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SHORT COMMUNICATION

Seroprevalence of N-methyl-D-aspartate glutamate receptor (NMDA-R) autoantibodies in aging subjects without neuropsychiatric disorders and in dementia patients

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Abstract N-methyl-D-aspartate glutamate receptors (NMDA-R) play a key role in learning and memory. Therefore, they may be involved in the pathophysiology of dementia. NMDA-R autoantibodies directed against the NR1a subunit of the NMDA-R, which were first identified as a specific marker for a severe form of encephalitis, cause a decrease in NMDA-Rs, resulting in cognitive impairment and psychosis. We examined the prevalence of NR1a NMDA-R autoantibodies in the serum and cerebrospinal fluid (CSF) of 24 patients with Alzheimer's disease (AD), 20 patients with subcortical ischemic vascular dementia (SIVD), and 274 volunteers without neuropsychiatric disorder. The latter cases showed an association of seropositivity with age. Notably, the overall seroprevalence was not statistically different between dementia patients and matched controls. Further analysis of the patient samples showed that four patients with AD and three patients with SIVD had positive NMDA-R IgM, IgG, and/or IgA autoantibody titers in serum. These patients suffered from psychosis (with the exception of one case). CSF samples were negative for NMDA-R autoantibodies. We conclude that the seroprevalence of NMDA-R-directed autoantibodies is age-related. It has to be clarified by larger studies whether NMDA-R autoantibodies in peripheral blood may predispose patients with AD and SIVD to susceptibility for psychotic episodes if disturbances of blood–brain-barrier integrity occur.

Keywords NMDA-receptor autoantibodies · Aging · Alzheimer's disease (AD) · Subcortical ischemic vascular dementia (SIVD) · Psychosis

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Introduction

The excitatory glutamatergic neuronal system plays a key role in the central nervous system (CNS). It is related to learning and memory function and its dysregulation contributes to neuropsychiatric disorders such as dementia [1]. The N-methyl-D-aspartate glutamate (NMDA) receptor belongs to the group of ionotropic glutamate receptors [2] and is important in neuronal development and physiology—apart from its implications in CNS diseases [3].

Alzheimer's disease (AD) and subcortical ischemic vascular dementia (SIVD) are the most frequent disorders associated with slow cognitive impairment. According to the amyloid hypothesis, an excessive amount of beta amyloid (Aβ) [4] and its downstream effector tau [5] is

responsible for the cognitive impairment in AD. Since NMDA-Rs are involved in learning and memory, the NMDA-R hypofunction hypothesis is based on a decreased expression of NMDA-R mRNA in selected regions of AD brains [6]. SIVD is caused by a cerebral microangiopathy [7, 8]. Although the etiologies of AD and SIVD differ, vascular risk factors, such as hypertension, hyperlipidemia, diabetes mellitus, and metabolic syndrome, predispose to both diseases and may be associated with blood–brain-barrier (BBB) impairment [9, 10].

The importance of inflammation was shown in SIVD [11] and AD [12–15]. It has been suggested that an increased production of quinolinic acid (QUIN, an endogenous NMDA-R agonist with neurotoxic properties) could be involved in the pathogenesis of AD [16] since activated microglia surrounding the amyloid plaques are highly immunoreactive for QUIN [17]. Other immune processes such as the production of anti-NMDA-receptor autoantibodies (NMDA-R Abs) could also be involved in the pathophysiology of dementias, particularly in those cases who suffer from psychosis. This idea was driven by previous studies on NMDA-R encephalitis, acutely psychotic schizophrenia patients, and the increased seroprevalence of NMDA-R Abs with aging [18–20]. NMDA-R antibodies (Abs) against the NR1a subunit of the NMDA-R were initially described in NMDA-R encephalitis, a disease picture that is associated with memory disturbances and psychosis [19]. NMDA-R Abs cause a selective and reversible decrease in NMDA-R surface density and synaptic localization that correlates with the autoantibody titer. An increased prevalence of NMDA-R Abs has also been described in the blood of acutely psychotic schizophrenia patients [18]. Moreover, Hammer et al. [20] have reported an age-related increase in NMDA-R Abs in the general population. We have re-assessed this recently described effect of aging in control samples from subjects without neuropsychiatric disorders (aged 0–90 years). Moreover, we investigated the distribution of NMDA-R Abs in patients with AD and SIVD as well as in matched controls, hypothesizing an association of NMDA-R Abs with psychosis in dementia.

Materials and methods

The study was performed in accordance with German laws, the Declaration of Helsinki, and the guidelines of the local institutional review board. The dementia patients were diagnosed according to DSM-IV criteria [21]. Psychiatric symptoms were described by the Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie system. Twenty-four AD patients (17 female and 7 male; age 67–89 years) and 20 SIVD patients (12 females and 8 males; 56–87 years) were included in the study. Patients were first diagnosed at the University of Magdeburg with AD or SIVD according to the following features: MRT of AD patients showed bitemporal and/or hippocampal atrophy and SIVD patients had cerebral microangiopathy without bitemporal and hippocampal atrophy. Magnetic resonance imaging of the brain, electroencephalography, and routine blood tests was performed. The diagnosis was further confirmed by cerebrospinal fluid/CSF criteria (tau, Aβ). Patients with a history of severe other disorders were excluded. The mini-mental status test of patients ranged between 2 and 27 (detailed demographic data and diagnostic test results of dementia patients are shown in the Supplementary table). Control sera were obtained from 274 healthy volunteers (aged 0–90 years) without neuropsychiatric disorders and no history of brain trauma or birth complications (recruited at the University of Magdeburg and Euroimmune Lübeck).

Antibody testing (NR1a NMDA-R Abs) of all samples was performed using a standardized laboratory technology as previously described [22–24]. The diagnostic group differences regarding the distribution of cases with positive antibody titers were calculated by Fisher's exact test (with Bonferroni correction for separate analyses of IgA, IgG, IgM antibody classes). Statistical significance was defined as $p < 0.05$ (Bold values in Tables 1 and 2).

Results

Age distribution of serum NMDA-R Abs in healthy controls

As summarized in Table 1, NMDA-R Abs were undetectable in serum from young healthy volunteers (younger than 20 years), but they were found in 6.2–12.8 % of subjects without neuropsychiatric disorders aged over 60 years. IgA NMDA-R Abs were observed in 1.5–5.1 % of the samples from controls aged 71–90 years. IgG antibodies were absent in controls, while IgM NMDA-R Abs were detected in 6.2–10.3 % of all serum samples obtained from healthy volunteers aged over 60 years, no volunteer suffered from a psychotic state. Thus, overall seropositivity for NMDA-R Abs was associated with aging but not with the presence of psychosis in the control group ($p = 0.016$; Table 1).

Prevalence of serum NMDA-R Abs in dementia patients compared to age-matched controls

Although only 7.1 % of age-matched healthy volunteers, but about 16 % of demented patients had positive NMDA-R Abs from any subtype (Table 2), there was no statistical significance between these diagnostic groups ($p = 0.134$).

Table 1 Age distribution of serum NMDA-R Abs in healthy controls

NMDA-R Abs	Age group					
	0–10 years $N = 44$	11–20 years $N = 32$	61–70 years $N = 16$	71–80 years $N = 65$	81–90 years $N = 117$	Statistics p value
Any [N (%)]	0 (0.0)	0 (0.0)	1 (6.3)	4 (6.2)	15 (12.8)	**0.016**[a]
IgA [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	6 (5.1)	0.114[b]
IgG [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
IgM [N (%)]	0 (0.0)	0 (0.0)	1 (6.3)	4 (6.2)	12 (10.3)	0.015[b]
IgA + IgG [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
IgA + IgM [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	3 (2.6)	0.594[b]

N number of cases, *NMDA-R* N-methyl-D-aspartate glutamate (NMDA) receptor

[a] Fisher's exact test

[b] Fisher's exact test, alpha corrected by Bonferroni

Table 2 Prevalence of serum NMDA-R Abs in dementia patients compared to age-matched controls

NMDA-R Abs	Study group					
	Age-matched controls ($N = 84$)	All dementia patients ($N = 44$)	Statistics controls versus all dementia patients: p value	AD patients ($N = 24$)	SIVD patients ($N = 20$)	Statistics controls versus AD and SIVD: p value
Age [years ± SD]	75.2 ± 4.8	77.1 ± 11.4	0.330[a]	80.9 ± 4.9	72.5 ± 15.0	**0.001**[e]
Sex [N, f/m]	43/41	29/15	0.111[b]	17/7	12/8	0.216[b]
Any [N (%)]	6 (7.1)	7 (15.9)	0.134[c]	4 (16.7)	3 (15.0)	0.140[c]
IgA [N (%)]	1 (1.2)	4 (9.1)	0.235[d]	1 (4.2)	3 (15.0)	0.090[d]
IgG [N (%)]	0 (0.0)	1 (2.3)	1.000[d]	1 (4.2)	0 (0.0)	1.000[d]
IgM [N (%)]	6 (7.1)	3 (6.8)	1.000[d]	3 (12.5)	0 (0.0)	1.000[d]
IgA + IgG [N (%)]	0 (0.0)	1 (2.3)	1.000[d]	1 (4.2)	0 (0.0)	0.940[d]
IgA + IgM [N (%)]	1 (1.2)	0 (0.0)	1.000[d]	0 (0.0)	0 (0.0)	1.000[d]

AD Alzheimer's disease, *N* number of cases, *NMDA-R* N-methyl-D-aspartate glutamate (NMDA) receptor, *SIVD* subcortical ischemic vascular dementia

[a] Student's t test

[b] Chi-squared test

[c] Fisher's exact test

[d] Fisher's exact test, alpha corrected by Bonferroni

[e] Analysis of variance

Table 3 Association of seropositivity for NMDA-R Abs and the occurrence of psychosis in dementia

NMDA-R Abs	Study group					
	All dementia patients		AD patients		SIVD patients	
	+	−	+	−	+	−
psychotic N	6	1	3	0	3	1
non-psychotic N	1	36	1	20	0	16
Fisher's exact test, alpha corrected by Bonferroni	$p < 0.001$		$p = 0.006$		$p = 0.011$	

AD Alzheimer's disease, *N* number of cases, *NMDA-R* N-methyl-D-aspartate glutamate (NMDA) receptor, *SIVD* subcortical ischemic vascular dementia

Similarly, the measured antibody classes (IgA, IgG, IgM) did not show diagnosis-related differences. NMDA-R Abs were absent in the CSF of the analyzed dementia patients.

Association of seropositivity for NMDA-R Abs and the occurrence of psychosis in dementia

Overall, 7 dementia patients (4 AD and 3 SIVD patients) were seropositive for NMDA-R Abs. Only one of these subjects did not suffer from a psychotic state during the time point of the blood sampling. The association of seropositivity with the occurrence of a psychosis was significant in the whole group of dementia patients ($p < 0.001$; Table 3) and in the diagnostic subgroups (AD: $p = 0.006$; SIVD: $p = 0.011$, Table 3). However, on the

other hand, 10 dementia patients showed psychotic symptoms but only six of them demonstrated NMDA-R Abs.

Discussion

We report the detection of NMDA-R-specific IgM, IgG, and IgA serum autoantibodies in mentally healthy aged controls and two different forms of progressive neurodegenerative disorders, AD and SIVD. In controls, the prevalence of IgA and IgM NMDA-R Abs was age-related. This finding is in-line with a recent study by Hammer et al. [20]. These authors proposed that a compromised BBB, induced by a history of brain trauma or birth complication, decides on the pathophysiological significance of the NMDA-R Abs. Our control cohort was chosen by excluding such previous events that could result in a compromised BBB. However, it is known that neurodegenerative disorders such as AD and SIVD could likewise affect the BBB—many years before clinical manifestation of dementia. Therefore, we cannot exclude that our seropositive controls will develop dementia within the next years.

IgG NMDA-R antibodies (directed against the NR1a subunit) were first identified in a severe form of encephalitis called NMDA-R encephalitis. This disorder is characterized by a multistage disease including psychosis and memory defects induced by high intrathecal titers of NMDA-R Abs [25]. Memory defects are also present in AD and SIVD, however, only a subgroup of patients develop psychosis-like symptoms. In the present study, about 16 % of the dementia patients and 7.1 % of age-matched healthy volunteers had positive NMDA-R Ab titers. Pointing to a considerable prevalence of NMDA-R antibodies also in normal controls, this difference did not reach statistical significance. The findings of considerable prevalence of NMDA-R Abs in controls resemble knowledge in systemic autoimmune disorders, and long-standing (years) prevalence of various autoantibodies may be observed before onset of autoimmune disorders. We could not detect an association between seropositivity and the mini-mental status (data not shown). Seven dementia patients were seropositive for NMDA-R Abs. Apart one of them, these patients suffered from psychosis. Thus, one could speculate on a link between the seroprevalence of NMDA-R Abs and psychosis in these cases. However, on the other hand, 10 dementia patients showed psychotic symptoms but only six of them demonstrated NMDA-R Abs. So from a pathogenic point of view, the latter finding may argue against a specific role of the antibodies for the pathogenesis of psychotic symptoms in dementia. NMDA-R antibodies were not detected in CSF samples. This is in-line with a previous report [26] about a subgroup of patients with *Herpes simplex* encephalitis suffering from memory impairment who had detectable Abs against NMDA-R in serum but not in CSF. Similarly, IgA NMDA-R antibodies were found in serum of patients with slowly progressive cognitive impairment, but simultaneously no or low intrathecal antibody levels were observed [27]. Recently, Steiner et al. [18] described NMDA-R Abs from Ig classes IgA, IgG, and IgM in the serum of 9.9 % acutely ill schizophrenia patients, which presented at the hospital with acute psychosis. Interestingly, most of the AD patients with positive NMDA-R Abs in serum showed psychotic-like symptoms. Thus, while the presence of IgG NMDA-R Abs in CSF has been considered as a marker for NMDA-R encephalitis [19], our data support the hypothesis that serum NMDA-R Abs can also be observed in other neurological and psychiatric disorders.

NMDA-Rs play several roles in Aβ-related mechanisms in the pathophysiology of AD: Aβ produces depression of the glutamatergic synaptic transmission which is associated with a decrease in NMDA-R [28, 29] and dendritic spine density [30–33]. Consequently, a progressive decline in cognitive function occurs which is found in patients with dementia. Patients with AD show a great variety in symptoms and duration of disease. Further studies have to clarify the correlation between the different anti-NMDA-R Ab classes, the occurrence of psychotic symptoms and the course of disease.

The present study has certain limitations and open questions that need to be considered. First, NMDA-R-specific IgA and IgM Abs were also detected in our group of healthy aged subjects without psychotic symptoms. It is currently unknown, whether these Abs increase the risk of developing neurodegenerative disorders with or without clinical psychotic signs in these subjects. Second, the influence of medication, especially antipsychotic drugs, remains unclear. Third, our study cohorts consisted of only 24 AD patients and 20 SIVD patients; only few of them suffered from psychosis. To further confirm our hypothesis that NMDA-R Abs are involved in the development of psychosis in dementia, more patients have to be recruited. Fourth, it is currently unknown whether the occurrence of NMDA-R Abs in AD is only a transient phenomenon which disappears after remission of psychosis. One could also speculate on an association of late states of dementia, when the BBB is affected, with seropositivity for NMDA-R Abs.

Summary and conclusion

Based on previous reports describing the detection of NMDA-R Abs in disorders associated with cognitive decline or psychosis, we examined the presence of NMDA-

R Abs in serum of 274 neuropsychiatric healthy controls, 24 AD and 20 SIVD patients. The seroprevalence of NMDA-R Abs increased with aging in healthy controls. In AD and SIVD patients, seroprevalence was often connected to the presence of clinical psychotic symptoms, but no overall diagnosis-dependent difference regarding seroprevalence was observed in comparison with matched controls. To further clarify the role of anti-NMDA-R-specific Abs in aging and dementia, larger cross-sectional and longitudinal studies are warranted, including patients in early as well as progressed stages of dementia.

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Conflict of interest Dr. Brix, Dr. Probst, and Prof. Stoecker are full-time employees of Euroimmun AG. Prof. Stoecker holds shares of Euroimmun AG. The other authors declare that they have no conflict of interest.

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