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IgG Fc N-glycosylation: Alterations in neurologic diseases and potential therapeutic target?

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ABSTRACT

Immunoglobulin G (IgG) is the most abundant antibody subclass of the human circulatory system and has important functions in the adaptive immune response. On the one hand, recognition and neutralization of antigens is mediated by the fab fragment, and on the other hand, processes such as phagocytosis, complement activation and inflammatory reactions are triggered by the Fc fragment. Here, the composition of conserved N-glycans attached to asparagine 297 of the IgG CH2 domain is a major critical factor that particularly modulates the effector functions of IgG. Additional attachments of fucoses, galactoses, *N*-acetylglucosamines, and sialic acids have been identified as factors that influence the affinity to a wide range of complement proteins and receptors and, thus, secondarily induce the secretion of pro- and anti-inflammatory cytokines. Consequently, alterations in the IgG Fc N-glycosylation pattern can provoke disruptions in the immunological state and are accompanied by various diseases, although the involvement of changed IgG glycosylation in disease outbreaks remains unknown. In addition to many autoimmune diseases, which have already been extensively reviewed, there are a number of further disorders related to altered IgG glycosylation patterns. In the present review, we focus on neurologic diseases, as in the last few years, an increasing number of studies have been published in this field. Due to the absence of reliable early biomarkers as well as therapeutic options in many cases, such analyses are of great interest and reveal possible future approaches.

1. Introduction

As part of the adaptive immune system, immunoglobulin G (IgG) is the most abundant class in the human antibody pool and is involved in defence mechanisms against pathogens. Although IgGs are subdivided into four different classes (IgG1 – IgG4), all of them share a common structure with more than 95% homology in their amino acid sequence [1–3]. Four polypeptide chains, including two identical light chains (L chain, 25 kDa) as well as two identical heavy chains (H or γ chain, 50 kDa), build the scaffold of the protein, which are covalently connected by disulfide bonds. The heavy chains consist of one variable (VH) and three constant domains (CH1 – CH3), whereas the light chains encompass only one of each domain type (CL and VL). A flexible, unfolded hinge region between CH1 and CH2 causes the typical Y-shaped structure and separates the antibody into two functional units: the Fab (**f**ragment **a**ntigen **b**inding) fragment including the light chain as well as VH and CH1 and the Fc (**f**ragment **c**rystallizable) fragment including CH2 and CH3 [3–6]. In human beings, B lymphocytes produce more than 10^{12} different immunoglobulin (Ig) molecules by mechanisms including V(D)J rearrangement, somatic hypermutation, and class switch recombination [7–12]. IgG Fab fragments recognize and bind complementary structures of the antibody's antigen, e.g., on the surface of pathogens, and show enormous diversity as a result of small variations in the amino acid sequence of the variable domains. In contrast, sequences of IgG Fc fragments are more conserved and activate immunological cells or molecules [5,13]. After antigen binding, diverse self-made (without the requirement of additional factors) as well as inducible mechanisms can be triggered. Neutralization of specific antigens is a completely Fab-mediated and self-made mechanism that prevents steric interactions in diverse ways and, thus, avoids detrimental processes induced by the antigenic substrate [13–18]. In addition, IgGs have a comprehensive spectrum of Fc-mediated functions with predominantly immunological effects [19]. The most prominent encompass the activation of Fc receptors and the classical pathway of the complement system resulting in proinflammatory reactions. Within the CH2 domain, IgG possesses recognition regions for the initial complement protein C1q as well as the Fcγ receptor (FcγR) family including FcγRI, IIa, IIb, IIc, IIIa, and IIIb. Antigen opsonization or

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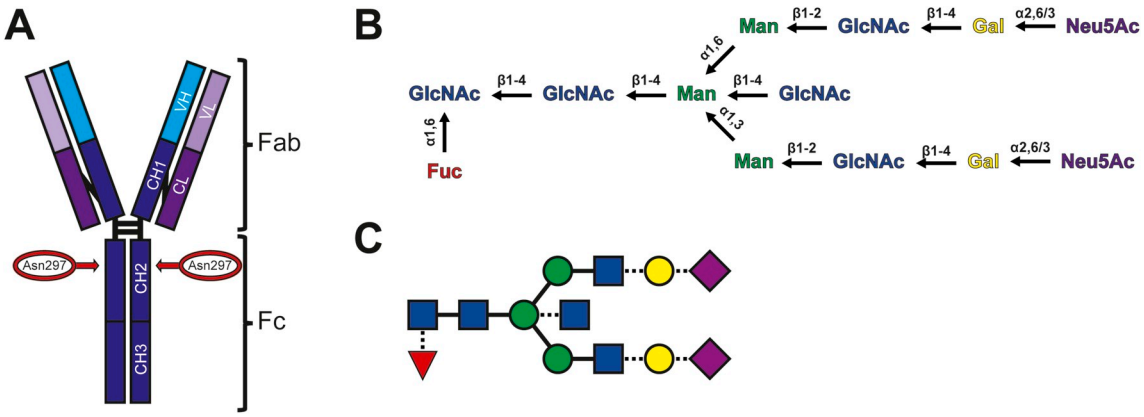

Fig. 1. IgG Fc N-Glycans. (a) Human IgGs comprise 2 identical heavy (blue) and light chains (purple), each with one variable domain responsible for antigen binding. IgGs can be separated into Fab and Fc fragments, and within the latter, one conserved N-glycosylation site is present at asparagine 297 (Asn297) in both CH2 domains. **(b)** N-Glycans attached to Asn297 may consist of up to 13 sugar molecules, each connected via α- or β-glycosidic bonds. **(c)** Schematic representation of Fc N-glycans: the core structure contains seven sugar moieties (solid lines) and can be modified with further sugar moieties (dotted lines); however, the CH2 domains may exhibit asymmetrical N-glycans. Blue square = *N*-acetylglucosamines (GlcNAc), red triangle = fucose (Fuc), green circle = mannose (Man), yellow circle = galactose (Gal), purple square = *N*-acetylneuraminic acid (Neu5Ac).

building immune complexes increases the affinity to these effector structures, with the exception of the high-affinity receptor FcγRI, which can already be activated by monomeric IgGs [20–24]. While the classical pathway of complement activation mediates cell lysis (complement-dependent cytotoxicity, CDC) and C3b receptor mediated phagocytosis by opsonizing the antigenic structure with the complement protein C3b, FcγR activation modulates antibody-dependent cell-mediated cytotoxicity by degranulation (ADCC), antibody-dependent cellular phagocytosis (ADCP) and the secretion of pro- and anti-inflammatory cytokines. Here, FcγRIIB is the only FcγR that inhibits these processes and has anti-inflammatory effects [6,13]. A major qualitative factor that influences the above-described Fab- and Fc-mediated functions represents the N-glycosylation of IgG [25]. While Fab fragments are variably N-glycosylated in only 15–25% of all cases – and if so, only at the variable domains – each heavy chain of the Fc fragment shows one conserved glycosylation site at asparagine 297 (Asn-297) in the CH2 domain (Fig. 1). Depending on their presence and composition, antigen binding and effector functions such as phagocytosis, complement activation and inflammatory processes are induced with varying effectiveness [26–29]. During the last few decades, researchers have increasingly focused on IgG glycosylation as a critical qualitative attribute, especially in regard to future diagnostic and therapeutic options. In this review, we will take a closer look at altered IgG Fc N-glycosylation patterns in the course of neurological diseases and discuss the potential utilization of IgG glycosylation in prospective diagnostic as well as therapeutic approaches.

1.1. IgG Fc N-glycosylation

IgGs as well as all other classes of Igs belong to the glycoprotein family, as sugar molecules (oligosaccharides or glycans) are attached to the immunoglobulin as posttranslational modifications. Glycosylation per se affects the biological function and biophysical properties of polypeptides, and two types of protein glycosylations are known: O- and N-linked glycosylation [30,31]. Glycans linked to oxygen atoms (O-glycosylation) of the amino acids serine (Ser) or threonine (Thr) are generally present in the Ig superfamily but are rarely represented within the IgG class [25]. The second form of glycosylation, N-glycosylation, is linked to the nitrogen atom of the amino acid asparagine (Asn), specified by the consensus sequence Asn–x–Ser/Thr (x = amino acid except proline) [32]. Contrary to O-glycosylation, which is only present at the hinge region of 10% of all IgG3, N-linked glycans can be found at the Fab and Fc fragments of all IgG subclasses [25,27,33,34].

Attachment and maturation of IgG N-glycans occur in the endoplasmic reticulum (ER) and Golgi apparatus with the aid of glycosyltransferases and glycosidases [35]. First, a precursor oligosaccharide is built up and modified via trimming and adding sugar molecules leading *inter alia* to a seven-sugar-containing core structure consisting of four *N*-acetylglucosamine (Glc-NAc) residues and three mannose (Man) residues. Different glycosyltransferases of the Golgi system are able to modify this formation by adding additional sugar molecules including fucose (Fuc), bisecting GlcNAc (b-GlcNAc), galactose (Gal) and the sialic acid *N*-acetylneuraminic acid (Neu5Ac) at specific positions (Fig. 1) [35–38]. In this manner, the generation of complex bi-, tri-, and tetra-antennary N-glycans is possible, but IgG Fc fragments only show complex biantennary N-glycans, each with more than 30 possible compositions [39,40]. These glycans are attached to a highly conserved N-glycosylation site at Asn297 that is present in both constant CH2 domains and can be asymmetrical (i.e., both CH2 domains exhibit different glycans with different compositions). Their absence causes a reduction in affinity to interaction partners – including the initial complement protein C1q and membrane receptors of the FcγR family – revealing Fc N-glycans as a determining factor for IgGs to induce the diverse effector functions [25,41–43]. Responsible for this finding are steric effects between the carbohydrate and amino acids that stabilize the Fc backbone and generate an open conformation (pocket) for binding interactions [44]. Furthermore, IgG binding to FcγR can be elevated by direct glycan-glycan interactions, as some receptors also belong to the glycoprotein family [45,46]. In addition to the presence of the total N-glycan, it has been shown that the effector function also depends on the modification of the glycan with additional sugar molecules. As described above, during N-glycan synthesis, one Fuc residue, one b-GlcNAc residue, one or two Gal residues, and one or two Neu5Ac residues can be linked to the carbohydrate core structure. Depending on its composition, different mechanisms including phagocytosis, complement activation, and inflammation are modulated and triggered in different strengths elicited by altered affinities to the effector structures [26,27,29,47,48] (Table 1, Fig. 2).

1.1.1. Fuc (FUT8 α1,6-fucosyltransferase)

The addition of an α1,6-linked Fuc to the innermost core GlcNAc reduces the IgG affinity to all FcγR classes, resulting in decreased ADCP and ADCC mediated by macrophages, monocytes, natural killer (NK) cells and granulocytes. With a 50- to 100-fold affinity reduction, FcγRIII is the most affected Fcγ receptor potentially due to a sterically disturbed interaction of the IgG (Asn297) and receptor glycan (Asn 162)

Table 1
Effects of Fc N-glycan composition on different IgG effector functions.

Core Structure +	Receptor Binding	Complement protein binding	Effect
Fucose (Fuc)	↓ FcγR (especially FcγRIII: 50x)	→ C1q	↓ ADCC and ADCP → CDC
N-acetylglucosamine (b-GlcNAc)	↑ FcγR		↑ ADCC and ADCP
Galactose (Gal)	FcγR binding controversial	↑ C1q ↓ MBL	Controversial, probably anti-inflammatory
N-acetylneuraminic acid (Neu5Ac)	↓ FcγR ↑ DC-SIGN	↓ C1q	↓ ADCC ↓ CDC

IgG Fc N-glycans consist of a seven-sugar-containing core (4x *N*-acetylglucosamine, 3x mannose), which can be modified with further sugar moieties. The attachment of an additional fucose, *N*-acetylglucosamine, one or two galactoses, and one or two *N*-acetylneuraminic acids impacts IgG binding to receptors (Fc gamma receptor (FcγR) and dendritic cell-specific ICAM-3-grabbing non-integrin receptor (DC-SIGN)) and complement proteins (C1q or mannose-binding lectin (MBL)) resulting in altered complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP).

[27,49–53]. On the other hand, complement-dependent mechanisms such as CDC as a result of C1q binding remain unaffected [49,51].

1.1.2. b-GlcNAc (MGAT3 β1,4-N-acetylglucosaminyltransferase-III)

A contrary effect is suggested for the attachment of b-GlcNAc to the central mannose residue; however, this effect has not yet been fully clarified. Zou et al. (2011) as well as Davies et al. (2001) reported significantly increased FcγRIII affinities and, thus, elevated ADCC activity of IgGs carrying bisecting Fc N-glycans [54,55]. However, due to steric suppression of the enzymatic activity of fucosyltransferases by the addition of b-GlcNAc, studies based on IgGs produced in genetically modified systems with altered glyco-enzyme expression should be carefully assessed [56,57]. Here, differences may be the result of secondary consequences and are difficult to attribute to one of the sugar moieties.

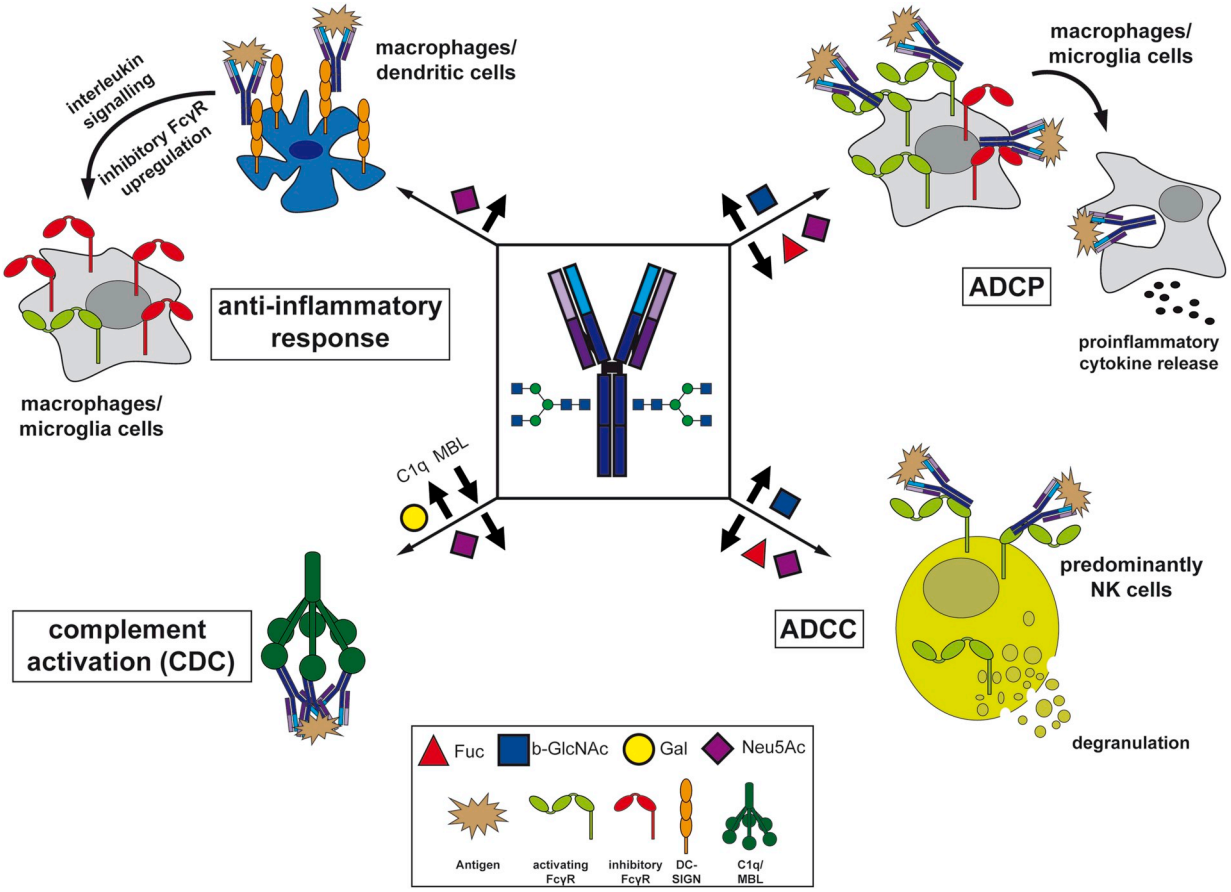

Fig. 2. IgG-mediated effector functions depending on Fc N-glycan composition. Processes such as antibody-dependent cellular phagocytosis (ADCP), cytokine release, antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and induction of anti-inflammatory responses are triggered by IgGs after antigen binding. Depending on the composition of the IgG Fc N-glycans, these processes become more or less activated. Accordingly, in many states, the presence of single sugar moieties has been linked to a distinct increased or decreased immunological response. Blue square = *N*-acetylglucosamines (GlcNAc), red triangle = fucose (Fuc), green circle = mannose (Man), yellow circle = galactose (Gal), purple square = *N*-acetylneuraminic acid (Neu5Ac), ↑ = increased activity, ↓ = decreased activity.

1.1.3. Gal (B4GALT β1,4-galactosyltransferase)

The presence or absence of additional Gal residues at the glycan arms has been controversially linked to altered affinities to diverse IgG effector structures. First, it has been shown that galactosylation influences complement activation in terms of increased C1q binding of corresponding IgGs and, thus, enhance CDC [58,59]. On the other hand, the lack of terminal Gal leads to more accessible mannose within the core structure that increases the affinity to the mannose-binding lectin as a further, and actually antibody-independent initiator of the complement system [60]. Second, many studies have revealed elevated FcγR affinities in cases of increased galactosylation status of IgG Fc N-glycans, albeit the effect is much weaker than the loss of the core fucosylation. Consequently, ADCC and ADCP activity was described to be amplified [61–63]. This finding contrasts with data published by Nimmerjahn, Anthony, and colleagues, who revealed unchanged or elevated FcγRIIB and FcγRIII affinities to IgG1 and ADCC activity after cleavage of terminal Gal [64,65]. These inconsistent findings may be the result of a wide range of variables within the experimental setup, including IgG subtype, Fcγ receptor class, cellular model organisms, analytical verification of glyco-modifications, and background glycan structures such as fucosylation. Nevertheless, the presence of additional Gal at the glycan arms seems to have a decisive influence on the functional properties of IgG and promotes anti-inflammatory processes as patients suffering from autoimmune diseases such as rheumatoid arthritis (RA) as well as lupus erythematosus (LE) express increased agalactosylated total IgG [66,67]. Furthermore, Ito et al. (2014) and Rademacher et al. (1994) determined that agalactosylation strengthens the pathogenicity of autoantibodies [68,69].

1.1.4. Neu5Ac (ST6GAL/ST3GAL α2,3/α2,6-sialyltransferase)

In contrast to b-GlcNAc and Gal, consequences of capping Neu5Ac (sialylation) are more evident. Sialylated Fc N-glycans are approved as mediators of anti-inflammatory processes; however, underlying mechanisms are still discussed [25,26,29,70]. Conformational changes or a more flexible CH2 domain of IgGs exhibiting Neu5Acassociated glycans are believed to increase the affinity to the dendritic cell-specific ICAM-3 grabbing non-integrin receptor (DC-SIGN), a further IgG interaction partner [71,72]. The activation of this C-type lectin is associated with signaling cascades leading to an interleukin (Il)-33 and Il-4 mediated enhanced gene expression of the inhibitory FcγRIIb and, thus, anti-inflammatory processes as the result of an increased activation threshold of immune cells [27,73]. In different *in vitro*-assays the activity of the mouse analog specific ICAM-3-grabbing non-integrin-related 1 receptor (SIGN-R1) was inhibited and revealed a deficiency in the anti-inflammatory effect of intravenous immunoglobulins (IVIg). Knock-in of DC-SIGN restored that phenomenon and revealed its involvement; however, some further surface lectins may also contribute to the anti-inflammatory IgG function [74–77]. In addition to the increased DC-SIGN affinity, the presence or absence of Neu5Ac also negatively impacts IgG binding to all FcγR classes, resulting in decreased ADCC and CDC [27,78–80].

2. Altered IgG Fc N-glycosylation

2.1. Altered IgG Fc N-glycosylation in homeostasis

A number of factors such as age, gender, and environment as well as a wide range of diseases have been identified to influence glycosylation processes, leading to altered glycosylation patterns during physiological conditions. First, well-documented influences on glycan composition could be attributed to aging and gender. For example, children and elderly individuals show Fc glycans with reduced portions of Gal and Neu5Ac. In detail, Bakovic and colleagues discriminated between male and female adults older and younger than 57 years. They found enormous diversity, including strongly reduced Gal and Neu5Ac portions in the elderly group – as already mentioned – but also increased b-GlcNAc [26,81,82]. Furthermore, correlation analyses revealed dependencies between combined as well as single glycan compositions and age in both male and female individuals. However, in most cases, IgG glycan modifications during ageing were identified to be more strongly affected in females [81,83]. In particular, gender-dependent effects seem to be a result of hormonal conditions due to a distinct involvement of estrogen and progesterone, whereby the latter additionally mediates increased Fc glycan sialylation and galactosylation in pregnancy [84–86]. Further signaling molecules such as cytokines have also been identified to impact IgG Fc N-glycosylation. Il-21, for example, was identified to increase Fc-linked galactosylation with a simultaneous decrease in b-GlcNac [87].

In addition to these processes that very likely impact gene expression, there are further metabolic, dietary but also environmental factors influencing the general and, thus, IgG-glycosylation mechanisms [88]. Metabolites such as carbohydrates and oxygen are necessary and limiting factors for the production of sugar nucleotides as glycan components. Physiological fluctuations in their availability can occur in different phases of life and action and have been connected with changed IgG glycosylation patterns [89,90]. In addition, proteins, including glycosylated IgG in patients suffering from type 2 diabetes mellitus (a carbohydrate metabolism disorder), have been identified to exhibit altered and distinct glycan patterns [91]. Furthermore, changes in pH, which depend on parameters like carbon dioxide, electrolyte metabolism, and acidity, directly affect enzyme activities and were shown to induce mislocalization of Golgi glycosyltransferases, resulting in disturbed glycosylation processes [92].

2.2. Altered IgG Fc N-glycosylation in neurologic diseases

In the last few decades, many diseases have been attributed to altered IgG glycosylation patterns; however, for most of these diseases, etiologic or diagnostic significance has not yet been uncovered. The autoimmune diseases rheumatoid arthritis and lupus erythematosus were among the first disorders in which pathological Fc N-glycosylation patterns of IgG were identified. Fc N-glycans show a decreased Gal and/or Neu5Ac portion resulting in exposed GlcNAc [67,93–95]. Such structures are typical for non-mammalian vertebrates, non-vertebrates and lower organisms and therefore are ligands for various immune receptors, resulting in inflammatory processes [30]. Similar changes in IgG Fc N-glycosylation were observed in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, patients with multiple myeloma and patients suffering from gastric cancer [96–98].

In addition to such non-neurologic diseases accompanied with altered IgG Fc N-glycosylation patterns, in the last few years, an increasing number of studies have been published for neurologic disorders (Table 2). In particular, autoimmune diseases are of central interest, as the participation of the immune system suggests a potential role of immunoglobulins in disease onset and progression. For multiple sclerosis (MS), an autoimmune neurologic disorder characterized by inflammatory demyelination of axons in the central nervous system, a variety of underlying pathological proinflammatory processes have been identified, including autoreactive T cells, increased NF-κB signaling and the presence of autoantibodies against myelin proteins (myelin basic protein [MBP] and myelin oligodendrocyte glycoprotein [MOG]) [99–103]. In line with these findings, different studies dealing with the N-glycosylation of IgG have revealed proinflammatory patterns in the cerebrospinal fluid (CSF) in MS patients. Decker et al. isolated total IgG from the serum and CSF of patients with MS, patients with viral meningitis, and control subjects without inflammatory or autoimmune neurologic diseases. While the meningitis cohort did not show any significant alterations in the glycosylation status compared to age-matched controls, MS patients exhibited significantly decreased galactosylated IgGs in the CSF, and the degree was strongly correlated with disease progression [104]. In contrast, such differences were not detectable when investigating serum IgG of the same cohorts. Although

Table 2
Alterations in the IgG Fc N-glycosylation pattern in different neurologic diseases.

	Fucose (Fuc)	*N*-Acetylglucosamine (b-GlcNAc)	Galactose (Gal)	*N*-Acetylneuraminic acid (Neu5Ac)
Multiple Sclerosis (MS)	↑ CSF IgG1 + 2	↑ CSF IgG1 + 2	↓ CSF IgG → Serum IgG	→ CSF IgG1 + 2
Myasthenia Gravis (MG)	→ Serum IgG1 + 2	→ Serum IgG1 + 2	↓ Serum IgG1	→ Serum IgG1 + 2
Lambert-Eaton Myasthenic Syndrome (LEMS)	↓ Serum IgG2	↑ Serum IgG1 + 2	↓ Serum IgG1 + 2	→ Serum IgG1 + 2
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	n.a.	n.a.	↓ Serum IgG	↓ Serum IgG
Guillain-Barré Syndrome (GBS)	n.a.	n.a.	↓ Serum IgG1 + 2	↓ Serum IgG2
Alzheimer's Disease (AD)	↑ Serum IgG1	n.a.	↓ Serum IgG1	↓ Serum IgG1
Parkinson's Disease (PD)	→ Serum IgG	→ Serum IgG	↑ Serum IgG	↓ Serum IgG

Fc N-glycans of total IgG or special subtype(s) isolated from serum/plasma or cerebrospinal fluid (CSF) reveal changed compositions in the course of many neurologic diseases. In comparison to healthy controls, patients often show IgG Fc N-glycans with increased (↑) or decreased (↓) portions of additional fucose, *N*-acetylglucosamine, galactoses, and/or *N*-acetylneuraminic acids. In some cases, the number of additional sugar molecules is unchanged (→).

Decker and colleagues were not able to distinguish between Fab and Fc N-glycosylation as they used a lectin-binding assay with entire IgGs including Fab and Fc, it is very likely that these alterations occur at the conserved site of the Fc fragment. This is also indicated by a study of Wuhrer et al. who did not investigate total IgG but examined the most frequent subtypes IgG1 and IgG2 [105]. In contrast to Decker and colleagues, they were able to distinguish Fab and Fc glycans by tryptic digestion of IgG with subsequent mass spectrometric analyses of the glycopeptides. Accordingly, they determined a significantly decreased portion of galactosylated IgG1 in the CSF but not in the serum of patients suffering from MS. Using mass spectrometry, they were also able to further analyze Fc-associated N-glycans, including fucosylated, *N*-acetylglucosaminated and sialylated ones. While IgG1 oligosaccharides with additional b-GlcNAc and Fuc were increased in the CSF of the MS group, sialylated glycans were comparable between the cohorts.

Another autoimmune neurologic disorder connected with altered IgG Fc N-glycosylation is the group of myasthenic syndromes including myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS). Both diseases are characterized by disrupted signal transmission at the neuromuscular junction, resulting in muscle weakness that worsens with physical strain [106]. Here also, autoantibodies play a pivotal role in the pathology, as they recognize pre- and postsynaptic structures [107–109]. Selman and colleagues investigated the Fc N-glycosylation pattern of IgG1 and IgG2 purified from serum and plasma samples from healthy individuals as well as patients suffering from LEMS (with or without lung carcinoma) and patients suffering from MG, the latter subdivided into groups exhibiting autoantibodies against the acetylcholine receptor or muscle specific kinase [110]. In LEMS patients, both IgG1 and IgG2 showed significantly decreased galactosylation levels, including increased agalactosylated and decreased mono- and digalactosylated glycoforms. In contrast, in MG patients, only IgG2 Fc N-glycans carried less Gal. Although all diseased individuals had lower Gal portions, there were no significant differences in the levels of total sialylation, which directly depends on the presence of Gal at the glycan arms. In addition to the altered Gal status, b-GlcNAc as well as Fuc levels were also changed in LEMS patients compared to healthy controls. While IgG1 and IgG2 Fc N-glycans exhibited higher portions of b-GlcNAc, IgG2 fucosylation was significantly decreased [110]. Such alterations were missing when comparing MG patients with the control cohort. However, it should be mentioned that despite missing differences in the total levels of galactosylation, sialylation, fucosylation, and *N*-acetylglucosamination, single sugar compositions may have also differed between the groups.

The decreased Gal level of IgG in disease cases is also shown in two additional immunological diseases: chronic inflammatory demyelinating polyneuropathy (CIDP) and Guillain-Barré syndrome (GBS) [111]. Various autoantibodies recognizing gangliosides, which are very frequent in the membrane of nerve cells, are detectable in the serum of affected people and seem to induce inflammatory processes jointly responsible for both disorders [112–115]. In a study by Fokkink et al. the serum IgG1 and IgG2 Fc N-glycosylation patterns of 91 GBS patients were compared with healthy controls before and after IVIg treatment. They revealed a significantly decreased Gal level for both IgG subclasses and, furthermore, a significantly decreased Neu5Ac level of IgG2 in the GBS patients [116]. After IVIg treatment, the portion of Gal and Neu5Ac IgG Fc N-glycans recovered to a physiological state due to a high portion of IVIg-originating immunoglobulins within the serum samples. Another group addressed similar questions and investigated serum samples from patients suffering from CIDP and healthy controls. Wong et al. used lectin binding assays to quantify galactosylated and sialylated IgG Fc N-glycans, and accordingly to the findings of Fokkink et al., CIDP patients exhibited significantly decreased Gal levels [83]. While Fokkink and colleagues described only IgG2 and not IgG1 glycans as being less sialylated, Wong et al. revealed a significant reduction in the Neu5Ac level of the total IgG. Given that IgG2 is less frequent than IgG1 and that sialylated glycans comprise only approximately 10%, both studies suggest a greater relevance for a decreased sialylation status in CIDP patients [6,57]. Indeed, this would make sense, as CIDP, in contrast to GBS with a disease duration up to 4 weeks, shows stronger inflammatory processes [117].

In addition to the already described cases, there are also further neurological diseases accompanied with altered IgG glycosylation patterns that do not belong to the classical autoimmune disorders. First, Alzheimer's disease (AD), which is characterized by extracellular cortical deposits of the proteins beta-amyloid (Aβ) and Tau [118–120]. Currently, there is no evidence to classify AD as an autoimmune disease, albeit patients show neurological inflammatory processes. The finding that microglial activation and inflammatory mediators are increased indicates the involvement of the immune system [121,122]. Lundström et al. investigated the Fc N-glycosylation patterns of plasma IgG1 and IgG2 in 31 patients suffering from AD, 92 patients with prestage MCI (mild cognitive impairment; subdivided into stable and progressive MCI) and 23 healthy controls [123]. They detected up to 19 different Fc N-glycans and used the seven (IgG1) and six (IgG2) most abundant glycoforms to perform their comparative analyses. Particularly in AD cases, Lundström et al. found a significantly altered glycan profile with an increased portion of single fucosylated oligosaccharides. Simultaneously, they determined a decline in Gal and Neu5Ac levels; however, all of these changes were only observable for IgG1. Furthermore, Lundström and co-workers investigated potential gender differences but revealed one significantly decreased glycan structure only in the progressive MCI group. Age-dependent effects were also examined using the Glyco-Age index (logarithm of the ratio of fucosylated G0 to G2 structures) as an indicator for the ageing process [124]. The Glyco-Age index was calculated for two age ranges of each group, and within the smaller age range, the index was significantly increased in the AD cohort compared to controls. This finding indicates a progressive alteration and faster aging of the IgG Fc N-glycosylation pattern in AD patients.

In Parkinson's disease (PD), a second non-autoimmune neurologic

disorder, the protein alpha-synuclein (α-Syn) forms aggregates that are the main component of the histopathological intracytoplasmic inclusions, called Lewy bodies. The disruption of the α-Syn metabolism is considered to be a causal event and is restricted to neurons of the substantia nigra pars compacta, provoking loss of neurons and the typical motor symptoms [125–127]. Like in AD, inflammatory processes play an important role in the PD-associated pathology [128]. Russel et al. recently published a study in which they focused on this immunological aspect and investigated the glycosylation pattern of plasma total IgG in 96 PD patients and 102 age- and gender-matched, healthy controls using hydrophilic interaction liquid chromatography-ultra-performance liquid chromatography (HILIC-UPLC). Analyses of single and combined glycan structures revealed significantly decreased total Neu5Ac levels in PD patients, whereas monosialylated glycans were most affected [129]. While total Fuc and b-GlcNAc levels did not show any differences between the patient and control groups, Gal levels were changed. In contrast to all other described studies, Russel and colleagues determined a significantly increased portion of galactosylated IgG glycans in the patient cohort. A simultaneous gain in Gal and reduction in Neu5Ac is highly unusual, as the molecular and structural requirements for an enzymatic attachment of Neu5Ac is given. Nonetheless, this finding may indicate a crucial role for altered Neu5Ac levels of IgG in PD.

Taken together, the results of the studies we have outlined herein suggest common structural properties of IgG Fc N-glycans in pathological states. The decline in Gal and/or Neu5Ac levels of IgG has been identified in autoimmune, autoimmune-neurologic and neurodegenerative disorders and may illustrate a common effect in the humoral component of the immune system during inflammatory processes. However, whether such alterations induce or are a result of the inflammatory mechanisms remains an open question like the famous chicken-and-egg discussion: which came first? Both options are justifiable, as it has been shown that the glycosylation process can be temporarily adapted under homeostatic conditions, which may provoke IgG-mediated inflammation when the state becomes permanent [130–132]. Furthermore, it has been shown that altered glycosylation can be based on genetic defects in the glycosylation machinery, which represents a causal factor in various disorders that are sometimes accompanied by neurologic symptoms [133,134]. On the other hand, proinflammatory cytokines secreted as a result of an already activated immune system are capable of inducing changes in protein glycosylation [135–137]. Whatever the case, it results in a proinflammatory pattern of IgG with reduced Gal and Neu5Ac levels, albeit the distinct effect of IgG galactosylation remains to be clarified. This finding is also demonstrated by the study of Russel et al., which, in contrast to all other provided studies, revealed increased Gal levels in diseased patients [129]. These results as well as the controversially discussed impact of Gal on IgG effector functions may support postulating only secondary effects of IgG galactosylation in terms of the structural prerequisites for adding anti-inflammatory Neu5Ac.

2.2.1. What we further know about altered IgG glycosylation in neurologic diseases

Regarding neurologic diseases, it is not surprising that to the best of our knowledge, nothing is known about altered IgG Fab N-glycosylation or altered IgG O-glycosylation, as IgG O-glycans have only been discovered in the last years, and studies dealing with N-glycans at the Fab arms are difficult to execute and interpret due to the low glycan abundance and variable glycosylation sites. However, in the autoimmune non-neurologic disease RA, total IgG Fab glycosylation was found to be 3-fold increased with higher levels of monogalactosylated oligosaccharides exhibiting additional b-GlcNAc and Fuc [138]. Furthermore, analyses of specific autoantibodies against the anti-citrullinated protein – a diagnostic biomarker in RA – have also revealed increased Fab glycosylation [139].

Regarding specific autoantibodies, there are many studies dealing with Fc glycosylation in disease cases. In addition to a number of non-neurologic disorders accompanied with pathological autoantibodies, there is one interesting study dealing with the autoimmune neurologic disorder neuromyelitis optica (NMO) [140–142]. Autoantibodies against the astrocyte-associated water channel aquaporin-4 (NMO-IgG) play an etiological role and are thought to induce CDC and ADCC, resulting in astrocyte degeneration and inflammatory processes [143]. Tradtrantip et al. performed enzymatic deglycosylation of NMO-IgG using endoglycosidase S and revealed highly reduced CDC and ADCC activity as well as a preventive impact on lesion formation in an *ex vivo* and *in vivo* mouse mode [142]. Due to a simultaneously unchanged binding to aquaporin-4, the authors uncovered a prospective therapeutic option for NMO as deglycosylated, non-pathogenic NMO-IgG competes with untreated, pathogenic NMO-IgG for aquaporin-4 binding and, thus, prevents CDC and ADCC. In the following chapter, we will examine these not only therapeutic but also diagnostic potentials of IgG Fc N-glycosylation in more detail.

3. IgG Fc N-glycosylation as a potential diagnostic and therapeutic target in neurologic diseases?

A systematic literature research with the key words “IgG”, “glycosylation”, and “disease” yields numerous results of studies revealing altered IgG glycosylation patterns in various pathological states. However, in this context, the idea of a promising diagnostic biomarker is mentioned inflationarily considering that most of the studies miss defined criteria for the assignment to a disease or healthy state, specificity and sensitivity calculation, as well as verification of the testing. Furthermore, the therapeutic interventions of many diseases depend on an early diagnosis; therefore investigations of only two fixed cases (health and disease) may often not be sufficient. Rather, longitudinal analyses that will allow researchers to follow alterations in glycosylation patterns over an extended period of time should be performed to determine the critical time point of disease onset and a potential correlation with glycosylation changes. Accordingly, all of these immatureness in combination with a generally complex analytical effort have caused IgG glycosylation to not yet attain status as a medically approved biomarker. Nonetheless, some of the studies revealing altered IgG glycosylation patterns in diseases have also characterized its capability as a promising biomarker, and we exemplarily want to take a closer look at the already provided study of Russel et al. [129]. As described above, the authors found significantly increased Gal and decreased Neu5Ac levels in PD patients. In addition, using serum samples of 196 subjects, they developed a model based on the frequency of four glycan peaks determined by HILIC-UPLC to forecast disease or health cases. Calculations yielded a sensitivity of 87.2% and a specificity of 92.2% for correct classification; however, validation with another cohort is missing [129]. Despite such promising but rarely performed studies, more consequent and purposeful investigations regarding IgG glycosylation patterns are needed to identify and verify potential reliable diagnostic markers in the future.

It is an interesting fact that almost all of the above-described diseases accompanied with IgG Fc N-glycosylation changes show an improvement after IVIg treatment [144–146]. Especially in the autoimmune neurologic disorders MS, MG, LEMS, GBS, and, CIDP, IVIg is even indicated as an immune modulatory therapeutic agent [147,148]. Furthermore, it is assumed that IVIg application also ameliorates AD-associated symptoms [149]. The benefit of IVIg is hypothesized to be a result of a replacing or diluting effect, whereby pathological alterations within the IgG pool are covered but unchanged. This also includes proinflammatory Fc N-glycosylation patterns, which are observable in all the described disorders. In line with that, high doses of IVIg were described to have anti-inflammatory properties due to glycans exhibiting Neu5Ac [64,150,151]. This shows that IVIg application may be

a generally suitable treatment strategy for diseases associated with proinflammatory IgG glycosylation patterns and could be extended to further disorders.

In special cases, it is conceivable that the investigation of the glycosylation pattern of specific, physiological and naturally occurring autoantibodies (nAbs) instead of total IgG creates a major benefit. Alterations within that autoantibody pool are believed to participate in disease onset and progression, as nAbs are responsible for the maintenance of homeostasis including clearance of damaged structures and the regulation of protein metabolisms [152,153]. Consequently, in AD and PD, for example, nAbs recognizing the disease-associated proteins Aβ and α-Syn have been increasingly focused on by neurobiologists, as the presence of these autoantibodies in every human being may represent an innate defence mechanism. Thus, quantitative and/or qualitative alterations bear diagnostic and therapeutic potential. Interestingly, AD and PD patients show significantly decreased titers of these specific nAbs; however, a reliable biomarker model is still missing [154,155]. Comparable investigations of nAbs Fc N-glycosylation patterns between patients and control subjects would illuminate qualitative aspects but have not been executed so far. Nonetheless, such analyses could enable the development of a new and more specific and sensitive diagnostic biomarker (instead of total IgG) as well as a therapeutic approach. For the latter, it would be conceivable to recombinantly generate humanized monoclonal antibodies recognizing Aβ or α-Syn. Many clinical studies are already based on that idea; however, to date, none has successfully reached phase III [156–158]. For the production of such antibodies, the selective addition of distinct Fc N-glycans based on a comprehensive knowledge of glycosylation patterns and the resulting immunological reactions would be necessary and has been neglected in most cases, which might be a reason for side effects and the study failures. For instance, the recombinant synthesis of therapeutic antibodies is usually achieved in mammalian cell systems such as Chinese hamster ovary (CHO) or human embryonic kidney (HEK) cells. Despite executed humanization steps, both cell systems feature their own glycosylation process, resulting in distinct and discriminable glycosylation patterns [159]. It has been shown that IgG Fc N-glycans produced in normal CHO cells exhibit less Neu5Ac, more Fuc, and no b-GlcNAc and that the glycosylation pattern of HEK-cell-derived IgGs greatly depends on culture properties and shows considerable differences in comparison to the physiological, human pattern [160–163]. These findings should prompt researchers to perform and confirm future studies more faithfully and in more detail.

Glycoengineering – the targeted modification of antibody-attached glycans – could represent the missing jigsaw piece to generate prospective therapeutic antibodies [164]. This method allows the attachment or selective production of specific Fc N-glycans that counteract potential pathologic alterations in the glycosylation pattern and replace missing or modulate elevated and extenuated effector functions such as phagocytosis, secretion of pro- or anti-inflammatory cytokines, and activation of complement cascades. In particular, a recently published study by Pagan and colleagues demonstrated glycoengineering to be a promising future therapeutic tool, as an artificially increased sialylation status was shown to improve inflammation in an animal study [165].

In general, there are many possibilities to influence and determine glycan compositions or to attach defined glycan structures to IgG Fc fragments. Especially when generating antibodies in non-mammalian expression systems, glycoengineering becomes very important as the glycan compositions as well as the incorporated sugars differ between organisms [29]. Here, the knockdown or knockout of species-specific enzymes of the glycosylation machinery in combination with mammalian-specific enzyme treatment may represent a suitable strategy to improve therapeutic efficacy of antibodies and has been applied for the rituximab antibody used in cancer therapy [166]. The knockdown and knockout approach is also suitable when producing therapeutic antibodies in mammalian cell lines, e.g., CHO, as the most frequent cell line. Different targets including genes encoding glycosyltransferases, glycosidases, but also other enzymes, are conceivable to generate antibodies with defined Fc N-glycans [167–169]. Further methods to alter glycosylation include overexpression of enzymes and utilization of enzyme blockers or inhibitors such as tunicamycin and castanospermine [170–173]. Especially the overexpression of GlcNAc transferase III would enormously affect Fc N-glycan compositions, as the attachment of a bGlcNAc suppresses the activation of fucosyltransferases [54]. Despite these methods – most of them directly influencing genetic factors – there are also possibilities to control the glycosylation process by the selection of certain culture properties [26,174,175]. At this point, it should be noted that in addition to the typical human saccharides, it would be possible to add sugar moieties from different species to IgG Fc N-glycans to induce and enhance defined effector functions. It is an interesting fact that even within mammals, species-specific differences occur in not only the glycosylation pattern but also the utilization of single sugars molecules (e.g., mice exhibit the sialic acid *N*-glycolylneuraminic acid in addition to Neu5Ac) [162,176]. Of course, in most cases, such structures would activate immunological reactions against the antibodies; however, there is a small chance that in specific diseases, such glycan compositions may yield beneficial effects [29,177].

Glycoengineering of antibodies could also be a promising approach to treat diseases accompanied with pathological antibodies. Based on the idea of Tradtrantip et al., who determined that deglycosylated pathologic NMO autoantibodies compete with untreated autoantibodies without activating detrimental reactions, such approach could be transferable to the already described autoimmune neurologic disorders MS, MG, LEMS, CIDP, and GBS in which pathologic autoantibodies are also detectable in human body fluids. Although less is known about the efficacy of such treatment, a similar effect has already been described for thrombocytopenia, a platelet destruction disorder associated with harmful alloantibodies [178].

4. Summary and conclusion

Fc N-glycosylation of IgGs plays an important role for the functional properties of the immunoglobulins. Various studies have already demonstrated the dependency of IgG-mediated processes such as CDC, ADCC, ADCP, and inflammation on the composition of Asn297-attached N-glycans. Especially, the presence or absence of additional fucoses, *N*-acetylglucosamines, galactoses, or sialic acids have been shown to extensively influence these mechanisms.

In many neurological diseases, the IgG Fc N-glycosylation pattern has been shown to be changed and usually displays a decreased Gal and/or Neu5Ac level. Both reductions may be connected with an elevated proinflammatory status including increased CDC and ADCC indicating a potential participation in disease onset or progression; however, in most cases, the source of altered glycosylation remains unknown. In general, connecting functional consequences with altered IgG Fc N-glycosylation patterns may enable a better understanding of underlying disease processes and represent the basis of new diagnostic and therapeutic approaches in the future. Therefore, more comprehensive IgG glycosylation analyses over time are needed, especially when glycoengineering of promising therapeutic antibodies is the main objective.

Conflicts of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2018.10.006.

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