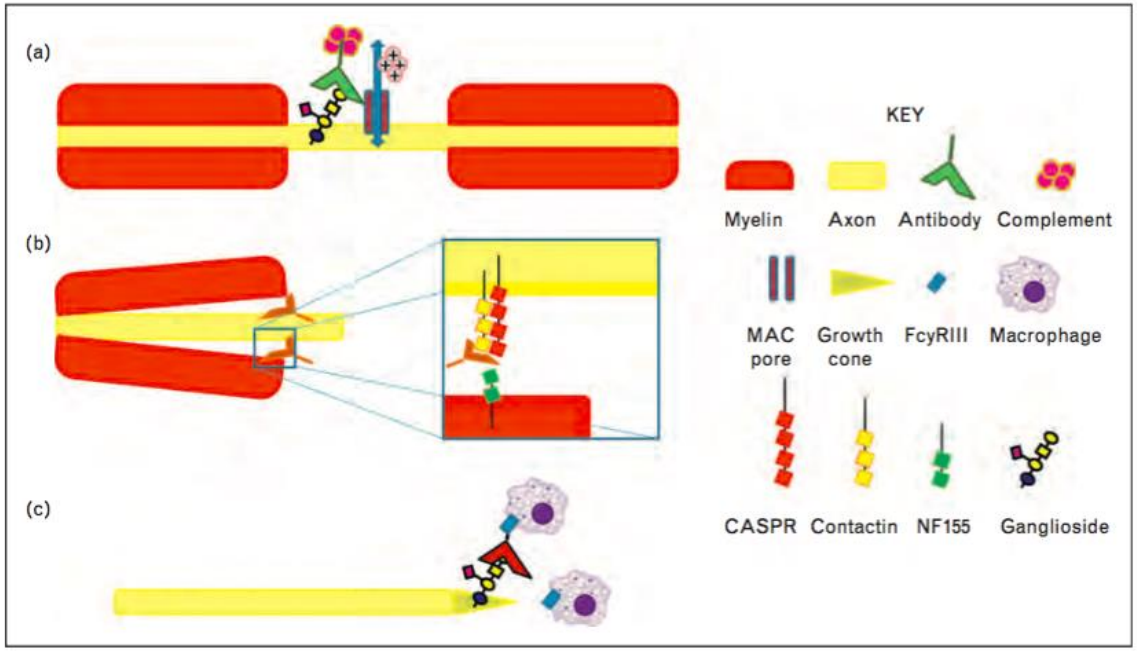
Mechanism of Guillain–Barré syndrome pathogenesis mediated by Campylobacter jejuni: molecular mimicry



A molecular mimic of gangliosides in CJ leads to the production of anti-ganglioside antibodies (IgG1 e IgG3) that bind to gangliosides in the axonal membrane at the node of Ranvier. Consequent activation of complement leads to disruption of VGSC clusters, disruption of the nodal architecture, and formation of the membrane attack complex, which leads to calcium influx. These changes cause axonal injury and attract macrophages, which can then migrate between the axon and myelin.

Goodfellow JA & Willison HJ NATURE REVIEWS,NEUROLOGY 2016

The potential diverse pathophysiological mechanisms of neuropathy-associated autoantibodies.



(a) Antibody binding at the **node of Ranvier**, which may be directed against **gangliosides** or nodal proteins, activates the complement cascade. MAC pores are deposited in the axolemma, forming a nonspecific ion channel which disrupts control of the membrane potential and thus transmission of the action potential. In addition, calcium influx through the pore can activate calpains and subsequently lead to axonal degeneration.

(b) Antibodies directed against **paranodal** proteins such as contactin-1 inhibit axoglial interactions in a complement independent fashion (IgG4). Antibodies may also cause a loss or mislocalization of voltage-gated ion channels.

(c) **Antibodies targeting gangliosides** inhibit axonal regeneration by interaction with specific Fc receptors on macrophages

Rinaldi S & Bennet DLH Neurology 2014

TAKE HOME MESSAGE

- Anti-GM1/GD1a/GQ1b IgG can interfere with nodal function
- any disruption of nodal function interfere with normal nerve excitability and membrane potentials, contributing to conduction failure by interfering with saltatory conduction
- Anti-gangliosides may allow identification of specific clinical subtypes, predict clinical progression…
- ….better understanding the pathophysiology of inflammatory neuropathies and the potential therapeutic interventions such as prevention of axonal damage, the most important limiting factor for a good outcome