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Review Article

Antiganglioside antibodies in neurological diseases

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ABSTRACT

Gangliosides are sialylated glycosphingolipids, highly abundant in our nervous system. Antibodies targeting gangliosides are usually developed as a consequence of molecular mimicry following infections. Antiganglioside antibodies are implicated in many neurological disorders such as acute and chronic polyradiculoneuropathies which includes different variants of Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy and multifocal motor neuropathy. Presence of such antibodies in paraneoplastic peripheral neuropathy, neurodegenerative disorders, multiple sclerosis, myasthenia gravis and amyotrophic lateral sclerosis have also been reported. Recent evidence supports a role of antiganglioside antibodies in the pathogenesis of acute vestibular syndrome. Binding of antibodies to gangliosides on axonal membranes, nodes of Ranvier, myelin sheath components, Schwann cells, neuromuscular junctions or other neural cell surfaces may elicit inflammatory damage through complement-dependent and independent mechanisms, resulting in nerve conduction blocks and subsequent axonal degeneration. Gangliosides are essential for proper cell signaling, transduction and influences neuroplasticity, all of which are affected by autoimmune mediated damage. Better insight into the pathophysiological role of antiganglioside antibodies in different neurological diseases may improve their utility as diagnostic and prognostic biomarkers.

1. Introduction

Gangliosides are glycosphingolipids containing at least one sialic acid linked to the carbohydrate moiety. They are found in all cells and body fluids, with highest abundance in the nervous system [1]. Located on neural cell surfaces, gangliosides reside within microenvironments known as lipid rafts and are required for proper brain development and cell functioning through modulation of cell signaling and transduction [2]. Neuroplasticity is essential for the process of neural development, repair and normal brain function. It refers to the ability of our nervous system to undergo functional and structural modifications following neurological injury, or as a response to other internal or environmental stimuli [3]. Gangliosides are believed to play a role in neuroplasticity through influences on neurogenesis, synaptic plasticity, neurotransmission and axonal growth. Furthermore, they also mediate neuronal differentiation, maintenance and repair [4].

Antibodies targeting gangliosides are implicated in many autoimmune mediated peripheral neuropathies such as acute and chronic polyradiculoneuropathies. Acute immune-mediated polyradiculoneuropathies encompass Guillain-Barre syndrome (GBS) and its variants [5]. Chronically occurring ones include multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [6]. Other diseases in which antiganglioside antibodies have been detected are acute unilateral peripheral vestibulopathy [7] and paraneoplastic peripheral neuropathies [8]. Antiganglioside antibodies have also been detected in neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) [9].

Extensive research has focused on molecular mimicry as a process of antiganglioside antibody generation following infection [10]. Accumulating evidence supports the presence of antiganglioside antibodies in patients with celiac disease. Antibody levels were found to correlate with the degree of neurological impairment, therefore it is important to address possible underlying celiac disease in patients presenting with neurological dysfunction [11].

Gangliosides act as receptors for axon-glia interactions required for stabilization of cytoskeletal structures and axonal regeneration. Therefore, binding of antiganglioside antibodies may lead to inhibition of nerve reparative processes [12]. Since the axonal membrane is highly saturated with gangliosides, antibody binding to locations of exposed membrane such as the neuromuscular junctions and nodes of Ranvier may lead to disorganized ion channel regulation and disturbances in axonal conduction [12,13]. Besides conduction block, complement fixation at the node of Ranvier following antibody binding may also

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result in axonal degeneration [14]. Several studies support the role of complement activation in mediating axonal damage in inflammatory neuropathies and differences in mechanisms have been observed, depending on the type of antiganglioside antibodies involved. Nodal damage may be induced by anti-GM1 IgG antibodies through IgG and complement deposition, resulting in disruption of voltage-gated Na + channels and neuron-glia interactions in peripheral motor nerve fibers [15]. Anti-GD1a IgG antibodies may also activate complement, leading to nodal protein disruption and dysregulation of ionic homeostasis at the nodes of Ranvier [16].

Peripheral polyneuropathies are typically categorized as axonal or demyelinating, which may result in diagnostic and prognostic inaccuracies. Since nerve injury in some antiganglioside antibody associated acute and chronic peripheral neuropathies involve disruption of the nodal area, they are given a new classification entitled 'nodoparanodopathies', which better represents the specific location of autoimmune damage and avoids misleading electrophysiological diagnosis [17,18].

A variety of different antiganglioside antibodies are identified in different diseases, with GM1, GD1a, GD1b and GT1b being major nervous system gangliosides targeted [19]. A single antibody is able to recognize and bind to a large number of gangliosides due to structural similarities [13]. Nevertheless, more research is required to fully understand the complex pathophysiological mechanisms underlying the development of autoantibody mediated neuropathies and neurodegeneration. This review will explore different types of antiganglioside antibodies associated with neurological disorders and their contributions to disease pathogenesis.

2. Guillain-Barré syndrome and related disorders

Guillain-Barré syndrome is an immune-mediated acute inflammatory polyradiculoneuropathy which usually occurs 2–4 weeks following *Campylobacter jejuni* enteritis, upper respiratory tract infections or other infectious processes. Patients present with pain and distal limb paresthesia which spreads proximally, followed by progressive symmetrical ascending motor weakness, starting from the lower limbs [20]. GBS is categorized into many variants according to the type of injured nerve fibers (sensory, motor or autonomic involvement), mechanism of injury (axonal or demyelinating) and the presence or absence of altered consciousness [21,22] (Fig. 1). Various antiganglioside antibodies present in GBS are believed to be produced post-infection as a consequence of molecular mimicry due to shared epitopes between gangliosides and the infectious agent. Cross-reactivity with peripheral nerves through myelin or axon binding leads to disease development. Major antibodies identified in GBS are directed towards GM1, GD1a, GD1b, GT1a, GQ1b and GT1b, with anti-GT1b being the most common [23]. High levels of antiganglioside antibodies were identified in the acute motor axonal neuropathy (AMAN) subtype, the axonal variant of GBS exhibiting node of Ranvier pathology [24]. IgG anti-GD1a and anti-GM1 antibodies are strongly associated with AMAN but not acute inflammatory demyelinating polyneuropathy (AIDP) [25,26]. This illustrates that antibody positivity more commonly accompanies the electrophysiological diagnosis of motor axonal dysfunctions than AIDP, the demyelinating variant which is the consequence of Schwann cell and myelin sheath injuries [27]. Anti-GM2 IgM and IgG antibodies have been identified in rare cases of GBS, with predominance of IgG anti-GM2 in patients presenting with cranial nerve pathologies. However, they are not GBS-specific as other neuropathies such as CIDP are also associated with anti-GM2. Such antibodies may induce neuronal damage through complement-mediated cytotoxicity [28,29].

Besides individual gangliosides, complexes of gangliosides may also be targeted by autoantibodies in GBS and its variants [30,31]. Patients may develop antibodies which are reactive towards complex, but not isolated gangliosides. Kaida et al. [32] described the presence of antibodies towards ganglioside complexes such as GD1a/GD1b, GD1a/GM1, GD1b/GT1b and GM1/GT1b in GBS patients. Higher disease severity was observed in patients with positive anti-GD1a/GD1b or anti-GD1b/GT1b antibodies [33]. Antibodies targeting GD1a/GD1b have also been associated with the presence of cranial nerve deficits [32].

Antiganglioside antibodies play a role in blood-nerve barrier damage, allowing infiltration of inflammatory cells from the periphery resulting in further nerve injury [34]. Moreover, presence of increased levels of cerebrospinal fluid (CSF) IgG in GBS patients with high serum titers of antiganglioside antibodies suggest probable entry from the periphery due to damaged blood-CSF barrier and nerve roots, which also contributes to conduction slowing or blockades [35]. Another probable mechanism mediating axonal and nodal damage is formation of antigen-antibody immunocomplexes which activates Fcγ receptor on macrophages and microglia, eliciting inflammatory damage, as observed in animal models [36]. Different antiganglioside antibodies are associated with particular subtypes of GBS (Table 1) and correlates with presenting symptoms [37–40]. Disease severity was proven not to be antibody-dependent [24].

Achieving greater understanding of immune-mediated nerve injury is essential and would be beneficial in the development of future targeted therapies.

C.jejuni lipopolysaccharide epitopes mimic GM1, GM1b, and GD1a,

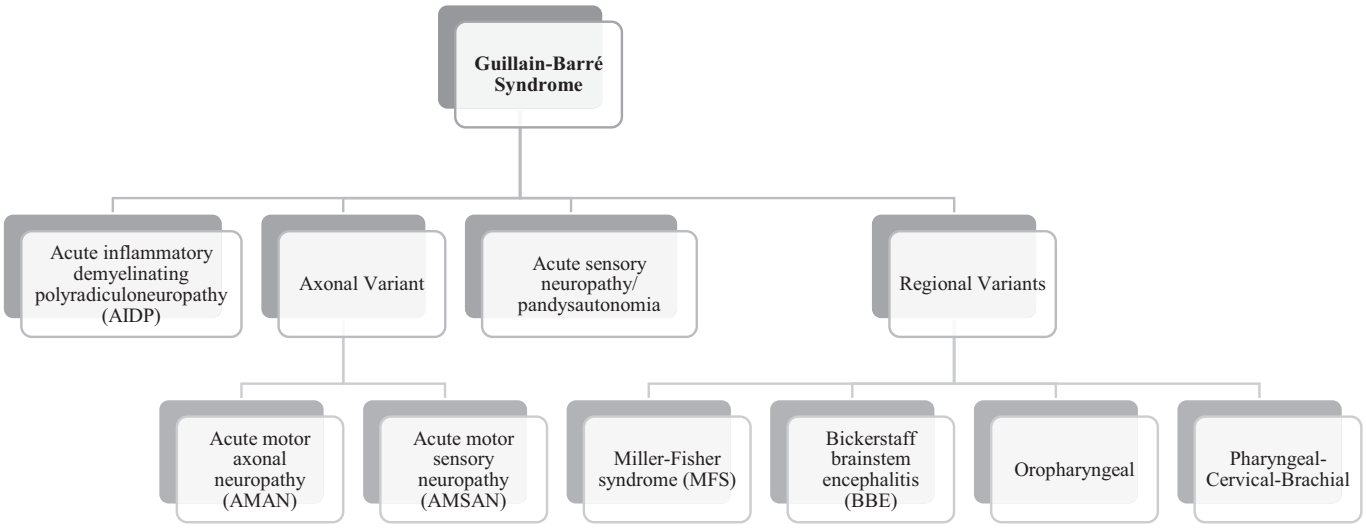

Fig. 1. Variants of Guillain-Barré syndrome.

Table 1
Antiganglioside antibodies in different neurological disorders.

Neurological disorder	Antiganglioside antibodies
AIDP	No significant associations (GT1b IgG in 50% of cases)
AMAN	GM1, GM1b, GD1a, GD1b IgG
AMSAN	GM1, GM1b, GD1a IgG
MFS	GQ1b IgG
BBE	GQ1b IgG
ASAN	GD1b IgG
MMN	GM1 IgM
CIDP	LM1, GM1, GD1b, GM2 IgG
Paraneoplastic peripheral neuropathy	DLBCL: GD1b, GD3 IgM Lung carcinoma: GM1 IgM and IgG, GD1a IgG Melanoma: GM2, GD3, GQ1b IgM
Myasthenia Gravis and Lambert-Eaton syndrome	GT1b, GD1a IgG
Multiple sclerosis	GM3, GQ1b, GD1b, GM1 IgM
AUPV and acute vestibular syndrome	GQ1b, GD1b IgG
Cryptogenic partial epilepsy	GM1 IgM and IgG
Parkinson's disease	GM1, GD1b IgM
Alzheimer's dementia	GM1 IgM

AIDP, autoimmune inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor sensory axonal neuropathy; MFS, Miller-Fisher syndrome; BBE, Bickerstaff brainstem encephalitis; ASAN, acute sensory ataxic neuropathy; MMN, multifocal motor neuropathy; CIDP, chronic inflammatory demyelinating neuropathy; DLBCL, diffuse large B-cell lymphoma; AUPV, acute unilateral peripheral vestibulopathy.

resulting in production of antibodies targeting those gangliosides. The presence of antiganglioside antibodies in patients who were not previously infected implies that other factors may be involved in antibody production [25]. In the absence of GM1b, presence of GD1a/GM1 complexes were able to induce production of anti-GM1b antibodies in GBS patients [41]. Antibodies targeting ganglioside complexes, in comparison to single ganglioside antibodies, were discovered to have higher frequency of complement activation and exhibits pro-inflammatory properties [42]. Anti-GM1 antibodies are naturally occurring in serum of healthy individuals, denoting the presence of normal B-lymphocyte clones [43]. After infection, these normal B cells are able to undergo spontaneous mutation of their V genes, enhancing their GM1 binding affinity. Thus, some mutated B cells are now able to be stimulated by both self and foreign GM1, generating different populations of anti-GM1 antibodies. This particular process is known as 'binding site drift', which occurs at random and is involved in both IgM and IgG production [44]. Absence of this process in some individuals may explain why *C.jejuni* strains containing GM1 does not always induce GBS [45,46].

Miller-Fisher syndrome is a clinical variant of GBS, presenting with a triad of symptoms featuring ataxia, areflexia and ophthalmoplegia. Bickerstaff brainstem encephalitis presents with overlapping features of ataxia and ophthalmoplegia, plus symptoms suggesting a central pathology including loss of consciousness and hyperreflexia, which could be due to blood-brain barrier disruption in BBE patients [47,48]. Anti-GQ1b antibodies are associated with both disorders and plays a role in complement mediated nerve damage, sodium channel disruption [47,49] and non-demyelinating conduction failure [50]. Evidence supports binding of anti-GQ1b antibodies to fibers of the spinocerebellar tract and cerebellar granule cells, also to GQ1b/GM1 and GT1a/GM1 complexes, causing cerebellar ataxia [51,52]. Due to the abundance of GQ1b expression in oculomotor, trochlear and abducens nerves, [53] binding of IgG antibodies to GQ1b and GT1a containing complexes may precipitate ophthalmoplegia [54]. Since GT1a gangliosides are present on glossopharyngeal and vagus nerves, antibodies towards GT1a may be responsible for bulbar palsy [55]. Cross-reaction also occurs between GT1a and GQ1b antibodies [53]. The mechanisms behind CNS contribution in MFS and BBE are still unclear and necessitates further research. Endocytosis of antibodies bound to nerve terminals and retrograde transport to motor neurons with subsequent release into the spinal cord and brainstem serves as a potential mechanism, although supporting evidence is still limited [56,57]. Future studies should aim to explain why CNS involvement occurs only in some patients with GBS.

Anti-GQ1b antibodies are present in GBS, MFS and BBE. Due to the involvement of a common antibody and overlapping clinical presentations, these diseases are also referred to as 'anti-GQ1b antibody syndrome' [58]. Presence of ataxia, ophthalmoplegia and changes in level of consciousness, together with symmetrical weakness should alert physicians about possible anti-GQ1b antibody syndrome [59].

With regards to the diagnostic utility of antiganglioside antibodies, detection of IgG strongly supports diagnosis of GBS. However, the usefulness of IgM antibodies is controversial since they can also be detected in patients without GBS, possibly as a normal response to infection, therefore presence of IgM does not always indicate GBS [60]. Detection of antiganglioside antibodies, in combination with nerve conduction studies, may be helpful in forming an electrophysiological diagnosis to minimize any errors in GBS classification [37]. However, a study performed to assess the diagnostic role of antiganglioside antibodies failed to show positive antibodies in GBS patients, which challenges their usefulness as an alternative diagnostic tool [61].

Laboratory tests available for antiganglioside antibody screening vary in their reactivity towards different gangliosides. Besides enzyme-linked immunosorbent assay (ELISA), which is most commonly used, other methods include microarrays, immunodot-blot, line immunoassay and agglutination immunoassay. Improvements in laboratory test specificity and sensitivity, as well as standardization of current diagnostic methods are matters to be addressed by future research. Broadening the spectrum of detectable antiganglioside antibodies would also be desirable [13].

3. Chronic dysimmune neuropathies

Multifocal motor neuropathy affects purely motor function, without sensory involvement. Patients present with progressive asymmetric distal limb weakness with upper limb predominance, suggested to be a consequence of conduction block [62]. Although the exact pathomechanism of MMN development is still unknown, successful use of intravenous immunoglobulin (IVIg) in the treatment of MMN strongly supports an autoimmune etiology [63]. Anti-GM1 IgM antibodies are present in MMN patients and plays a role in complement-mediated nodal and paranodal damage through classical pathway complement activation, leading to axonal degeneration. The influence of anti-GM1 IgM antibodies on $Na+$ and $K+$ current alterations are dependent on the presence of complement. Binding of antibody-complement complexes to nodal membranes may lead to $Na+$ channel blockade and subsequent membrane damage. In the absence of complement, anti-GM1 has been discovered to increase $K+$ currents which may lead to paranodal demyelination [64]. Since antibody level correlates with severity of weakness, anti-GM1 antibodies may prove valuable in prediction of clinical course and outcome [65]. Sensory nerve fibers contain very low concentrations of GM1 ganglioside in comparison with motor nerves, which might explain why sensory deficits are not observed in MMN [66]. Due to low sensitivity of serum anti-GM1 IgM detection, growing evidence supports the use of anti-GM1-galactocerebroside complex antibodies as a diagnostic tool [67]. Although there is a strong association of anti-GM1 IgM with MMN, studies claim that these antibodies are absent in > 50% of patients [62]. Since IgM antibodies are found in patients with MMN, presence of IgG anti-GM1 may allow us to distinguish MMN from multifocal acquired sensory and motor neuropathy, a condition with similar clinical presentation [68].

Chronic inflammatory demyelinating polyneuropathy is a demyelinating disease, presenting as symmetrical proximal and distal

sensorimotor deficits [69]. Myelin in peripheral nerves express LM1. GM1 and GD1b are present in higher amounts in motor and sensory nerves, respectively. Antibodies targeting LM1, GM1, GD1b, as well as ganglioside complexes containing LM1 were identified in CIDP [70,71].

4. Paraneoplastic peripheral neuropathies

Novel gangliosides are expressed by tumor cells after the process of cancerogenesis. These gangliosides may contain shared epitopes with peripheral nerves, thus, antibodies can cross-react and trigger immune mechanisms, leading to development of paraneoplastic neuropathy [8]. Paraneoplastic neuropathy is associated with various types of cancers such as melanoma, lung cancer and lymphomas. Since melanocytes and Schwann cells are both neural crest derivatives, they may share expression of surface gangliosides such as GM2, GM3, and GD3. Although rare, the process of molecular mimicry and antibody binding to surface molecules may lead to neuropathies in melanoma patients [72,73]. Shihashi et al. [74] identified IgM anti-disialosyl antibodies GD1b and GD3 in a patient with diffuse large B-cell lymphoma with polyneuropathy which resolved after IVIg administration. Associations with Hodgkin and non-Hodgkin lymphomas are rare [75]. A lung cancer patient with subacute sensorimotor neuropathy was tested positive for IgM anti-GM1 [76]. Jazebi et al. [77] also found increased antibodies targeting GM1 and GD1a in a squamous cell lung carcinoma patient with symptoms of neuromuscular junction disorder who also stabilized after treatment with IVIg. However, its pathogenic role is yet to be more clearly established since the paraneoplastic hypothesis of antiganglioside antibody mediated neuropathy still remains controversial. The course of paraneoplastic peripheral neuropathy is progressive and debilitating. Therefore, emphasis should be placed on the importance of early anti-ganglioside antibody detection whenever a paraneoplastic cause is suspected, in order for appropriate treatment to be promptly initiated.

5. Other neurological disorders

Anti-GQ1b and anti-GD1b antibodies have also been found in acute unilateral peripheral vestibulopathy, an imbalance of vestibular tone leading to nystagmus and vertigo [7]. Recently, a study reported increased anti-GQ1b antibodies in acute vestibular syndrome [78]. Although antiganglioside antibodies may be detected in amyotrophic lateral sclerosis (ALS), levels have been found to be close to that of healthy controls. No associations were found between antiganglioside antibodies and any particular type of ALS, disease progression or severity, denoting the limited usefulness as a diagnostic indicator in ALS [79]. Increased anti-GT1b and anti-GD1a levels in myasthenia gravis and Eaton-Lambert syndrome were reported [80]. Studies have proposed that T-cells specifically targeting glycolipid components of myelin contributes to demyelination and axonal degeneration in multiple sclerosis (MS). Antibodies targeting GM3 and GQ1b were often found in primary progressive MS [81]. Anti-GM1 is more frequently found in secondary progressive than relapsing-remitting courses [82]. Involvement of anti-GM1 as a possible autoimmune cause of epilepsy remains unclear and requires further investigation [83].

The role of antiganglioside antibodies have been described in neurodegenerative diseases, particularly with presence of dementia [84]. Gangliosides are involved in β-amyloid and α-synuclein aggregation in Alzheimer's dementia and Parkinson's disease, respectively [85]. Anti-GM1 and anti-GD1b IgM antibodies were detected in patients with Parkinson's disease [86]. Evidence supports increased levels of circulating anti-GM1 IgM antibodies in patients with tremor-dominant PD and PD associated with dementia [87,88]. Studies have reported the connection between increased anti-GM1 IgM with symptoms such as higher degree of cognitive impairment, bradykinesia dominance, dyskinesia and depressive symptoms [86]. However, there is still limited evidence supporting the role of antiganglioside antibodies in Parkinson's disease. More research is warranted regarding the pathological role of anti-GM1 in AD and other types of dementia.

6. Conclusion and future perspectives

A still unresolved question is whether antiganglioside antibodies in neurological disorders are biomarkers produced secondarily to infection and inflammation, or actually primary autoantibodies mediating neuronal damage. Current research has shed light on the association between antiganglioside antibodies and various peripheral neuropathies, especially in different variants of GBS. Although gangliosides are widely expressed in cells of all types, they are most abundant in the nervous system, expressed on axonal membranes, nodes of Ranvier and neuromuscular junctions. Besides neural development, they are known to play a significant role in maintaining axonal integrity and mediating neuroplasticity. Antibodies targeting gangliosides, including LM1,GM1, GM1b, GD1a, GD1b, GQ1b, GT1b, GT1a, GM2, GD3, and their complexes have been identified in various neurological diseases, inducing damage through complement-dependent and independent mechanisms, resulting in axonal conduction derangements. (Table 1) summarizes the types of antiganglioside antibodies which may serve as immunological markers of different neurological disorders. More research is essential to understand the pathological role of antiganglioside antibodies, mechanisms triggering antibody production and their involvement in disease progression. This would increase their value as biomarkers, enabling their utilization as prognostic indicators and for treatment guidance. It is suggested to screen for antiganglioside antibodies in patients presenting with symptoms of neurological deficits, together with a history that strongly suggests autoimmune etiology, such as prior infection. Detection of novel antiganglioside antibodies will be favorable as potential targets of future immunomodulatory therapies. Increased standardization, specificity and sensitivity of laboratory diagnostic methods, along with higher availability of diagnostic tools will enable prompt treatment initiation if antibodies are detected early in the course of disease, thus, improving patient prognosis and survival.

Declarations of Competing Interest

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