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A Quantitative View on Naturally Occurring Autoantibodies in Neurodegenerative Diseases

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ABSTRACT

Accumulation and aggregation of Beta-Amyloid (Aβ) and Alpha-Synuclein (α-Syn) are considered as central or even causative for the development of Alzheimer's (AD) and Parkinson's disease (PD). Therefore, the regulation of these proteins seems to be an essential aspect for prevention and is of central interest in current research aiming to find therapeutic approaches. The human immunological repertoire already contains such a regulatory system. Naturally occurring autoantibodies (nAbs) against the proteins Aβ (nAbs-Aβ) and α-Syn (nAbs-α-Syn) are part of the innate immune system and modulate the metabolism of their specific antigens including protein clearance and inhibition of aggregation. Thus, many researchers hypothesize that in the course of AD and PD, quantitative alterations of nAbs-Aβ and nAbs-α-Syn arise resulting in impaired proteastasis. Such alterations would represent promising, reliable biomarkers and indicate potential approaches for therapeutic strategies. Hence, it is not surprising that many studies dealing with nAbs-Aβ and nAbs-α-Syn titers in AD and PD patients in comparison to control participants are available in the literature. In this mini review, we summarize the current evidence. Furthermore, we critically discuss problems and future requirements for nAbs quantification when a clinical application is the overriding goal.

Introduction

The human antibody repertoire can be subdivided into conventional and naturally occurring antibodies, based on their originating B cell type. While conventional antibodies derive during life from plasma and memory B cells differentiated from B2 or marginal zone B cells after antigenic activation, naturally occurring antibodies arise in fetogenetic periods and thus are present from birth[1-4]. They are produced from B1 cells without extrinsic stimuli and T cell assistance. A special characteristic of B1 cells is the germline-closed configuration of the recombined immunoglobulin genes resulting in less hypermutated and affinity matured antibodies with lower affinities[5]. Although conventional antibodies are usually the main subject in textbooks, naturally occurring antibodies account for the greatest portion in humans[6]. Among them, a fraction shows autoreactivity and is termed naturally occurring autoantibodies (nAbs), which are mostly from the IgM and IgA, fewer from the IgG type[7]. They circulate through human body fluids, maintain physiological homeostasis, support the clearance of distinct secreted proteins and apoptotic cells, and protect from pathologically altered structures like oxidatively damaged, aggregated, and non-functional lipids and proteins[8,9]. In the following sections we want to focus on the beneficial aspects of nAbs and their potential clinical applications, especially for therapeutics and diagnostics in neurodegenerative disorders.

Clinical Potential of AD and PD Associated nAbs

The two most common neurodegenerative disorders – Alzheimer's (AD) and Parkinson's disease (PD) – are among others histopathologically characterized by extra- and intracytoplasmic protein deposits primarily consisting of the proteins beta-amyloid (Aβ) in the case of AD or alpha-synuclein (α-Syn) in the case of PD[10,11]. Albeit the accurate pathomechanism has not been fully clarified, neither for AD nor for PD, it is widely accepted that the metabolic dysregulation of the proteins has etiological significance[12]. For Aβ, especially the isoform containing 42 amino acids ($A\beta_{42}$) has been identified as minatory as it exhibits heightened hydrophobicity. The accumulation and aggregation of both, Aβ and α-Syn into small soluble oligomers and fibrils have been connected to many (in)direct neuro- and cytotoxic effects indicating their participation in disease onset and progression[13-16]. Furthermore, especially for α-Syn, a transmitting pathological mechanism is highly hypothesized within literature encompassing the spreading of aggregates from cell to cell[17].

Although AD- and PD-associated protein deposition and the resulting detrimental effects are more obvious in the central nervous system (CNS), Aβ as well as α-Syn dysregulation also occurs in the periphery. In particular, this is indicated by vascular Aβ deposition – very common in AD – as well as α-Syn pathology detectable in erythrocytes and nerve cells of the enteric system in PD patients[18-20] .

Thus, since many years and considering all aspects, researchers follow the idea of an early and preventive intervention counteracting protein dysregulation, aggregation, and propagation as it is believed to modify disease progression in AD, PD, and other proteinopathies. Here, $A\beta_{42}$ and/or α-Syn specific antibody treatment could represent a promising therapeutic strategy due to a targeted modulation of the metabolism of their antigen. Such approaches have already been tested in diverse *in-vitro* and *in-vivo* experiments and revealed positive effects including reduced protein deposits and decreased neurodegeneration, however, failed in phase three at the latest when tested in the clinical state of AD[21-25].

It is an interesting fact that antibodies that maintain tissue homeostasis and proteostasis are already present in humans[26,27]. In child- and adulthood as well as in health and disease, nAbs recognizing the proteins $A\beta_{42}$ (nAbs-$A\beta_{42}$) and α-Syn (nAbs-α-Syn) but also further proteins that become misfolded in disease cases (such as prion and tau protein) are detectable in the serum and cerebrospinal fluid (CSF) suggesting the presence of innate protective mechanisms[2,27-32]. Quantitative or qualitative alterations of nAbs could impair their normal functions, worsen the protection system, and thus represent causal or supporting factors for the development of AD and PD. Especially quantitative alterations, namely changed titers, may act as biomarkers in clinical applications and illustrate restoring of $A\beta_{42}$ and α-Syn specific antibodies as a promising therapeutic strategy. It is not surprising that a number of studies investigating titers of nAbs-$A\beta_{42}$/α-Syn have already been published in the past and will be following discussed.

nAbs-Aβ titers

A large body of literature exists harboring inconsistent, even contrasting data regarding nAbs-Aβ titers in AD patients. In a comprehensive study by Britschgi et al. (2009), nAbs-Aβ recognizing various natures of its antigen could be detected within serum and CSF samples of AD patients and nondemented control subjects of different ages[33]. Using ELISA technique and antigen microarrays the highest reactivity was uncovered for aggregated and posttranslationally modified $A\beta_{40}$ and $A\beta_{42}$ forms. Between AD patients and controls, no significant differences of nAbs-$A\beta_{42}$ plasma titers against oligomeric or monomeric protein forms were identified. However, comparing mildly to moderately and severely affected AD patients, the latter group showed in one sample set significantly decreased nAbs-$A\beta_{42}$ plasma titers suggesting a role in disease progression. Unchanged nAbs-Aβ titers in AD patients were also verified in further studies examining nAbs-$A\beta_{40}$ and -$A\beta_{42}$[26,28]. Marcello and coworkers (2011) revealed similar results even the experimental setup was limited to IgM autoantibodies[34].

Although they were not able to detect altered nAbs-$A\beta_{42}$ titers, plasma level of nAbs recognizing N-truncated Aβ consisting of the amino acid sequence three to seven and a modified pyroglutamate ($_{pGlu}A\beta_{3-7}$) was significantly decreased in patients suffering from AD. Such peptides have often been detected in the brains of AD patients and were shown to strengthen the aggregation process[35]. Three further studies identified significantly changed blood titers of nAbs against distinct Aβ forms using ELISA techniques. Qu et al. (2014) demonstrated reduced serum titers of nAbs recognizing $A\beta_{1-15}$ but unchanged nAbs-Aβ against soluble and aggregated full-length peptides in AD patients[36]. Moir and colleagues (2005) found decreased nAbs levels against redox-modified $A\beta_{40}$ and again unchanged nAbs-$A\beta_{40}$ in AD patients[37]. In contrast, Gruden and coworkers (2007) detected significantly increased nAbs portions in female AD patients, namely autoantibodies against oligomeric Aβ consisting of the amino acids 25 to 35[38]. This peptide fragment – inter alia detectable in AD brains – is often used as a model system as it maintains the neurotoxic properties of Aβ with the simultaneous option of better controlling the aggregation process[39]. Elevated titers of unbound autoantibodies recognizing these eleven amino acids containing and most toxic sequence may be a hint

for decreased but necessary antigen binding and thus regulation of $A\beta_{25-35}$ what may result in disease onset or progression. The exclusive investigation of such antibodies has the ability to be a critical step and advantage as all further Aβ targeting nAbs with various epitopes could overlap a specific effect of the indeed crucial sequence.

As mentioned above, there are also contrary data available including studies that revealed increased or decreased nAbs portions recognizing the full-length peptide $A\beta_{42}$. On the one hand, some ELISA as well as radiolabeled immuno-precipitation based experiments have uncovered lowered nAbs-$A\beta_{42}$ serum titers in AD patients when compared to healthy or cognitively unremarkable subjects[40,41]. On the other hand, Nath and colleagues (2003) determined elevated nAbs serum titers against soluble and pre-aggregated $A\beta_{42}$ in AD patients[42]. In the same study, CSF samples have also been investigated, however, only three of the AD patients – but interestingly the severely affected ones – and none of the controls contained detectable amounts of nAbs-$A\beta_{42}$. Since CSF data are generally less frequent than serum data –it encompasses a more invasive clinical method – only a few more studies dealing with variable nAbs structures have been published. For example, Du and colleagues (2001) revealed decreased nAbs-$A\beta_{40}$ titers in CSF of AD patients using ELISA[43]. Within a second study published by Maftei et al. (2013) the same method was applied to analyze nAbs/$A\beta_{42}$ immune complexes. Here, a significantly increased portion in the CSF of people suffering from AD was detected[44]. Although the studies investigated nAbs targeting different antigenic structures, similar effects can underlie both observations as decreased free nAbs titers can be the result of increased Aβ bound nAbs (immune complexes).

nAbs-α-Syn titers

Conflicting results of nAbs-α-Syn titers are also available in literature about PD. Two exemplary studies using ELISA technique and dealing with serum and CSF nAbs-α-Syn demonstrate significantly elevated autoantibody titers in patients suffering from PD[45,46]. While Horvath and colleagues (2017) found differences between PD patients and control subjects in both, CSF and serum, Akhtar and coworkers (2018) detected only increased nAbs levels in the CSF. This is of particular interest as Horvath revealed a stronger effect size for changed serum titers and the loss of significant differences of CSF titers when separating the patient cohort into mild and moderate affected individuals. In line with these observations, Gruden et al. (2011) as well as Yanamandra et al. (2011) performed serum ELISA experiments and surface plasmon resonance spectroscopy with monomeric and aggregated α-Syn, identified increased nAbs-α-Syn titers against both protein forms in PD

Table 1. NAbs Serum/Plasma and CSF titers in AD patients compared to control subjects. Summary of exemplified studies investigating changed serum/plasma and CSF concentration of nAbs-Aβ. For each study and if information were available (n.a. = not available), *p*-value of the statistical analysis, age- (AM), gender-matching (GM), and Mini-Mental-State-Examination Score of the study participants as well as the used method are shown. *No comparison possible as nAbs-Aβ42 were only detectable in the CSF of severely affected AD patients.

Serum/plasma concentration						CSF concentration					
titer	**nAbs**	**reference**	***p*-value**	**AM/GM/ MMSE**	**method**	**titer**	**nAbs**	**reference**	***p*-value**	**AM/GM/ MMSE**	**method**
						only detectable in severe cases*		42	n.a.	+/+/17 vs 29	ELISA
Increased in AD	nAbs-$A\beta_{42}$	42	0.005	+/+/17 vs 29	ELISA	**Increased in AD**	bound nAbs-$A\beta_{42}$	44	0.03	+/+/20 vs 29	ELISA
	nAbs-$A\beta_{25-35}$	38	< 0.01	+/+/15 vs 27	ELISA						
	bound nAbs-$A\beta_{42}$	44	0.03	+/+/20 vs 29	ELISA						
unchanged	nAbs-$A\beta_{42}$	26	0.85	+/+/n.a.	ELISA	**unchanged**					
		28	0.056	+/+/17 vs 29	ELISA						
		33	n.a.	+/-/23 vs 30	ELISA						
		34	n.a.	+/+/17 vs n.a.	ELISA						
		36	n.a.	+/+/20 vs 29	ELISA Dot Blot						
	nAbs-$A\beta_{40}$	28	0.19	+/+/17 vs 29	ELISA						
		37	n.a.	+/+/n.a.	ELISA						
Decreased in AD	nAbs-$A\beta_{42}$	40	< 0.02	+/n.a./n.a.	ELISA	**Decreased in AD**	nAbs-$A\beta_{40}$	43	0.02	+/n.a./n.a.	ELISA
		41	0.001	-/-/21 vs 29	IP						
	nAbs-$_{pGlu}A\beta_{3-7}$	34	0.021	+/+/17 vs n.a.	ELISA						
	nAbs-$A\beta_{1-15}$	36	0.02 0.0008	+/+/20 vs 29	ELISA Dot Blot						
	nAbs-$_{red}A\beta_{40}$	37	0.018	+/+/n.a.	ELISA						

Table 2. NAbs Serum/Plasma and CSF titers in PD patients compared to control subjects. Summary of exemplified studies investigating changed serum/plasma and CSF concentration of nAbs-α-Syn. For each study and if information were available (n.a. = not available), *p*-value of the statistical analysis, age- (AM), gender-matching (GM), and Hoehn & Yahr Scale (H&Y; median or *mean) of the study participants as well as the used method are shown.

Serum/plasma concentration						CSF concentration					
titer	**nAbs**	**reference**	***p*-value**	**AM/GM/ H&Y***	**method**	**titer**	**nAbs**	**reference**	***p*-value**	**AM/GM/ H&Y***	**method**
Increased in PD	nAbs-α-Syn	[46]	< 0.05	n.a./+/2	ELISA	**Increased in PD**	nAbs-α-Syn	[45]	0.016	+/-/3	ELISA
		[47]	< 0.01	+/+/2.1*	ELISA			[46]	< 0.05	n.a./+/2	ELISA
		[48]	< 0.007 < 0.001	n.a.	ELISA/WB SPR						
		[49]	< 0.001	+/+/1	ELISA						
unchanged	nAbs-α-Syn	[45]	0.19	+/+/3	ELISA	**unchanged**	nAbs-α-Syn				
		[51]	0.5	-/-/2	ELISA						
		[52]	0.69	+/+/1.3*	ELISA						
		[53]	n.a.	-/-/2.4	ELISA/WB						
Decreased in PD	nAbs-α-Syn	[30]	< 0.05	+/+/2	ELISA	**Decreased in PD**	nAbs-α-Syn				
		[50]	0.005	-/-/2	ELISA						
	bound nAbs-α-Syn	[50]	0.042	-/-/2	ELISA						

patients, and revealed an attenuated effect with increasing disease duration[47,48]. In a further publication, Shalash and colleagues (2017) expanded the comparison of nAbs-α-Syn serum levels to PD patients, controls, and AD patients and again detected an elevated portion in the PD cohort[49].

These studies provide the impression of increased nAbs-α-Syn titers in especially early stages of PD suggesting disease duration as a critical factor for such findings. However, contrasting hints with both, short- and long-term affected PD patients and correspondent differences in age and disease severity exist as well. Besong-Agbo et al. (2013) as well as Brudek et al. (2017) demonstrated significantly decreased nAbs-α-Syn serum titers in the plasma and serum of PD patients[30,50]. Additionally, in the latter paper PD patients were also shown to exhibit lower titers of α-Syn/nAbs immune complexes resulting in a decreased total nAbs-α-Syn fraction.

As opposed to the already outlined studies, Maetzler and coworkers published in 2014 the presence of comparable nAbs-α-Syn serum levels in PD and healthy persons[51]. Such unchanged nAbs-α-Syn titers have also been confirmed in two further publications investigating serum or plasma samples of PD patients and healthy controls[52,53]. Here, especially the publication by Smith et al. (2012) is of great interest as they additionally summarize and demonstrate conflicting studies regarding α-Syn protein[52].

Conclusion and Future Perspectives

For the development of reliable diagnostic markers but also as therapeutic targets, the determination of nAbs-Aβ and nAbs-α-Syn titers are of certain interest in AD and PD research. However, as mentioned above, in both cases many different and contrasting results have been published in the last years including increased, decreased, and unchanged nAbs levels in affected persons. Not until this drawback is eliminated, the application of nAbs titers has a chance to receive clinical significance.

A number of reasons might be responsible for the great variance and contrary data of altered nAbs titer in AD and PD. In many cases, typical parameters like incorrect diagnoses of the included participants, small sample sizes and technical limitations are cited as causes. However, it is largely impossible that the contrasting findings are a method-based effect as in almost all cases ELISA technique was applied to determine nAbs titers. Within the experimental setups, differences in the sample preparation are more likely responsible for contrary results. The utilization of different body fluids including plasma, serum, or CSF harbors also risks for fluctuations like a previous antibody purification. Additionally, a number of further variabilities may account for inconsistent data on nAbs-Aβ and nAbs-α-Syn titers. Here, two main factors represent 1) the choice of the incorporated participants and 2) the antigen that is used to determine its corresponding nAbs titer. Control probands often range from younger healthy controls to age-matched patients without disease-associated symptoms[36,51]. Furthermore, patient cohorts often differ in disease severity and duration. Such variabilities result in different physical and immunological conditions and may significantly influence nAbs titer analyses. Especially, the latter aspect is of utmost importance as directly age dependent and indirectly medication mediated effects on antibody titers have been identified[54-56]. This should not be disregarded even though authors including individuals without age-matching usually argue that their cohorts do not show positive correlation between age and antibody titers.

Different protein states can also greatly influence results of ELISA and related assays. The choice between recombinant or synthetic peptides including the expression system with its particular posttranslational modifications (PTMs), full-length or peptide fragments, and monomeric or oligomeric structures probably impact antigen binding. Regarding the last aspect, especially nAbs-Aβ analyses exhibit great potential for variability as Aβ shows a naturally high aggregation property that complicates the control of its exact state e.g. during the ELISA coating process[57].

Additionally, most of the performed studies feature limitation in their experimental setup in general as their analyses are restricted to either the antigen bound or the unbound nAbs fraction. However, to draw a comprehensive picture about the immunological status in AD and PD, information about both conditions as well as the antigen concentration are important to be considered.

Overall, for the clinical application of quantitative analyses of nAbs-Aβ and nAbs-α-Syn, the primary future goal has to be the elimination of the already described major drawbacks within the experimental setups. This includes both, the possible causes of failure and variability as well as the consideration of antigen/nAbs immune complexes and free circulating nAbs. Here, a standardization of the experimental setup with the formulation of guidelines within a consortium would be helpful to decreased variabilities across studies and laboratories. A similar procedure has been applied for biomarkers in AD, called Global Biomarker Standardization Consortium (GBSC)[58].

If nAbs-Aβ and nAbs-α-Syn quantification will be reliably and reproducibly executed in future studies, thresholds for concentration can be set for its application as a diagnostic biomarker provided that actual differences between healthy and diseased people are present. Furthermore, such findings would demonstrate the necessity of an antibody targeted therapy. On the other hand, quantitative differences do not represent the only possible disease-causing alteration as especially qualitative properties like avidity, immune activation, or PTMs are also crucial properties of nAbs.

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