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Immunoadsorption of Agonistic Autoantibodies Against α1-Adrenergic Receptors in Patients with Mild to Moderate Dementia

Petra Hempel,[1,†] Bente Heinig,[2,†] Carola Jerosch,[2] Imke Decius,[2] Peter Karczewski,[1] Ursula Kassner,[2] Rudolf Kunze,[3] Elisabeth Steinhagen-Thiessen,[2,†] and Marion Bimmler[4,†]

[1] *E.R.D.E-AAB-Diagnostics GmbH,* [2] *Charité - University Medicine Berlin,* [3] *Science Office, and* [4] *Max-Delbrück-Center for Molecular Medicine, Berlin, Germany*

Abstract: Dementia has been shown to be associated with agonistic autoantibodies. The deleterious action of autoantibodies on the α1-adrenergic receptor for brain vasculature has been demonstrated in animal studies. In the current study, 169 patients with dementia were screened for the presence of agonistic autoantibodies. 47% of patients suffering from mild to moderate Alzheimer's disease and/or vascular dementia carried these autoantibodies. Eight patients positive for autoantibodies underwent immunoadsorption. Patients treated on four consecutive days were subsequently negative for autoantibodies and displayed stabilization of cognitive and mental condition during 12–18 months' follow-up. In patients treated for 2–3 days, autoantibodies were reduced by only 78%. They suffered a rebound of autoantibodies during follow-up, benefited from immunoadsorption too, but their mental parameters worsened. We provide first data on the clinical relevance of agonistic autoantibodies in dementia and show that immunoadsorption is safe and efficient in removing autoantibodies with overall benefits for patients. **Key Words:** Autoantibodies, Brain vasculature, Dementia, Immunoadsorption, α1-Adrenergic receptor.

Dementia is a widespread progressive disease with devastating effects on the patient and caregivers and, due to demographic changes, presents a massively growing economic burden as well. Currently, more than 1.4 million people in Germany aged 65 years and older suffer from dementia, with two-thirds of those having Alzheimer's disease (AD) – with an anticipated incidence of 300 000 patients per year (1).

Alzheimer's disease is the most common form of dementia, followed by vascular dementia (VaD) caused by lesions in blood vessels supplying the brain. A significant number of patients with dementia suffer from a mixed-type dementia (2). AD pathology is characterized by deposits of β-amyloid containing senile plaques and cerebral tangles containing phospho-tau. Beta-amyloid has long been thought to be a promising therapeutic target. However, several clinical approaches to remove and/or decrease the synthesis of β-amyloid failed to yield a significant benefit (3–5). There are multiple causes of dementia. Lifestyle, genetic risk factors, and vascular impairments have been acknowledged as playing important roles (6–8). Lesions of blood vessels in particular are thought to play an important role in AD pathology as well. Vascular risk factors that have been shown to increase the risk for AD may act both independently and by amplifying each other. These include diabetes, hypertension, obesity, and high blood-cholesterol levels (9). Interestingly, in several clinical studies focusing on the effect of treating hypertension and examining dementia as a secondary outcome, decreased incidence of dementia (10) or cognitive decline (11,12) has been observed.

Agonistic autoantibodies (agAAB) directed against G-protein-coupled receptors (GPCR) are increasingly discussed as modulators of the pathology and outcome of diseases with vascular complications,

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Address correspondence and reprint requests to Ms Marion Bimmler, Max-Delbrück-Center for Molecular Medicine, Berlin-Buch, Robert-Rössle-Straße 10, 13125 Berlin, Germany. E-mail: bimmler@mdc-berlin.de
[†]These authors contributed equally.

such as dilated cardiomyopathy (13,14), hypertension (14,15), type-2 diabetes mellitus (16), dementia (17,18), thromboangiitis obliterans (19), preeclampsia (20,21), and humoral-mediated kidney transplant rejection (22). In these instances, agAAB directed against the α1-adrenergic receptor (15,18), the β1-adrenergic receptor (13,14), the β2-adrenergic receptor (17), the endothelin A receptor (14,19) and the angiotensin-1 receptor (20,22) have been described. The pathogenic potential of circulating agAAB has already been demonstrated in animal models as well as in clinical studies (13,15,21,23). The pathogenic effect of agAAB (fulfilling Koch's criteria) has been demonstrated in rat models for the β1-adrenergic receptor autoantibodies in dilated cardiomyopathy (13) and for the α1-adrenergic receptor (18).

Elimination of IgG by immunoadsorption is highly effective in removing agAAB (14,19). Several smaller case studies have revealed improvement in cardiac function, i.e. improved left ventricular ejection fraction, natriuretic peptide levels, and hemodynamic conditions, with a long-lasting effect on the symptoms of heart failure by removal of agAAB through immunoadsorption (14).

The potential for agAAB to act against the α1-adrenergic receptor (α1-AR) and thereby cause damage in the macro- and microvasculature of the brain has been shown in rats for aorta and mesenteric arteries (23) and arteries of the brain (18). AgAAB acting against the α1-AR cause a significant reduction of blood flow in certain parts of the brain, such as the hippocampus, and a significant decrease of vessel density in parts of the cortex (24). These findings imply a general significance of the α1-AR-agAAB interaction in the pathogenesis and progression of diseases having a strong vascular component such as dementia.

In an earlier study that investigated the incidence of agAAB against the α1-AR in patients suffering from AD combined with VaD (AD/VaD), agAAB were detected in approximately 50% of the patients (17). We hypothesized that agAAB against the α1-AR play a substantial role in the pathogenesis of AD/VaD.

In this study, immunoadsorption was used as a novel therapeutic approach for patients with dementia. To our knowledge, there have been no studies on the benefit of immunoadsorption in patients with AD/VaD to date. In an exploratory study, patients with mild to moderate dementia and positive for agAAB acting against α1-AR received immunoadsorption. Over a follow-up period of up to 18 months, the agAAB level and cognitive changes were observed.

PATIENTS AND METHODS

Patients with AD/VaD were screened for the presence of agAAB. AgAAB were determined using a peptide based ELISA as described in (17). The cut-off value of the ELISA was defined using samples of patients who were negative for agAAB in the functional bioassay (17).

A random sample of patients with mild to moderate AD/VaD, affirmed by Mini-Mental State Examination score (MMSE; ≥18–26), and positive for α1-AR-agAAB were selected for immunoadsorption with the intention of removing agAAB from their blood circulation. These patients had to meet the following two additional criteria: capacity to provide consent and stable pharmacological antidementive treatment for a period of at least three months. Exclusion criteria were an age >90 years, hemodialysis, severe cardiac diseases (infarction, insufficient cardio capacity, cardiac bypasses, etc.), cerebral bleeding, immunodeficiency, and oncologic diseases.

Cognitive and noncognitive testing was performed prior to immunoadsorption and at 3, 6, and 12–18 months after immunoadsorption. The following tests were used in the diagnosis of AD/VaD and have proven to be reliable tools for initial evaluation of a patient as well as for monitoring the progress of cognitive deficits: Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment scale (ADAS-cog and -noncog), Bayer Activities of Daily Living (Bayer-ADL), Clinical Global Impression Scale (CGI), Geriatric Depression Scale (GDS), and Short Cognitive Performance Test (Syndrom-Kurz-Test, SKT) (Table 1).

Immunoadsorption was performed over a period of four consecutive days (centrifuge for blood cell/plasma separation: COM.TEC, Fresenius Kabi, Bad Homburg, Germany; immunoadsorption system: ADAsorb, medicap GmbH, Ullrichstein, Germany; adsorber: Immunosorba, Fresenius Medical Deutschland GmbH, Bad Homburg, Germany). The Fresenius Immunosorba is based on protein A and selectively removes all immunoglobulins without affecting other serum proteins. Patients were treated as outpatients. One day of immunoadsorption was made up of several cycles. The daily processed plasma volume was in the range of 2.0–2.5-fold. After the last cycle of immunoadsorption, the IgG level was <15% and human immunoglobulin (>98% IgG) was substituted. During immunoadsorption

TABLE 1. *Cognitive tests used, with qualitative scores and scales*

Cognitive tests	No impairment	Severe impairment	Reference / normal range
Mini-Mental State Examination diagnoses dementia and assesses its progression and severity	30 points	0 points	26–30 points
Alzheimer's Disease Assessment scale – cognitive assessment of cognitive functions (language and memory)	0 points	70 points	0–5 points
Alzheimer's Disease Assessment scale – noncognitive assessment of noncognitive functions (mood and behaviour)	0 points	50 points	0–5 points
Bayer Activities of Daily Living assessment of impairments to performance of daily activities	1 points	10 points	1–2 points
Clinical Global Impression Scale clinician's view of the patient's global functioning	1 point	7 points	1 point
Geriatric Depression Scale assessment of depression in the elderly	0 points	15 points	0–5 points
Short Cognitive Performance Test assessment of memory and attention deficit in dementia patients	0 points	27 points	0–4 points

and IgG substitution, patients were monitored by measuring blood pressure and heart rate under the constant supervision of a physician and a specially trained nurse. The study was conducted in compliance with the Declaration of Helsinki and approved by the ethical review committee of the Charité - Universitätsmedizin Berlin (EA1/058/10).

Blood samples were regularly taken before the first and after the last cycle of immunoadsorption and whenever needed. AgAAB analyses were performed retrospectively.

RESULTS

A cohort of 169 patients with dementia diagnosed as being at different stages was screened for the presence of agAAB using the standardized in-house ELISA. 85 of the patients examined (>50%) were positive for agAAB. 74 (>43%) out of 169 patients tested positive for α1-AR-agAAB and 54 (73%) of these patients also harbored β2-AR-agAAB. AgAAB acting against the α1-AR or β2-AR only occurred in 20 and 11 patients, respectively. Focusing only on mild to moderate AD/VaD (MMSE 20-26), we found the incidence to be similarly distributed in the resulting 66 patients. 36 (>54%) patients with mild to moderate AD/VaD were positive for agAAB and 31 (47%) of them were harboring agAAB acting against α1-AR. Of these, 22 (71%) were positive for both α1-AR-agAAB and β2-AR-agAAB. Only five patients showed agAAB acting solely against the β2-AR. However, the pathological relevance of β2-AR-agAAB is still unclear, and there are no animal or clinical studies available that have tackled this problem. Therefore, patients carrying only β2-AR-agAAB were not included. Thus, 31 patients with α1-AR-agAAB were considered to be potential candidates for immunoadsorption.

Eight patients meeting the inclusion criteria mentioned above were selected for immunoadsorption and gave their consent for this treatment. Three individuals were female, five were male. Mean age was 66.8 ±2.9 years. All patients were positive for agAAB against the α1-AR and five also harbored β2-AR-agAAB.

Immunoadsorption treatment over the 4 day course carried out according to the protocol (Group 1) effectively removed 96 ±12% of α1-agAAB from the sera gradually (Fig. 1a). Due to the outpatient treatment regimen, permanent catheterization of the jugular vein was not feasible. The repeated daily puncture caused access to the vein of four patients to deteriorate. Therefore, these patients could only be treated for two to three consecutive days (Group 2). The shortening of treatment time led to incomplete removal of agAAB (78 ±10%, Fig. 1b). There were no safety or tolerability problems with the immunoadsorption in any of the patients. Follow-up examination of the agAAB status after 3, 6, and 12–18 months showed no reoccurrence of agAAB in Group 1 (only in one patient did α1-AR-agAAB reappear after 12 months), whereas agAAB reappeared after 3 months in two patients and after 6 months in three patients of Group 2.

To evaluate cognitive changes after removal of agAAB, several cognitive and noncognitive tests were performed prior to immunoadsorption and at 3, 6, and 12–18 months after immunoadsorption. These were MMSE, ADAS-cog and -noncog, Bayer-ADL, CGI, GDS, and SKT.

All eight patients treated showed a stable condition in different behavioral tests of daily living skills during the follow-up period without dramatic changes in the results of important tests (e.g. Bayer-ADL, CGI, GDS, SKT) (Table 2). This correlates with personal communications from relatives shortly after immunoadsorption. They reported an overall

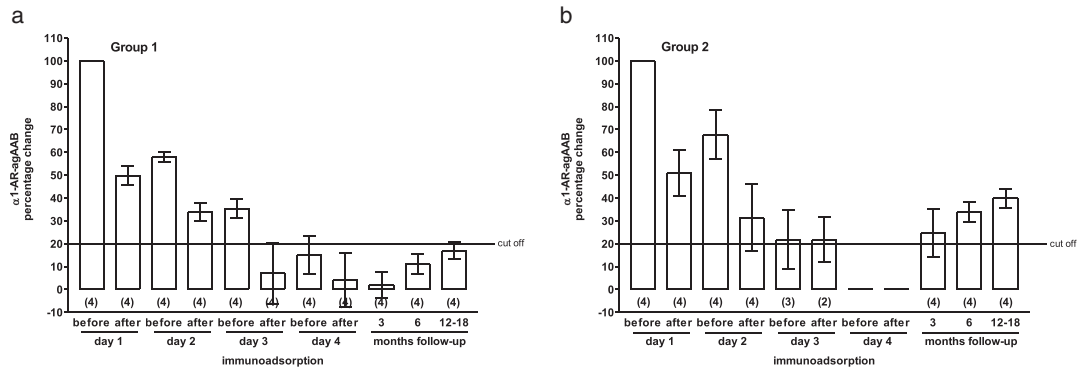

FIG. 1. Detection of agonistic autoantibodies against α1-adrenoceptors (α1-AR-agAAB) in sera of patients with dementia before, during and after immunoadsorption for 4 days (a) and for 2–3 days (b). Serum was collected on consecutive days prior and after immunoadsorption and at 3, 6, and 12–18 months after as follow-up. Peptide specific binding of α1-AR-agAAB was analyzed by ELISA and calculated as percentage change of the initial value. Values are means ± SEM of (*N*) analyzed patients.

TABLE 2. *Cognitive data from the study groups. Group 1 treated 4 consecutive days, Group 2 treated 2–3 days*

				Δ versus before immunoadsorption (IA)								
	Before IA			3 months			6 months			12–18 months		
	MEAN	SEM	*N*	MEAN	SEM	*N*	MEAN	SEM	*N*	MEAN	SEM	*N*
Group 1												
MMSE	22.25	1.31	4	0.00	1.29	4	–1.25	1.18	4	0.00	1.73	3
ADAS-cog	21.75	5.25	4	–0.25	1.31	4	–0.50	2.02	4	2.00	1.73	3
ADAS-noncog	3.25	0.25	4	1.50	2.02	4	1.75	3.25	4	2.17	2.89	3
BayerADL	4.52	0.83	4	–0.35	0.41	4	–0.13	0.44	4	0.45	0.50	3
CGI	3.50	0.29	4	0.25	0.48	4	0.50	0.50	4	1.33	0.33	3
GDS	3.00	1.08	4	1.25	0.85	4	1.50	1.55	4	–0.67	1.20	3
SKT	13.50	3.66	4	1.25	0.85	4	1.75	1.11	4	3.67	1.20	3
Group 2												
MMSE	22.00	1.83	4	0.00	0.71	4	–1.75	1.18	4	–5.25	4.61	4
ADAS-cog	23.25	4.37	4	–0.50	3.66	4	–4.00	2.68	4	1.88	5.18	4
ADAS-noncog	3.25	0.85	4	0.25	1.11	4	0.50	1.04	4	2.00	1.58	4
BayerADL	4.05	0.40	4	0.41	0.48	4	0.68	0.27	4	1.56	0.37	4
CGI	3.50	0.29	4	0.00	0.00	4	–1.00	1.47	4	1.50	0.65	4
GDS	3.75	0.63	4	0.25	0.85	4	0.50	0.29	4	–0.25	0.63	4
SKT	8.25	1.11	4	–2.75	1.11	4	0.75	1.65	4	3.00	3.74	4

positive feeling about the mental health and behavior of the patients. Of course, the precise changes are very different for each individual, but the patients' relatives pointed out that their condition had immensely improved.

Interestingly, MMSE remained stable in Group 1 and showed the same results prior to and 12–18 months after immunoadsorption, while MMSE in Group 2 declined by 5.25 points (Fig. 2a, Table 2). This is similar to changes in untreated patients (MMSE decline by about 2–4 points annually, 25).

ADAS-cog and ADAS-noncog changed over the observed follow-up period in Group 1 by 2.00 ±1.73 points and by 2.17 ±2.89 points, respectively, and in Group 2 by 1.88 ±5.18 points and by 2.00 ±1.58 points, respectively (Fig. 2b and c). Cognitive decline of dementia patients without proper medication changes over the same time period by 7–11 points (25).

Immunoadsorption led to long-lasting elimination of agAAB from the blood circulation only in patients treated for 4 days. Cognitive development in these patients stabilized and daily living skills clearly improved.

DISCUSSION

AgAAB directed against GPCR are increasingly recognized as a significant factor in widespread diseases. In particular, agAAB directed at the α1-AR were found to be characteristic of various pathologies having in common the involvement of vascular impairment as a necessary cause and in the progression of the disease. These include different forms of hypertension, type-2 diabetes, thromboangiitis obliterans and dementia (15–17,19). Alzheimer's disease, the predominant form of dementia, continues

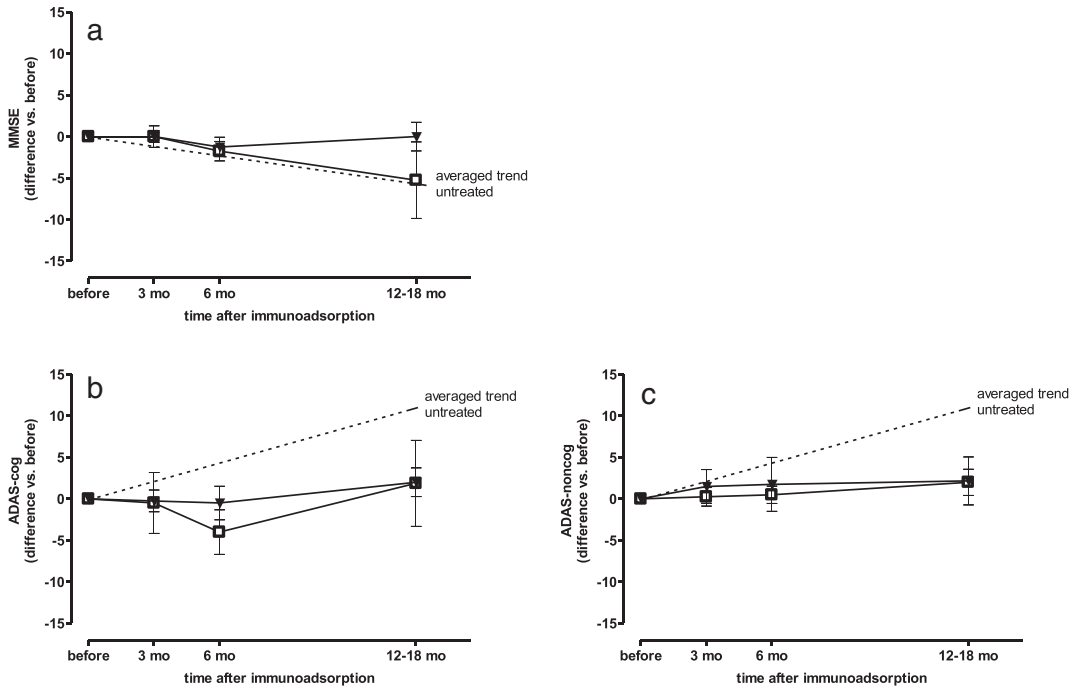

FIG. 2. Evaluation of Mini-Mental State Examination score (MMSE) (a) and Alzheimer's Disease Assessment Scale (ADAS-cog and -noncog) (b, c) in patients with mild to moderate Alzheimer's and/or vascular dementia before and after immunoadsorption of 4 days (Group 1, filled triangle) and 2–3 days (Group 2, open squares). Cognitive tests were performed before and 3, 6, and 12–18 months after immunoadsorption under controlled clinical conditions. Data are given as differences to the estimates obtained prior to immunoadsorption. Means were calculated ± SEM of $N = 4$ (Group 1) and $N = 2$–4 (Group 2) analyzed patients. The averaged trend of cognitive progression in untreated dementia patients is indicated as a dotted line (25).

to increase as a health problem of aging. Despite tremendous efforts to determine the cause of Alzheimer's disease or slow its progression, no successful treatment has been established up to now.

Here we report on the prevalence of agAAB directed against the α1-AR in a cohort of patients suffering from dementia, mostly of the Alzheimer's type, and provide the first data on eliminating agAAB from the blood circulation of dementia patients through immunoadsorption. To our knowledge, immunoadsorption has not been applied as a therapeutic strategy for patients with dementia before. Immunoadsorption has proven to be a safe and efficient procedure in antibody-mediated dilated cardiomyopathy accompanied by agAAB against the β1-AR (14). After removal of β1-AR-agAAB, cardiac performance of patients improved significantly and persistently, in some cases obviating the need for heart transplantation (14).

The present study used immunoadsorption to remove α1-AR-agAAB quantitatively from dementia patients' blood circulation. Immunoadsorption was to be performed on 4 consecutive days according to the study protocol. Due to outpatient treatment arrangements, repeated daily puncture of the vein was necessary. Access to the vein deteriorated so much in a group of patients (retrospectively termed Group 2), that they could only be treated for 2–3 consecutive days. However, this allowed us to gather additional valuable information on the time schedule that is critical for the complete removal of agAAB from the blood circulation by comparing these patients with the group treated for 4 days. The significant reappearance of agAAB during the follow-up in patients treated for 2–3 days correlates with the tendency for a decline of the MMSE status, whereas the level of the agAAB in the patient group treated for four days appeared to be stabilized. Patients with the 4-day apheresis remained negative for agAAB with one exception.

The availability of agAAB for detection is restricted to the fraction of circulating antibodies. However, the pathologically active agAAB are those bound to the α1-AR. In vivo data on time constants of agAAB binding to the receptor and their dissociation from the receptor are not available. This also suggests that estimations of total serum immunoglobulins do not reflect the present agAAB situation of the patient, especially regarding the receptors in their physiologic milieu. In vitro data on the tight and durable association of antibodies

with their target sites revealed EC50 (half maximal effective antigen concentration) values in the low nanomolar range (15,17). It may be concluded that immunoadsorption for less than 4 days is not sufficient to remove agAAB from their binding compartments. Thus, the present study proves that immunoadsorption is a safe and effective procedure to relieve dementia patients persistently of α1-AR-agAAB. The data suggest immunoadsorption should be performed for five consecutive days to ensure the complete removal of the non-circulating receptor-bound fractions of agAAB as well. Moreover, we recommend hospitalization of the patient to avoid possible problems arising from repetitive vein puncture.

Dementia is a progressive disease characterized by cognitive decline and mostly irreversible pathological changes in the brain. Therefore, the complete cure of this disease may be an unrealistic goal at present. To stop or at least to slow the progression of dementia accompanied by stabilization of the cognitive situation of the patient represents a significant therapeutic success. Follow-up examinations of patients who received 4-day immunoadsorption demonstrated the absence of the α1-AR-agAAB up to 18 months after immunoadsorption and stabilized cognitive performance as verified by stable results in cognitive tests such as ADAS and MMSE. Some aspects of abilities needed in daily life and subjective well-being even appeared to improve. Thus, the removal of α1-AR-agAAB from the blood circulation of dementia patients by immunoadsorption produced an impressive therapeutic success that has not even been approached by current pharmacological treatments (3–5). The data presented underscore the importance of a sufficient number of consecutive days of immunoadsorption for the complete removal of α1-AR-agAAB to ensure their long-lasting absence and to prevent a recurrence of the autoantibody.

In this context it should be noted that α1-AR-agAAB are also involved in hypertension (15). The elimination of α1-AR-agAAB from dementia patients with hypertension may require adjustment of their antihypertensive medication.

The present observations demonstrate for the first time evidence of the pathological effect of agAAB on the α1-AR in patients suffering from dementia. The damaging action of this type of agAAB on the vasculature has been demonstrated in animal studies for peripheral vessels and for macro- and microvessels of the brain (18,23). In addition to direct damage to and destruction of cerebral blood vessels, antibody-treated animals showed signs of neurodegeneration with increased dilation of Virchow-Robin spaces (unpublished data). This indicates that α1-AR-agAAB negatively affect both the blood supply of neuronal tissue and the drainage of cerebral fluids. Reduced drainage may attenuate the clearance of β-amyloid species from the vicinity of neuronal cells and constitute another mechanism by which α1-AR-agAAB contributes to the progression of the disease. The cohort studied consisted predominantly of patients suffering from dementia of the Alzheimer's and vascular type, with about 44% of patients being positive for α1-AR-agAAB. Given that the presence of α1-AR-agAAB represents a general risk for vascular impairments and neurodegeneration, these autoantibodies are likely to be of clinical relevance in other forms of dementia, such as frontotemporal dementia and Lewy body dementia.

However, on the negative side, while immunoadsorption achieves rapid and safe elimination of agAAB, it is costly and involved. Plasmapheresis is a less expensive procedure. However, the substitution of the patients' plasma with plasma from donors entails risk of distributing pathogens, such as various autoantibodies not identified by standard diagnostics used for certification of donor plasma. The interaction of agAAB with their target receptors might also be reduced by receptor antagonists. Most antagonists of relevant receptors are in clinical use for other indications. Antagonists of the α1-AR are used to treat hypertension and prostate hyperplasia. To achieve a significant effect of receptor antagonists on agAAB circulating in patients requires greater orders of magnitude of time compared to the removal of agAAB through apheresis (unpublished observation). Considering the relatively rapid decline in cognition of dementia patients, the receptor antagonist approach would suffer from this crucial drawback. Moreover, receptor antagonists act systemically, thereby affecting various organs carrying the respective receptor type.

CONCLUSION

In summary, we have demonstrated for the first time the therapeutic efficacy of immunoadsorption for treating dementia in a random sample of α1-AR-agAAB positive patients. The data confirm the neuropathogenic action of α1-AR-agAAB in humans as previously demonstrated in animal models (18). AgAAB-mediated cerebrovascular impairment may be a missing link in the pathogenesis of AD/VaD. In light of the lack of effective therapies for

dementia, immunoadsorption represents a promising treatment approach for at least agAAB-positive patients. In respect to AD pathogenesis, parallel chronic pathological cerebrovascular mechanisms may be modified by immunoadsorption, resulting in improved cerebrovascular blood circulation as well as regional clearance. It may be an ad hoc treatment tool to interrupt the vascular contribution to cognitive impairments. Long-lasting cognitive stabilization after a single 5-day treatment interval may be a pivotal advantage, considering the poor efficacy of current drug therapy. Larger controlled studies are needed to verify the present observations, optimize the treatment protocol, and evaluate immunoadsorption for clinical use.

There are limitations to this explorative study that should be stated. Due to the nature of the set-up and operation of specialized hospitals such as the EGZB, it was not possible to establish a control group of agAAB-positive patients not treated by immunoapheresis. The outpatients are examined only once in this hospital and then transferred back to their family doctor for care. The progressive worsening of dementia patients' cognitive and mental condition is beyond dispute and well documented by established tests. However, the averaged progression trend, used here for illustration, is inappropriate for control.

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