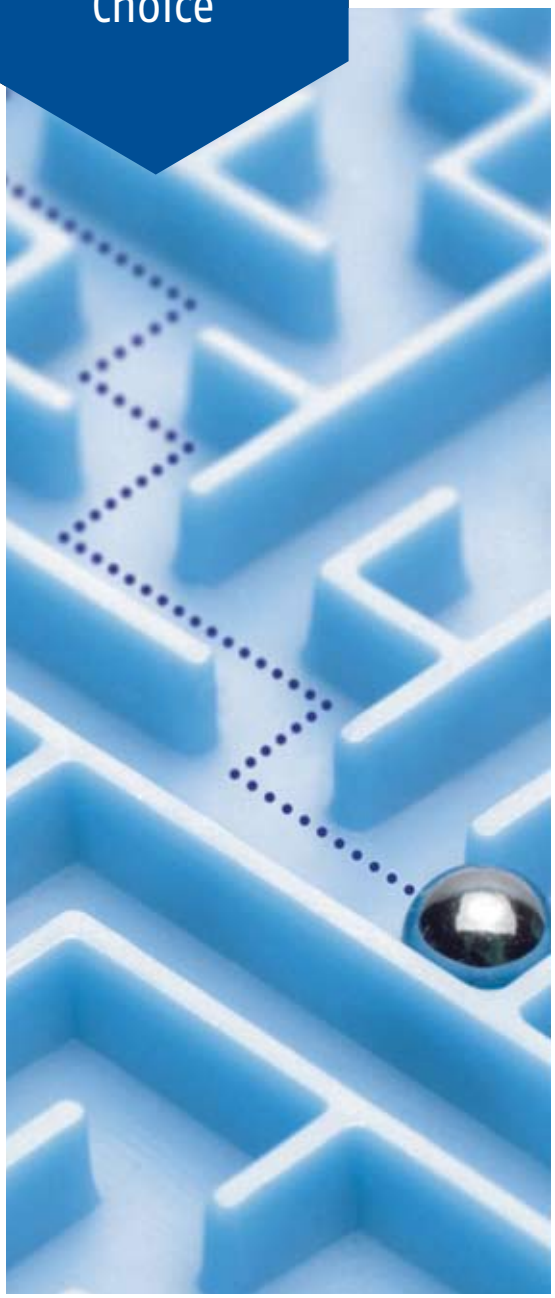
NeuroImmunology

Autoantibodies Associated with Peripheral Neuropathies

The Expert's Choice



Anti-glycoconjugate autoantibodies are regarded as potentially pathogenetic agents in a variety of peripheral neuropathies with autoimmune background. Autoantibodies frequently bind to carbohydrate epitopes exposed on the cell surface. Glycoconjugates comprise glycoproteins (*e.g.* MAG) or glycolipids such as gangliosides.

The significance of anti-glycolipid antibody assays for diagnostics is increasingly recognized by experts.

A significant correlation between particular clinical features and isotypes of anti-glycoconjugate autoantibodies in serum has been shown. IgG autoantibodies are associated with acute neuropathies, whereas IgM isotypes occur in chronic conditions.

A variety of peripheral neuropathies can be defined by their anti-glycolipid antibody profile.

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Background anti-Glycoconjugate Antibodies

Autoantibodies against Myelin- Associated Glycoprotein (MAG)

MAG is well known as an antigen for monoclonal IgM antibodies in neuropathies. The detection of anti-MAG IgM autoantibodies, particularly at high titers, is associated with sensorimotor demyelinating peripheral neuropathy. Sensory symptoms often dominate early stages of the disease, motor symptoms occur at later stages. Anti-MAG antibodies are associated with IgM monoclonal protein. The origin and purity of the MAG antigen is essential for this particular test. The method of choice for the determination of anti-MAG antibodies is ELISA. Purified antigen from human brain makes the BÜHLMANN anti-MAG ELISA to the method of choice for the routine determination of anti-MAG Neuropathies. In a recent study, Kuijf et al. (2009) confirm that anti-MAG antibodies canbe detected in over 70% of patients with anti-MAG neuropathy.

Autoantibodies against Gangliosides

Gangliosides belong to a family of glycolipids particularly abundant in membrane components of the peripheral nervous system. They are composed of a hydrophobic lipid (Ceramide) and hydrophilic oligosaccharide part. The hydrophobic element is immersed in the lipid bilayer of the membrane, whereas the hydrophilic carbohydrate portion protrudes from the cell surface. Thus, gangliosides are accessible to various autoantibodies.

The nomenclature proposed by Svennerholm (Svennerholm et al., 1994) is most widely used for gangliosides of the ganglioseries. The nomenclature is based upon the number of carbohydrate residues and the sialylation pattern.

The expression patterns of gangliosides is heterogeneous in the tissue of the peripheral nervous system: Whereas GM1 and GD1a predominantly occur in motor nerves, GQ1b is accumulated in cranial motor nerves.

GD1b is highly expressed in sensory nerves. Clear correlations between specific anti-ganglioside antibodies and different **Guillain-Barré Syndrome** (GBS) variants have been shown (*cf* table; Peripheral Neuropathies associated with specific auantibodies.

Nomenclature according to Svenneholm

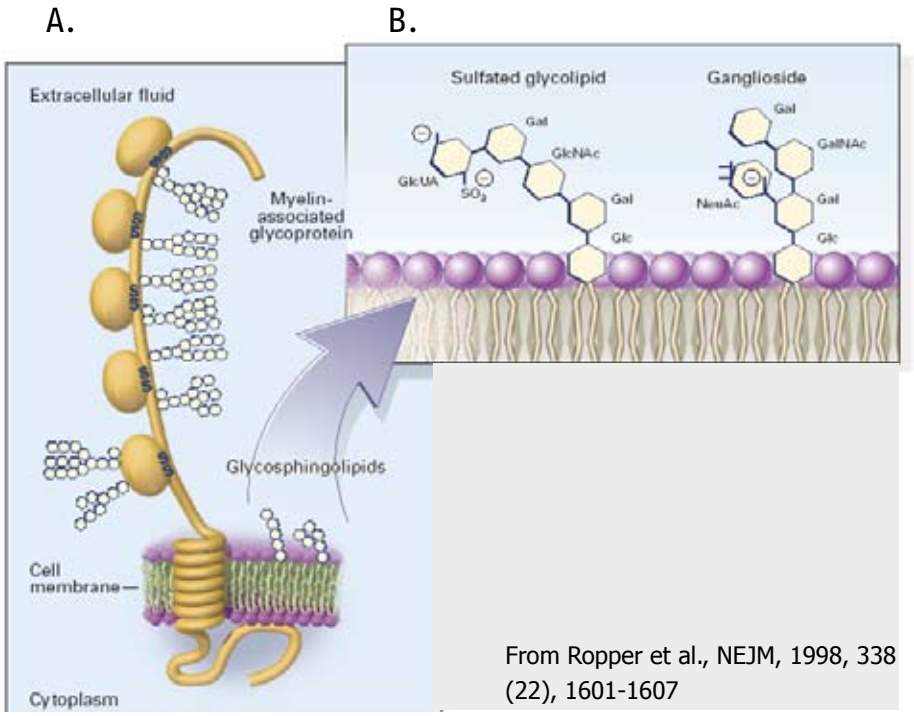
G: stands for ganglioside

M, D, T, Q: refer to the number of sialic acids, whereas M › mono-, D › di-, T › tri- and Q › quatro-sialosyl groups, respectively.

1, 2, 3: Gangliosides lacking the terminal galactose, pre-terminal galactosyl-N-acetylgalactosamine or internal galactose are assigned the number 2, 3, or 4, respectively

a, b: indicate the position of sialic acids, wheras
a refers to one sialic acid, which is attached on the internal galactose and

b is normally used to designate gangliosides with a disialosyl group attached to the internal galactose.



From Ropper et al., NEJM, 1998, 338 (22), 1601-1607

Figure 1. Structure and location of three main glycoconjugate antigens on peripheral Nerve.
A. Myelin-associated glycoprotein with its five immunoglobulin-like domains which are exposed extracellularly and accessible to antibodies, a transmembrane domain and cytoplasmic tail.
B. Smaller sulphated glycolipid and ganglioside GM1 with their oligosaccharide closer to the myelin lipid bilayer.

Diagnostic relevance of ganglioside ELISAs

- useful in additional to electrodiagnostic procedures in order to identify autoimmune neuropathies: a variety of neurologic symptoms are defined by their anti-glycolipid autoantibody profile.
- differential diagnosis: autoimmune mediated polyneuropathies may be successfully treated (*e g* neuropathies with monoclonal gammopathy, multifocal motor neuropathy with conduction block or Guillain-Barré Syndrome).
- therapy control of neuropathies associated with monoclonal gammopathies.
- provide insight into neuroimmunological diseases in research.

Associations with Specific Antibodies

1. In peripheral neuropathies with monoclonal IgM gammopathies **autoantibodies against MAG or SGPG** can be detected in more than 70% of patients.

The glycolipids MAG, SGPG and SGLPG share the same antigenic site centred on the terminal 3-sulfate-glucuronic acide residue.

2. Autoantibodies against GM1 and GD1b occur in 50% of treatable Multifocal Motor Neuropathies (MMN). In Amyotrophic Lateral Sclerosis (ALS) autoantibodies against GM1 and/or GD1b are either not detectable or at low titers.

3. Autoantibodies against gangliosides for the diagnosis of Guillain-Barré Syndrome and its variants: Autoantibodies against gangliosides, predominantely of IgG isotype, generally occur in acute diseases:

Acute Motor Axonal Neuropathy **(AMAN)** and Acute Motor Sensory Axonal Neuropathy **(AMSAN)** with anti-GM1 and -GD1a IgG antibodies.

Miller-Fisher Syndrome **(MFS)** with anti-GQ1b IgG antibodies, a very sensitive marker for MFS and its variants:

- GBS with ophthalmoplegia (O-GBS)
- Bickerstaff Brainstem Encephalitis (BBE)
- Acute Ophthalmoparesis (AO)

Frequency of anti-Ganglioside Antibodies

In a study including n=124 post-infectious GBS patients, the clinically most important anti-ganglioside autoantibodies were detected in the following frequency: GM1 (38%), GD1a (12%), GM2 (23%), GQ1b (9%) and GD1b (9%), (PhD-thesis, D. Taravel, 2008).

Peripheral Neuropathies associated with Specific Autoantibodies

Disease \ Antibodies against	MAG SGPG	GM1	GA1	GM2	GD1a	GD1b	GQ1b	
Guillain-Barré Syndrome (GBS)		+++ IgG IgG>IgM 20-30%	(+)	+ IgM 6%	+ IgG 5%	+ IgG 2%		Acute IgG
AMAN and AMSAN		+++ IgG	+		+++ IgG	+ IgG		Acute IgG
Miller-Fisher Syndrome and related diseases							+++ IgG > 90%	Acute IgG
GBS with Ataxia						++ IgG		Acute IgG
Post CMV infection-associated GBS				+ IgM				Acute IgG
CANOMAD - Chronic Ataxic Neuropathy, Ophthalmoplegia , IgM Paraprotein, Agglutinin, Disialosyl-antibodies						+++ mIgM	+++ mIgM	Chronic IgM
MMN - Multifocal Motor Neuropathy		++ IgM 20-80%				+ IgM		Chronic IgM
Motor Neuropathy with monoclonal IgM-Gammopathy		+++ IgM 10%				+++ IgM		Chronic IgM
Neuropathy with monoclonal IgM-Gammopathy with anti-MAG/SGPG (Anti-MAG-Neuropathy)	+++ mIgM 70%							Chronic IgM
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	++ mIgM	+						Chronic IgM

Explanation and reading example:
Symbols: designate level of antiglycolipid titer, whereas (+) weakly positive, + moderately positive, ++ positive, +++ strongly positive; Percentage [%].
Example 1: antibodies against GM1 in GBS occur frequently in high titers, IgG isotypes dominate IgM antibody isotypes. GM1 IgG Autoantibodies are detected in 20 - 30% of patients.

Figure 3: Normal peripheral nerve of adults. Note three populations of axons: large ones with thick myelin sheath, intermediate ones with thin sheaths and unmyelinated axons.

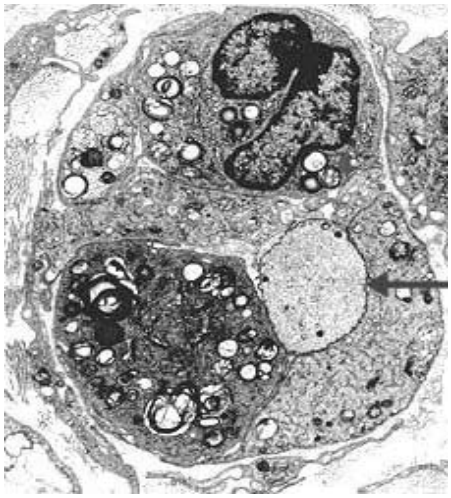


Figure 4: Peripheral nerve: Active demyelination (arrow), surrounded by phagocytic cells.

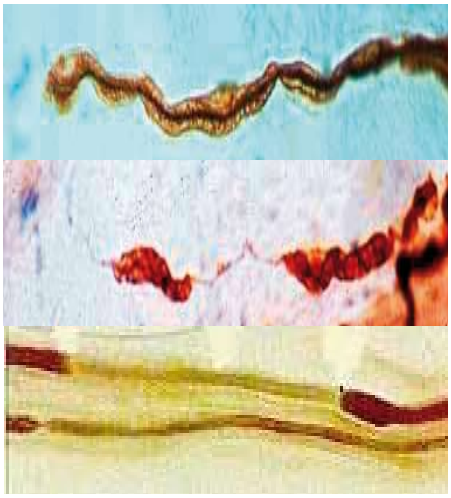


Figure 5: Myelin pathology: Multifocal Motor Neuropathy. (a) Normally myelinated motor axon in muscles; (b) segmental demyelination of a motor axon; (c) Myelin absent or thin in some of the internodes.

Source: pictures were taken from: http://www.neuro.wustl.edu

anti-Ganglioside and anti-MAG autoantibody Tests from BÜHLMANN

The BÜHLMANN GanglioCombi® product group offers a panel of quantitative ELISAs for clinical routine. **Different profiles** detecting the most frequently occurring and clinically relevant autoantibodies. **Anti-GM1 ELISA** completes the screening GanglioCombi assays:

BÜHLMANN GanglioCombi®: Profile of 6 gangliosides (GM1, asialo-GM1 (GA1), GM2, GD1a, GD1b and GQ1b).

BÜHLMANN GanglioCombi®-*Light*: Profile of 3 gangliosides (GM1, GD1b and GQ1b).

Each kit is available with Mix IgG/IgM or IgG and IgM enzyme labels. The assays have been validated using blood donors (n=100) and clinically defined patient samples (n=279). Based on three clinical studies, clinically relevant titer categories have been established: **Negative, grey zone, positive and strongly positive**. The frequency distribution of anti-ganglioside autoantibodies in blood donors and specified peripheral neuropathies perfectly matches with published data.

The combination of **anti-MAG ELISA** and **anti-SGPG ELISA** provides the best likelihood to detect anti-MAG Neuropathies.

Summary

Within the last decade abundant clinical data have emerged, which clearly show disease specific correlations between anti-ganglioside and-MAG autoantibodies in different forms of autoimmune neuropathy.

Both, anti-ganglioside and anti-MAG/-SGPG tests are useful tools for clinical classification and diagnosis.

Autoantibodies directed against GA1, GM1, GD1a, GD1b, GM2 and GQ1b occur in chronic or acute motor and sensory autoimmune neuropathies. Diagnosis of neuromuscular disease is increasingly relying on immunological laboratory tests. Conditions as the Guillain-Barré Syndrome and its variants may now be characterized in terms of specific autoantibody profiles.

The diagnosis of neuropathies is being supported by immunological tests among which the ELISA is regarded as state of the art technology.

Literature

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EK-GCL-GM	2 x 12 patient profiles
EK-MAG	96 wells
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EK-GM1-GM	96 wells