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Glycans as Possible Biomarkers in Diagnosis of Neurodegenerative Diseases

Uloga glikana kao biomarkera u dijagnostici neurodegenerativnih bolesti

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Abstract. Glycosylation is one of the most significant and common protein modifications. Many clinical biopharmaceuticals today are also glycosylated. The resulting glycoproteins may have one or more glycan structures attached through *N*- or *O*-glycosidic bonds. The profiles of glycosylation can change with aging, as well as in conditions like Alzheimer's, Parkinson's, and other neurological disorders. This means that many glycoproteins could serve as useful biomarkers for diagnosing diseases and tracking their progression. However, the role of glycosylation in the central nervous system is not well understood, even though it is quite prevalent. Future research will focus on creating detailed glycoprofiles from different body fluids and tissues and analysing this enormous amount of information by using conventional methods with the help of artificial intelligence lately.

Keywords: biomarkers; glycosylation; neurodegenerative diseases; polysaccharides

Sažetak. Glikozilacija predstavlja jednu od najvažnijih i najrazličitijih posttranslacijskih modifikacija proteina općenito. Velik je i udio kliničkih biofarmaceutika koji su glikozilirani. Glikoproteini ljudskog organizma mogu nositi jednu ili više glikanskih struktura vezanih *N*- ili *O*-glikozidnim vezama. Starenje, Alzheimerova i Parkinsonova bolest te ostale neurodegenerativne bolesti pokazuju promjene u glikozilacijskim profilima. Samim time i velik broj glikoproteina predstavlja potencijalne biomarkere za dijagnosticiranje, ali i praćenje tijeka bolesti. Ipak, usprkos sveprisutnoj reakciji glikozilacije, njezina uloga u središnjem živčanom sustavu nije dovoljno istražena. Buduća istraživanja tražit će izradu kompletnih glikoprofila različitih tkiva i tjelesnih tekućina te obradu takvih sveobuhvatnih podataka koristeći i pomoć metoda umjetne inteligencije.

Ključne riječi: biomarkeri; glikozilacija; neurodegenerativne bolesti; polisaharidi

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INTRODUCTION

One of the most important processes during and after protein synthesis is post-translational modification (PTM). PTM involves a covalent transformation of a protein by removing or adding different functional groups hence significantly affecting their function. Methylation, acetylation, and phosphorylation are some of the frequent ones but the most prominent and most diverse certainly is protein glycosylation[1]. Glycosylation reaction involves a transfer of a glycan (covalently attached monosaccharide/oligosaccharide) part onto the protein or a lipid. In the case of naturally present glycoconjugates (glycoproteins or glycolipids), the glycan part can have various contribution to their overall size. For instance, the cell surface is usually covered with a thick glycan layer called "glycocalyx"[2]. Furthermore, each monosaccharide can create α- or β-linkage to any position on another monosaccharide giving thousands of combinations just for three different hexoses (contrary, three different nucleotides can only generate six trimers). The glycoconjugate complexity rises with different monosaccharide units involved, but luckily, naturally occurring macromolecules contain only a few numbers of different monosaccharides. Even so, most of the glycans in other species are yet to be defined.

Glycoproteins carry one or more glycans connected via *N*- or *O*-linkages. *N*-glycans have sugar moiety connected to the asparagine residue of a polypeptide, with a common pentasaccharide core. There are three types of *N*-glycans: high-mannose-, hybrid- and complex-type. The second common type of glycans, *O*-glycans, has sugar moiety connected to the hydroxyl group of serine or threonine of a polypeptide. Several types of *O*-glycans also exist (e.g., *O*-fucose, *O*-mannose). Figure 1 shows some of the main glycan types[3].

Another important fact is that glycans are not encoded directly via genome but are secondary gene products and even small changes in the environment cause immense changes in glycan produced by certain cell. That being said, highly versatile nature of glycosylation makes glycan analysis much more challenging in contrast to proteins or nucleic acids.

There are many biological roles of glycans such as membrane organization, glycoprotein folding, extracellular matrix organisation, and protection from immune recognition just to mention a few of them. Consequently, many diseases are accompanied by abnormal glycosylation, altered glycan synthesis pathways, or are based on congenital glycosylation disorders.

Glycobiology is a rapidly growing discipline that connects basic research with medical and biotechnological fields, and it is a great source of potential biomarkers for a variety of disorders.

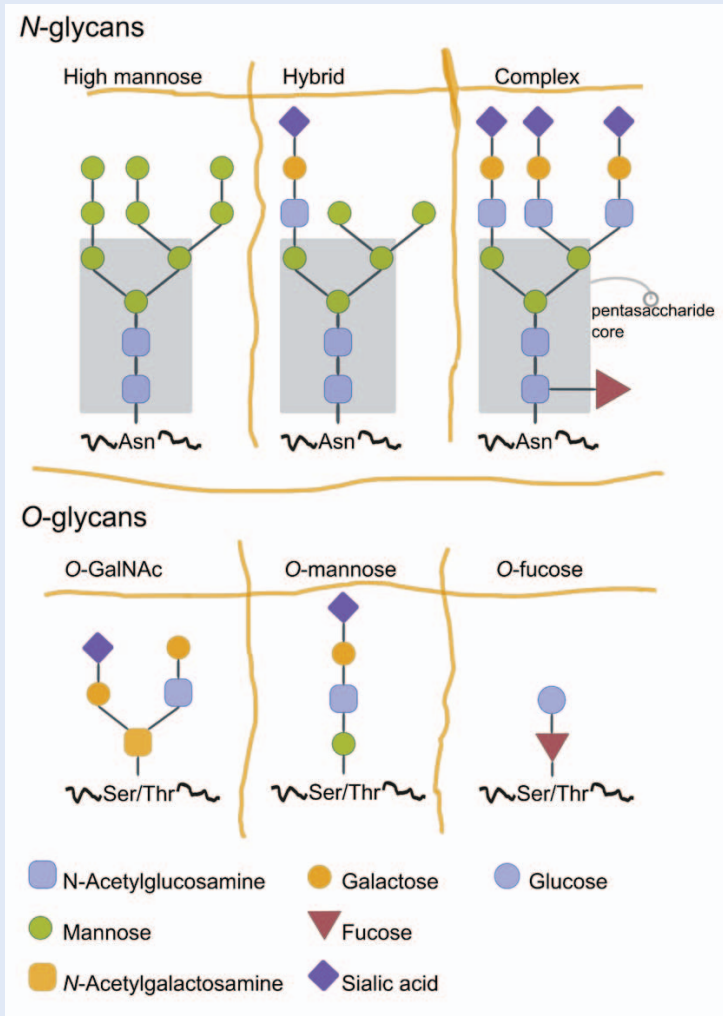

Figure 1. Different classes of *N*- and O-glycans. *N*-glycans are attached via *N*-linkage to Asparagine and *O*-Glycans are attached via *O*-linkage to Serine/Threonine of the protein chain. *O*-GalNAc – *O*-*N*-acetylgalactosamine.

Research areas are finding more and more connections between the process of aging in humans and glycosylation patterns, emphasizing a key role for glycosylation in regulating human lifespan on the one hand and age-related disorders on the other hand. The process of aging bare some mechanistic similarities with many disorders, especially with neurodegenerative disorders (NDs) probably through misfolding and aggregation of proteins. Aging and neurodegeneration are closely linked. The combined impacts of oxidative stress, protein aggregation, inflammation in the nervous system, and damage to blood vessels during aging process leads to conditions that favor NDs. Grasping these connections is important for creating early treatments and possible therapies to slow down or stop neurodegenerative diseases. Aberrant sialylation is present in Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS), specifically decreased in AD and increased in ALS for instance[4]. Additionally, Huntington's disease (HD) may be characterised with increased fucosylation and sialylation of *N*-glycans.

Furthermore, traumatic brain injuries (TBIs) increase the risk of several NDs with various PTMs common between TBI and AD[5]. The molecular background of aging and NDs may provide a necessary link between them opening the road for both new diagnostic as well as therapeutic strategies. Modifying glycosylation may alleviate the detrimental effects of disease progress.

In the sense of tumour progression, EVs can transfer miRNAs, DNA and oncogenic proteins and thus facilitate the process. In order to create a pro-tumorigenic milieu and get beyond non-cancerous cells' growth-inhibitory signals, cancer cells take advantage of EVs. Through the down-regulation of tumour-suppressive miRNAs and the promotion of tumour cell proliferation, this EV-mediated communication accelerates the course of the disease. In glioblastoma (GBM), EVs modulate anti-tumour response, they may serve as potential biomarkers and therapeutic vehicles[6].In the root of autoimmune diseases there are genetic and environmental variables that impair immune tolerance and result in self-antigen assaults. Through the transmission of inflammatory mediators, immune response modulation, and antigen presentation, EVs are essential to the advancement of illness. They encourage cytokine imbalances, affect autoreactive T and B cell activation, and aid in the creation of immunological complexes. EVs are prospective indicators and therapeutic targets in disorders like rheumatoid arthritis and systemic lupus erythematosus[7].

The field of Glycobiology is expanding at a rapid pace connecting basic research with areas of medicine and biotechnology materializing as a great source of potential biomarkers for various types of disorders.

GLYCOSYLATION CHANGES IN NDS

There are millions of people currently affected by NDs with old age being the biggest risk factor. In addition to age, other factors include a person's genetic composition and different environmental effects that can increase the risk of developing NDs. Progressive loss of neurons is associated with loss of synaptic function and deposition of biochemically altered proteins in the brain. The two most common types of NDs are Alzheimer's and Parkinson's disease (PD) but there are several other noticeable ones such as ALS, Huntington's disease and prion disease[8, 9]. Rates of the mentioned NDs are increasing rapidly as the world demographics changes towards older age. It is assumed that by 2050 number of people aged 60 years and older will double[10] and the associated number of NDs with it, thus imposing a substantial burden to potential patients, healthcare systems, and society in general[11]. CNS proteins are heavily glycosylated they are indispensable for the correct function and development of CNS. Furthermore, many diseases of the CNS, including NDs, are accompanied with changes in glycosylation. It is a known fact that, with Huntington's disease as well as AD, PD, defects in glycosyltransferases related to neurodegeneration had a number of functional consequences such as alterations in cell surface signalling, ganglioside biosynthesis alteration, or O-GlcNAcylation changes. This is where an advanced glycome analysis comes in to play to reveal changes in glycan profiles with an important upside; glycans are far more specific and sensitive than other biomarkers. Glycans are highly diverse in their

structures and are subject to dynamic changes. They represent essential biological processes and thus serve as suitable biomarkers. Their rapid response to diseases and specific tissue locales make them serve useful roles in diagnosis, prognostication and monitoring of therapy response. Nevertheless, glycan modification can be similar in different NDs creating a substantial obstacle to their biomarker application. As time passes, the glycomics and glycoproteomics data are accumulating more and more. Nowadays, (October 2024), the Glycan repository (GlyTouCan) lists 250 000 glycan structures while an average glycomics experiment measures up to hundreds of glycans. This calls for an Artificial intelligence (AI) methods which are now gaining in focus in the glycoinformatics branch[12].

CHANGES IN GLYCOSYLATION DURING ALZHEIMER'S DISEASE

AD affects millions of people worldwide and that number is expected to double in the next 30 years. AD is characterised with by irreversible loss of neurons leading to memory lapses and represents primary cause of all dementia patients. Pathologically, AD is featured by an accumulation of misfolded amyloid-beta (Aβ) peptides which requires a proteolytic cleavage of amyloid precursor protein (APP) by β- and γ-secretase. A study of APP trafficking showed that the replacement of asparagine by glutamine at two possible glycosylation sites changes the APP levels in the plasma membrane thus directly influencing the release of toxic Aβ or nontoxic peptides[13].

Formatted amyloid plaques induce an inflammatory response creating neurofibrillary tangles consisting of hyperphosphorylated tau proteins (p-tau)[4] with subsequent loss of brain function and cognitive abilities. Aβ42 represents a 42-amino-acid long form of Aβ and is used as cerebrospinal fluid (CSF) AD biomarker together with p-tau. The ratio of p-tau/Aβ42 correlates with positron emission tomography (PET) results and is very applicable in asymptomatic AD diagnostics[14]. AD pathology is irreversible with currently no effective treatment. Furthermore, AD may start decades before the first clinical symptoms so there is an enormous need for specific biomarkers discovery to diagnose and monitor its progression.

From the perspective of PTMs, they offer an interesting and valuable biomarker possibility since several proteins (like Aβ and tau) involved in AD pathology undergo PTMs[15]. Proteinopathies which are characteristic for NDs are strongly influenced by dysregulated PTMs. Schaffert and Carter identified several modulators of NDs proteinopathies in their review: phosphorylation of Aβ/tau in AD, phosphorylation of α-synuclein in PD, isoaspartate formation in Aβ and several others[15].

N-glycosylation is crucial for precise protein structural organiation and activity but also as a modality for bio-recognition. Genetic mutations in brain enzymes responsible for *N*-glycan attachment may cause severe neurological changes[16] and in terms of AD there is an increase in overall *N*-glycan levels of AD patients with aberrant protein *N*-glycosylation[17].

Zhang et al. performed an integrated proteomic and glycomic study to identify AD-altered glycoproteins with changes in *N*-glycosylation sites. It was one of the first, large-scale studies involving human brain *N*-glycoproteins which have revealed that 18% of human brain proteome bears *N*-glycosylated attachments. They have also confirmed the presence of *N*-glycosylation site on tau (N410 on tau 2N4R isoform) which is specific for AD brain and not found in the control. The group has also proposed that tau as cytosolic protein cannot undergo *N*-glycosylation but in AD tau reaches the enzymes in ER lumen and is being modified. Overall, this study offers a great mechanistic overview of *N*-glycosylation during AD, and uncovers 89 new *N*-glycosylated sites on 76 glycoproteins found exclusively in AD but not in control brains[18].

Losev et al speculated that *N*-glycosylation inside the Tau β-core (such as N410 and N359) vs fuzzy coat region (N167) greatly influences aggregation. Lack of *N*-glycans at N410 aggravates and on N359 alleviates AD symptoms making them good potential therapeutic targets[19].

In another later study, Zhang et al. analysed more than 10,731 *N*-glycoforms from 1184 unique *N*-glycoproteins and revealed oligomannosylation and fucosylation as two predominant types

of glycan PTMs in the human brain. Furthermore, their work uncovered a list of glycoproteins with altered paucimannosylation in AD brain. Paucimannosylation affects neuroinflammation, cell adhesion, and cell signalling during AD. Similarly, fucosylation PTM occurs at 40% of total glycoforms regulating synaptic plasticity and cognition. Moreover, 83 glycoproteins with hyperfucosylation were identified in AD[20].

Glycans play a wide range of biological functions, neuronal development, membrane organization, glycoprotein folding, and immunological recognition defence. As a result, aberrant glycosylation, modified glycan synthesis routes, or even congenital glycosylation abnormalities are associated with numerous diseases.

When discussing cognitive abilities, elevation in bisecting *N*-acetylglucosamine (GlcNAc) is found in CSF and brain of AD patients. Occurrence of bisecting GlcNAc precedes even amyloid/tau pathology and high levels of bisecting GlcNAc can prognosticate timely cognitive decline even in amyloid-/tau-negative patients[21]. Thus, the aforementioned study proposed bisecting GlcNAc to complement the ATN (amyloid, tau, neurodegeneration) classification system.

On the other hand, APP undergoes *O*-glycosylation as well and glycan positioning near the cleavage site influence protein processing. Cleavage of APP and Aβ production are surely affected by *O*-glycans. Halim et al identified 64 unique APP/ Aβ glycopeptides and their characteristic *O*-glycan attachment sites in human CSF samples and proposed further investigation regarding Tyr10 glycosylation and its importance in APP processing and subsequent amyloid accumulation[22].

A change in certain amino acids can result in improper *O*-glycosylation with APP being accumulated inside the cell. Furthermore, APP can be modified by *O*-GlcNAcylation at Thr576 to regulate its transfer to the cell surface. As a result, alpha-secretase will cleave such *O*-GlcNAcylated APP and produce nonamyloidogenic peptides of Aβ variety[23]. There a just a few studies on CSF *O*-glycosylation and they lack information on sialic acid because of the oxidation of sialic acid approach thus identifying only one subset of *O*-glycoproteome but Chen et al tried a different approach. They identified 308 intact *O*-glycopeptides and 292 unique *O*-glycoforms in CSF from healthy individuals and most of them had only single *O*-glycosite (72%) by using boronic acid strategy to enrich sialylated/non-sialylated *O*-glycopeptides. Additionally, they analysed CSF from AD and mild cognitive impairment (MCI) patients and found 366 *O*-glycopeptides were found in MCI CSF and 358 *O*-glycopeptides in AD CSF. Core 1 *O*-glycoform prevailed and there was a trend in decreased fucosylation with disease progression. Further investigation is needed given the small size of CSF samples, labor time, and expenses to find *O*-glycosylated proteolytic biomarker[24].

CHANGES IN GLYCOSYLATION DURING PARKINSON'S DISEASE

Parkinson's disease represents the second most prevalent ND and also the first among degenerative movement disorders. Some symptoms include dementia, depression, and loss of proper movement. The precise etiology is unknown and there is no viable cure at this moment. It is characterised by deterioration and loss of neurons in the *substantia nigra pars compacta* brain region. Loss of dopamine-producing neurons leads to movement abnormalities and, in some cases, cognitive decline. PD is a proteinopathy, specifically synucleinopathy where alpha-synuclein (aSyn) aggregates into Lewy bodies within affected neurons. Toxic aSyn causes degeneration and lesions and cell death further down the line[25]. The common risk factors for PD development include male sex and advanced age.

The different and unique composition of sugar moieties play a crucial role in proper neuronal function[26] and as the cells themselves are dependent on glucose, this emphasizes the important role of sugars in neuronal homeostasis. Enzymes responsible for sugar attachment are called glycosyltransferases and can produce a huge number of combinations which in turn enable many specific cell-to-cell interactions. Both AD and PD have shown to be associated with some form of defects in glycosyltransferase genes. The role of glycosylated proteins in PD has

been investigated just recently whereby it has been shown that parkin (E3 ubiquitin ligase) is involved in ubiquitination of an *O*-linked aSyn. Mutations in parkin and aSyn may result in autosomal recessive and dominant familial PD, respectively[27]. Another highly glycosylated protein, membrane dopamine transporter (DAT), regulates dopamine transport which is more efficient through *N*-glycosylated form of DAT. On the other side, during PD there is a change in glycosylation of triggering receptor expressed on myeloid cells 2 (TREM2). Changes in sialylated and fucosylated *N*-glycans diminish its antioxidant function which is closely related to PD onset[28]. Hwang et al found several overlapping proteins between the brain and CSF by gene ontology analysis. Proteins like neuroserpin and pentraxin 2 are important for proper CNS function and pentraxin 2 is highly up-regulated in PD[27]. CSF is isolated from the brain by the blood-brain barrier (BBB) but communicate with the brain interstitial fluid baring markers for neurological diseases. Transferrin (Tf) exists as two different glycan-isoforms in CSF; brain-type Tf1 and serum-type Tf2. Brain-type Tf have Glc-NAc terminated glycans and the ratio of Tf2/Tf1 can differentiate between hydrocephalus and AD. Moreover, this ratio in PD patients was higher than in the control. The same study concluded PD subgroups which differ in Tf1 and aSyn[29].

Besides brain tissue and CSF, more sensitive molecular changes are expected in urine as opposed to blood. Non-invasive sample collection makes urine an attractive and potent source of biomarkers. One mass spectrometry-based glycomic study of urine samples revealed S(6)1H5N4F1 as the most abundant *N*-glycan, both S(6)2H5N4 and N4H4F1 were present in serum and urine and ten galactosylated *N*-glycans were decreased in the urine of PD patients[30]. The same study showed PD-specific *N*-glycosylation changes in proteins RNase1 and AMBP presenting urine as a potential source of PD biomarkers.

Serum *N*-glycosylation was investigated by a novel capillary electrophoresis (CE) method combined with mass spectrometry (MS) and label-free quantification. The study revealed increased fucosylation and decreased sialylation on tri- and tetra-antennary glycans in predominantly male PD patients[31].

Furthermore, some reports point to the role of *O*-GlcNAcylation to neuronal function and development. It acts as an on/off switch for protein function and involves a binding of single sugar GlcNAc to Ser/Thr residues of proteins. Two enzymes are involved, *O*-GlcNAc-transferase and OGlcNAcase. The expression of *O*-GlcNAc-transferase modifies neuronal proteins and up to date more than 1000 proteins have been confirmed to be *O*-GlcNAcylated including pre- and postsynaptic proteins such as synapsin and bassoon[32]. *O*-GlcNAcylation regulates the toxicity of APP, Tau and aSyn. *O*-GlcNAcylation at serine 87 (S87) and threonine 72 (T72) proved to decrease aSyn aggregation but *O*-GlcNAcylation at S87 did not affect lipid vesicles interaction in contrast to phosphorylation at S87. In the case of phosphorylated S87 there are two negative charges and more electrostatic repulsion compared to *O*-GlcNAcylation at the same position thus *O*-GlcNAcylation will exhibit a smaller effect on the normal functions of aSyn. The same study highlighted the usage of synthetic approach for PTM and increasing *O*-GlcNAcylation as potential PD therapy[33]. Another study examined the *O*-GlcNAcylation of aSyn in the sense of its aggregation and protective role in PD and possibly some other protein aggregation disorders. aSyn can be *O*-GlcNAcylated at nine different positions from *in vivo* experiments on human and mice tissues. The authors of the same study proposed that aSyn with three *O*-GlcNAc at specific positions can inhibit the aggregation of unmodified protein[34] giving rise to the usage of *O*-GlcNAcylation tools and strategies. The *O*-glycome of human PD-affected tissues needs to be further examined and Wilkinson et al proposed a new microwave-assisted ammonia-based nonreductive O-glycan release with *O*-glycan analysis on hydrophilic-interaction liquid chromatography-ultraperformance liquid chromatography (HILIC-UPLC) with fluorescent labelling. That was the first study of whole *O*-glycome for healthy and PD-tissues showing male-driven sialylation increases in PD *substantia nigra* and a decrease in sulfation in the PD striatum[35]. Figure 2 shows some of the main glycosylation changes associated with Alzheimer's and Parkinson's disease.

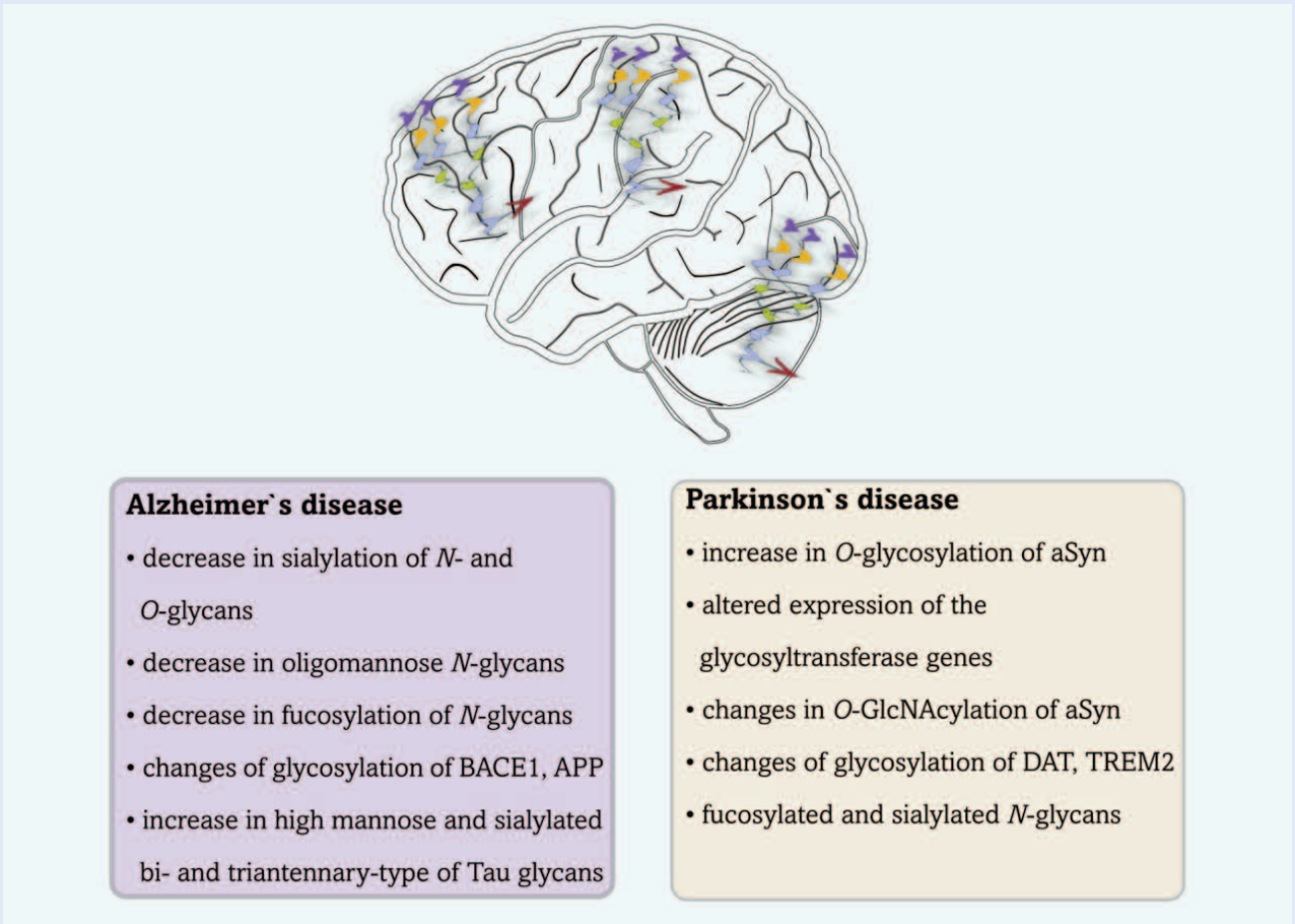

Figure 2. Glycosylation alterations in Alzheimer's and Parkinson's disease.

CONCLUSIONS

To summarize, glycans are vital for many cellular functions, cell-to-cell interactions, and immune response. Modification of glycan positions on glycoproteins of the CNS influences normal neuronal development. Nowadays, glycomic analyses discover alterations in glycan profiles through a broad range of common illnesses. Furthermore, glycan biomarkers are far more specific in diagnosing and monitoring such illnesses as opposed to some other biomarkers. Nevertheless, there are just a few glycan biomarkers approved for clinical use today and there is also a case of similar glycan alterations across different illnesses.

To improve their impact on medical practice, validated platforms at low cost are needed and their clinical utility must be substantiated in extensive, independent, and rigorous clinical research. Today we can use artificial intelligence (AI)-based glycomic analysis to facilitate such a transition. Glycomic data are vast and difficult to understand for average clinical chemist so there is a need for data processing software that is clear and easy to use.

Future glycomic studies must involve genetic and environmental risk factors in order to identify correct therapeutic strategies and offer personalized interventions given the individual's glycosylation profile in regard to their genetic composition.

Conflicts of Interest: Authors declare no conflicts of interest.

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