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Lowered Serum Amyloid-$\beta_{1\text{-}42}$ Autoantibodies in Individuals with Lifetime Depression

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Abstract. Reduced levels of naturally occurring autoantibodies against amyloid-β (Aβ) have been described in Alzheimer's disease (AD). Lifetime depression doubles the risk of AD, thus these autoantibodies may also be reduced in this group. We measured serum IgG autoantibody titers against $A\beta_{1\text{-}42}$, S100b and α-synuclein in 214 individuals with depression and 419 controls. Titers against $A\beta_{1\text{-}42}$ were lower in individuals with lifetime depression (5544.6 ± 389.3) compared to controls (7208.7 ± 482.4; $p = 0.048$). Titers against S100b and α-synuclein were comparable between the cohorts. These data suggest an AD-like impairment of the humoral immune response in a relevant proportion of individuals with depression.

Keywords: Alzheimer's disease, autoimmune disease, depression, risk factor

INTRODUCTION

There is great research emphasis on the search for blood-borne biomarkers indicative of Alzheimer's disease (AD) pathology, but to date, most attempts have had only limited success [1]. Current research supports a direct association between the occurrence of depression throughout life and AD [2], and occurrence of depression has consistently been associated with a more than two-fold increase in risk of developing dementia [2–4]. Proposed biological mechanisms linking depression to dementia include vascular disease, glucocorticoid metabolism, hippocampal atrophy, and neurotransmitter changes, but also proinflammatory changes and increased deposition of amyloid-β (Aβ) in the brain. In more detail, excessive secretion of IL-6, an increased CD4/CD8 ratio, an overall leukocytosis with a relative neutrophilia and relative lymphopenia, and changes of lymphocyte proliferative response to mitogen have been shown to occur regularly in depression [5] and are closely linked with multiple neurodegenerative pathways such as reduced synaptic plasticity and hippocampal neurogenesis, and consecutive

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occurrence of cognitive deficits and dementia [6]. According to *in vitro* and *in vivo* studies, these changes may also contribute to enhanced Aβ production [7–9], which is also closely related to AD. Another important defense mechanism against toxic metabolic products (such as Aβ) is the autoimmune system. Autoantibodies against Aβ have been shown to be surprisingly numerous in human sera [10], and there is increasing evidence that the autoimmune system is impaired in AD. In more detail, antibody reactivity specific for Aβ seems to be declined, accompanied by reduced blood levels of this autoantibody [11, 12].

As Aβ pathology starts in AD years or even decades before clinical symptoms are evident [13], we hypothesized that at least a small proportion of subjects with lifetime depression (who may then be at particular risk for future AD) may also have reduced naturally occurring autoantibodies against $A\beta_{1\text{-}42}$. We measured serum titers of this autoantibody in a considerably large and well-defined elderly cohort of depressed individuals, and compared these values with those of a cohort without history of depression. For control purposes, autoantibody titers against α-synuclein and S100b were determined.

SUBJECTS AND METHODS

Subjects

In 2009 and 2010, 715 subjects aged 50–85 years participated in the baseline assessment of the Tübinger evaluation of Risk factors for Early detection of Neurodegenerative Disorders (TREND) study, a 20-year prospective 2-year follow-up study aiming to define screening batteries for AD and Parkinson's disease (PD). The study has a particular focus on subjects with risk factors for AD and PD, namely hyposmia, depression, and rapid-eye-movement (REM) sleep behavior disorder (RBD). Out of the cohort, 43 subjects were not included into this analysis because they had mild cognitive impairment (MCI) which is a pre-stage of AD, defined by z-scores < -1.5 in vital cognitive areas of the German version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery [14] and a Mini-Mental State Examination score (MMSE) <28. Five subjects were excluded because they fulfilled diagnostic criteria for PD according to UK Brain Bank Society criteria [14]. Of the remaining 667 subjects, 635 donated blood for this study, and serum samples were processed. Two samples could not be used due to technical issues, thus biochemical values of a total of 633 individuals were analyzed.

"Lifetime depression" was defined as the occurrence of at least one major depressive episode in the lifetime assessed by history-taking in the participants, review of all medical history, and evaluation of current mood status according to International Classification of Diseases (ICD)-10 and Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria, as well as by use of the Beck's Depression Inventory (BDI) and the Centre for Epidemiological Studies Depression Scale (CES-D). The age that served as cut-off value for the differentiation between earlier-life and late-life depression was 60 years.

The local ethics committee approved the study, and written informed consent was obtained from all participants.

Blood sampling

Blood collection and processing of serum was performed according to standardized protocols [15]. In brief, samples were cooled after collection, transferred to the lab within 6 hours, centrifuged, and stored at –70°C until use.

ELISA

The detailed process of ELISA development and measurement procedures were conducted by Mediagnost and described previously [16]. In brief, high binding microtiter plates were coated with the following commercially available proteins/peptides: recombinant $A\beta_{1\text{-}42}$ expressed in E. coli (recombinant $A\beta_{1\text{-}42}$ may be superior to synthetic $A\beta_{1\text{-}42}$ for studying Aβ aggregation-related mechanisms [17]), recombinant scrambled $A\beta_{1\text{-}40}$ expressed in E. coli (for control purposes, amino acid sequence KVKGLIDGAHIGDLVYEF MASNSFREGVGAGHVHVAQVEF), recombinant α-synuclein (rPeptide, Bogart, GA, US), or purified native human S100b (Cell Sciences, Canton, US). Non-specific binding was blocked by BSA. Plates were incubated with human sera. The biotinylated detection antibody and horseradish-peroxidase streptavidin-conjugate were then added sequentially. After the addition of substrate and stop solutions, optical densities of the reactions were measured at 450 nm. For quantication, an internal serum standard was applied and arbitrary titer units were calculated. All samples were measured within the same test kit lot. Inter-assay variability was 12, 6, 13 and 5% for $A\beta_{1\text{-}42}$, scrambled $A\beta_{1\text{-}40}$, S100b, and α-synuclein, respectively.

Data analysis

Demographic and clinical data were analyzed with Student's *t*-test (presented as mean ± SEM) or Fishers exact test. To omit bias due to background noise of the ELISA method, titers of scrambled $A\beta_{1-40}$ autoantibody titers were subtracted from individual autoantibody titers. Autoantibody titers below threshold were set as half of the lowest value detected [16]. Since age and gender distribution were significantly different between cohorts and the TREND study also included subjects with hyposmia and/or RBD, we corrected biochemical data for all the above mentioned confounders by use of a logistic regression model, and assessed significance of each model effect by the likelihood ratio. Differences were considered significant at $p < 0.05$. Receiver-operating characteristic (ROC) analysis was used to compare accuracy of $A\beta_{1-42}$ autoantibody serum titers in differentiating between individuals with earlier-life depression and controls, and individuals with late-life depression and controls. For analysis, JMP software was used (version 9.0.0, SAS).

RESULTS

Detailed information is provided in Table 1 and Fig. 1. Of the 633 individuals included in this study, 214 were classified as having a history of depression, and 419 individuals had no history of depression and no actual depression. No significant differences between the cohorts were detectable regarding MMSE score, occurrence of hyposmia and RBD, and proportion of individuals with a positive history of dementia.

Autoantibody serum titers against $A\beta_{1-42}$ were lower in subjects with lifetime depression compared to those without lifetime depression ($p = 0.048$). Exclusion of all individuals with RBD ($p = 0.02$) and matching the control cohort with the depression cohort with regard to age ($p = 0.02$) did not relevantly influence this result.

Autoantibody serum titers against scrambled $A\beta_{1-40}$ (not shown), α-synuclein, and S100b were comparable between the groups.

Using autoantibody serum titers against $A\beta_{1-42}$ for differentiation between subjects with earlier-life depression and controls, the ROC analysis yielded an accuracy of 0.68. The respective ROC curve for differentiation between subjects with late-life depression and controls yielded a comparable accuracy of 0.72.

Autoantibody titers of individuals who were depressed at blood sampling ($n = 38$) compared to titers of individuals who were depressed at an earlier stage of their life ($n = 176$) did not significantly differ ($A\beta_{1-42}$, $p = 0.69$; α-synuclein, $p = 0.44$; S100b, $p = 0.87$). Eighty-five patients provided detailed data about age at first episode of depression and frequency of depressive episodes. Of those, 49 had one episode and 36 had more than one episode during lifetime. No relevant associations were found between these two groups with regard to autoantibody titers against $A\beta_{1-42}$ ($p = 0.54$), α-synuclein ($p = 0.48$), and S100b ($p = 0.99$), respectively. Similarly, no relevant correlations were found between age at first episode and respective autoantibody titers against $A\beta_{1-42}$ (rho = –0.09 $p = 0.19$), α-synuclein (rho = –0.03, $p = 0.63$), and S100b (rho = –0.07, $p = 0.28$).

DISCUSSION

Using synthetic unmodified Aβ peptides, a number of studies demonstrated the presence of naturally occurring autoantibodies against monomeric [11, 18] and oligomeric forms [19, 20] of Aβ in humans, and most of the studies showed reduced levels in AD compared to controls [18, 19]. This latter difference may even be pronounced when modified [12, 19] or, like in this study, recombinant [12, 17] Aβ peptides are used. Immunoglobulins purified from blood of AD patients are able to hydrolyze Aβ peptides at a considerable rate [21], indicating that rather a reduced activity than a dysfunctional state of the autoimmune system may be relevant for AD occurrence or progression. This hypothesis is corroborated by results of a recent study which described an indirect correlation between serum autoantibody titers against Aβ oligomers, and disease progression in AD [22]. Indeed, immunization against Aβ peptides leads to autoantibody distribution in the blood and CNS [23, 24], and reduces plaque load in transgenic mouse models of AD [24], and in AD [25].

Here we show reduced autoantibody titers against $A\beta_{1-42}$ in a large cohort of subjects with a risk factor of AD, namely lifetime depression. This finding confirms and extends previous studies showing that depression influences the immune system, e.g., through the hypothalamic-pituitary-adrenal axis [26]. According to our data, this effect seems to be specific: only autoantibody titers against $A\beta_{1-42}$ but not other autoantibody titers associated with neuronal (α-synuclein) and/or glial (S100b) changes were significantly

Table 1
Demographic, clinical, and biochemical data

	Healthy controls	Lifetime depression		*p*-value
		Earlier-life	*Late-life*	
Individuals (% females)	419 (49.2)	214 (64.5)		<0.001
		169 (66.7)	42 (52.1)	
Age [years]	64.5 ± 0.3	62.0 ± 0.5		<0.001
		60.3 ± 0.5	69.0 ± 0.6	
MMSE (0–30)	29.0 ± 0.1	29.0 ± 0.1		0.81
		29.0 ± 0.1	29.0 ± 0.1	
BDI (0–63)	6.2 ± 0.2	11.9 ± 0.6		<0.001
		11.8 ± 0.6	11.7 ± 1.3	
Hyposmia, *n* (%)	200 (47.7)	94 (43.9)		0.25
		68 (40.9)	23 (54.8)	
RBD, *n* (%)	77 (18.4)	36 (16.8)		0.63
		25 (15.1)	9 (21.4)	
Positive family history of dementia, *n* (%)	121 (31.8)	74 (39.6)		0.07
		57 (40.1)	14 (34.1)	
Elevated blood pressure, *n* (%)	182 (33.3)	82 (40.4)		0.09
		60 (38.2)	20 (50.0)	
Hypercholesterolemia, *n* (%)	154 (45.0)	114 (61.6)		<0.001
		95 (65.1)	16 (47.1)	
Body mass index ≥26, *n* (%)	151 (36.8)	82 (39.4)		0.53
		62 (38.5)	17 (40.5)	
At least one *ApoE ε4* allele [%]	92 (22.5)	47 (22.5)		0.99
		38 (23.3)	9 (22.5)	
Current smoking, *n* (%)	34 (8.2)	44 (20.9)		<0.001
		38 (23.3)	4 (10.0)	
Family status married, yes (%)	317 (80.1)	129 (69.9)		0.01
		100 (68.9)	26 (68.4)	
Children, yes (%)	331 (83.0)	160 (82.9)		0.98
		122 (80.8)	34 (89.5)	
Years of education	14.6 ± 0.2	14.7 ± 0.3		0.81
		14.7 ± 0.3	14.9 ± 0.5	
Regular physical exercise >1 h per week	73 (18.3)	50 (24.9)		0.07
		40 (25.8)	9 (22.0)	
$A\beta_{1\text{-}42}$ autoantibodies [titer]	7208.7 ± 482.4	5544.6 ± 389.3		0.048
		5582.9 ± 453.4	5326.1 ± 840.0	
α-synuclein autoantibodies [titer]	2613.5 ± 121.6	2845.6 ± 370.3		0.56
		2959.2 ± 468.4	2528.2 ± 358.6	
S100b autoantibodies [titer]	27006.7 ± 1364.9	26574.6 ± 1341.9		0.70
		27861.5 ± 1661.5	21590.2 ± 1621.4	

Data are presented with the mean and standard error of the mean, or with percentage of total. *p*-values of demographic and clinical data were determined using Students *t*-test or Fisher's exact test. Serum autoantibody titers were evaluated with a logistic regression model to correct for age, gender, occurrence of REM sleep behavior disorder (RBD), and hyposmia. Note that six individuals with lifetime depression could not be assigned to the earlier or late life depression subgroup due to missing data. This leads to "incorrect" sum values in the respective fields (hyposmia, RBD, positive family history of dementia). *ApoE*, Apolipoprotein E; BDI, Beck's Depression Inventory; MMSE, Mini-Mental State Examination.

different between individuals with lifetime depression and controls. In our view, this latter finding may be best explained rather by a "physiological" increase of naturally occurring autoantibodies against $A\beta_{1\text{-}42}$ during healthy aging (and a lack of this adaptive process in subjects with lifetime depression), than by a specific decrease of adaptation in subjects with depression(s) during their lives. Interestingly, there is some evidence that, during the course of AD, the reaction of the immune system may be biphasic, with rising autoantibody titers during the mild to moderate stage, and falling titers during more advanced stages [22].

Some authors differentiated earlier-life depression and late-life depression based on the assumption that the former may be more closely associated to risk factors for dementia, and the latter may rather display a prodromal stage of dementia [2], thus this differentiation could provide complementary information. This differentiation does not add relevant information in our study. In addition, number of depressive episodes and the age at the first episode were not relevantly associated with $A\beta_{1\text{-}42}$ autoantibody titers, arguing against a "cumulative" interaction effect between these autoantibodies and the clinical phenotype.

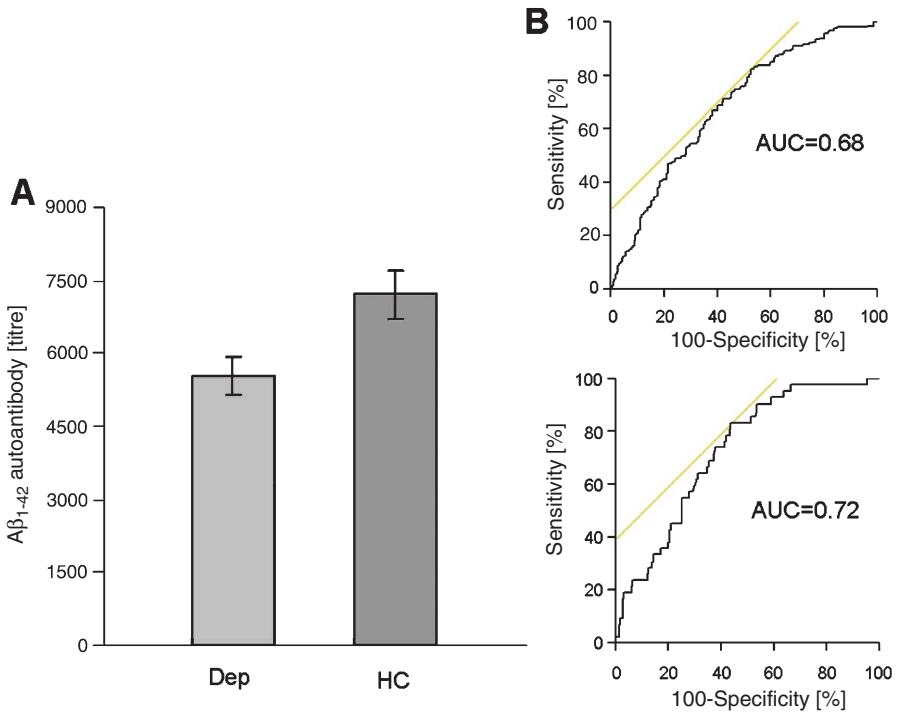

Fig. 1. Serum Aβ1-42 autoantibody titers in subjects with and without lifetime depression. A) Serum autoantibody titers against Aβ1-42 are lower in subjects with lifetime depression than in those without lifetime depression. B) Receiver operating curves demonstrate comparable accuracies of serum Aβ1-42 autoantibody titers for the differentiation between earlier-life (upper part) and late-life depression.

In conclusion, lowered autoantibody serum titers against Aβ1-42 in subjects with lifetime depression argue for relatively specific impairment of the humoral immune system in (a proportion of) these individuals. Follow-up studies of this cohort will enable us to test this hypothesis, and to clarify if this biochemical marker is indeed a prodromal sign of AD.

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