Role of alpha1-adrenergic receptor antibodies in Alzheimer's disease

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1. ABSTRACT

Agonistic autoantibodies (agAAB) for alpha-1 adrenoceptor were found in approx. 50% of patients with Alzheimer's disease. These antibodies activate the receptor and trigger the signal cascades similarly to how natural agonists do. The agAAB bond to the receptor is persistent and prolonged. This results in a non-physiological elevation of intracellular calcium. An animal model has shown that agAAB causes macrovascular and microvascular impairment in the vessels of the brain. Reduction in blood flow and the density of intact vessels was significantly demonstrated. The agAAB was removed through immunoadsorption in a small cohort of patients with Alzheimer's disease. Subsequent follow-up observations over 12-18 months noted stabilization of cognition levels.

2. INTRODUCTION

Alzheimer's disease and vascular dementia are the chief forms of disease causing dementia. In Germany, the number of persons afflicted with dementia is estimated to be 1.6. million (1). Two-thirds of them are afflicted with Alzheimer's disease. The number rises by 300,000 persons annually, or 800 daily. There is no satisfactorily effective therapeutic method thus far, despite diverse research approaches.

Circulatory problems due to impairment of the cerebral blood vessel system are the cause of vascular dementia and are increasingly discussed as a possible cause in the development and progression of sporadic, non-genetically determined Alzheimer's disease as well (2). The cause of the sporadic form is completely unknown. Two proteins, tau (τ) and amyloid-ß, have been comprehensively described as probable pathological molecules in the evolution of dementia up to now. In this scenario, the activation of the β2-adrenergic receptor appears to play a role in the stimulation of the gamma-secretase activity and accelerate the formation of the amyloid plaque (3).

The main risk factor for diseases causing dementia is age. Additional risk factors are hypercholesterolemia, hypertension, arteriosclerosis, coronary heart disease, smoking, obesity, and Type-2 diabetes (4, 5, 6). Studies support the hypothesis that changes in the vasculature of the brain in AD patients are partly responsible for the development of dementia (2). After Alzheimer's disease, vascular dementia is the second-most frequent form of dementia. These two forms of dementia are found together in a majority of patients. Persons with ischemic stroke have a four-times greater risk of contracting dementia (7).

The α1-adrenoceptor (α1-AR) is one of the adrenoceptors (G-protein-coupled receptors / GPCR) that are activated by adrenaline and norepinephrine, and occupy a key position in the regulation of heart and vessel musculature. The effect of α1-AR is mediated by the Gq protein, which in turn activates phospholipase C. This lipase cleaves membrane lipids such as phosphatidylinositol-4,5-bisphosphate (PIP2) into diacylglycerine (DAG) and inositol trisphosphate (IP3), which in turn influence cellular calcium homeostasis. Calcium ions are the most universal intracellular messengers and are part of the signaling pathways of GPCR. α1-AR is one of the GPCRs effectively coupled to intracellular calcium (8).

3. G-PROTEIN-COUPLED RECEPTOR (GPCR) AUTOANTIBODIES IN DEMENTIA

agAAB for α1-AR had already been shown in 2010 to be present in 54% of an initial, small cohort (54 patients) suffering from Alzheimer's disease and vascular dementia (9). In addition, an autoantibody for β2-AR was detected in several patients. The α1-AR autoantibody occurred most frequently in conjunction with the autoantibody for β2-AR compared to α1-AR alone. Detection of the agAAB was achieved by means of its functionality in a bioassay of neonatal cardiomyocytes. For in-house use an ELISA assay was designed using a peptide analogue of the first extracellular loop of the α1-AR (29). This peptide ELISA was validated against the functional neonatal cardiomyocyte bioassay. The cut off was derived from ELISA signals of serum dilutions from patients positively tested for α1-AR-agAAB that correspond to the bioassay detection threshold. Following this initial small-cohort study, the prevalence of the autoantibodies in sera was investigated for 400 dementia patients by means of the peptide-based ELISA test. The prevalence totaled 48%. This value is close to 54% obtained for the small cohort using the functional bioassay but needs confirmation by other large-scale studies (9). However, such studies are not available yet. Likewise, there are no functional assays suitable for large-scale studies on α1-AR autoantibodies. Investigations of the properties of the α1-AR autoantibody revealed that it selectively binds to the first extracellular loop of the α1-AR (9). This GPCR is involved with the regulation of contractile myocardial function and glucose metabolism, and is of pivotal importance for the functioning of vessel musculature. The proof of the occurrence of an autoimmune response at the α1-AR suggests the conclusion that non-physiological activity of the α1-AR caused by autoantibodies can be a pathological mechanism for vascular impairment that can play a substantial if not a causal role in dementia as well. This hypothesis was the motivation for our laboratory to more closely investigate mechanisms by which these autoantibodies for α1-AR operate, and also the pathological significance of this immune response for the development of vessel impairment.

4. RECEPTOR ACTIVATION BY AGONISTIC AUTOANTIBODIES IN PATIENTS WITH ALZHEIMER'S DISEASE

The activation of GPCR by agonistic autoantibodies triggers receptor-specific reactions in the cell. These can be, but are not necessarily identical to those activated by physiological agonists. The activation of the GPCR requires the binding of the antibody. Using a monoclonal antibody generated against the second extracellular loop of the ß$_2$-AR the authors demonstrated an agonist-like effect on beating neonatal cardiomyocytes probably by stabilizing the active receptor dimer (10). Beta1-AR autoantibodies were found in DCM patients and also in healthy controls both affecting receptor conformation, but mostly antibodies from DCM patients were agonistic inducing active receptor confirmation (11). The molecular mechanism of α1-AR activation by agonistic autoantibodies is largely unknown. The stabilization of the active configuration by mechanisms mimicking the agonist-induced dimerisation by intracellular covalently linking receptor molecules may be involved. However, experimental evidence for this is still lacking.

The antibody does not activate the GPCR to the degree that the physiological agonist does, but affects the cell nearly permanently through the stable bond to the receptor and preclusion of cellular protection mechanisms. We were able to demonstrate that α1-AR-specific autoantibodies for the familiar epitope of the receptor obtained from the sera of Alzheimer's disease patients produced mobilization of the intracellular calcium in a clonal cell line, just as antibodies from experimental animals did (model antibodies) (9,12). In this way, these antibodies activated important signaling molecules such as protein kinase C, they induced phosphorylation and thus a functional change in regulator proteins of cardiac calcium homeostasis, and influenced gene expression of the L-type calcium channel (13). A 15kDa protein was found from the phosphorylation of target proteins (12). This 15kDa potein was later identified as phospholemman (14). Phospholemman is a regulator for Na+/Ca 2+ exchanger and of Na+/K+ ATPase. Defective regulation or shortage of neuronal Na+/ K+ ATPase can lead to neuronal dysfunction and behavioral anomalies. Moreover, neurodegeneration can be triggered.

In studies of α1-AR-specific autoantibody preparations from patient sera, we were able to demonstrate concentrations for half-maximal effective binding (EC$_{50}$) to peptide sequences in the first extracellular receptor loop in the range of 30 nM (9). The persistent and prolonged non-physiological activation of cellular processes unrelated to current physiological demands on the organ, such as is caused by agonistic autoantibodies, leads to an increase of pathological conditions like calcium overload, alteration of cell structure (remodeling), through to cell death. If one considers the importance of α1-AR for the functioning of smooth musculature, then a pivotal role of agonistic autoantibodies binding these receptors must be assumed in the development of vessel impairment.

5. ANIMAL MODEL

The importance of an autoimmune response for GPCR in the development and course of diseases remained unclear for a long while and was a subject

of debate. Animal experiments were able to provide valuable insights on the causality of receptor-specific autoantibodies for the development of symptoms and the disease. The relationship between agonistic autoantibodies and dilated cardiomyopathy (DCM) had been most comprehensively investigated thus far (15). Moreover, the effect of autoantibodies on angiotensin-1-receptors (AT-1AR) in animal models had been demonstrated in preeclampsia (16) and in rejection of kidney transplants (17). An additional animal model demonstrated the participation of agAAB for α1-AR in the development of high blood pressure (18). We were able to demonstrate the damaging effect on vessels by autoantibodies for α1-AR in the brains of rats. The animals were immunized with receptor peptides and developed autoantibodies against α1-AR. The alteration to blood flow in vessels of the brain was documented by MRT techniques. A considerable reduction of blood flow in the macrovessels was observed (Figure 1) (19). Using ferumoxytol as a contrast agent, it was evident that the blood flow was reduced in the smaller vessels of the cerebrum and various other areas of the brain, such as the cortex and hippocampus. Immunofluorescence microscopy revealed a substantial reduction in vascular density within sections of rat cortex (Figure 2) (20). Subsequent histological evaluation of the cerebral sections from control animals and agAAB-positive animals showed evidence of a slight-to-moderate level of dilatation to Virchow-Robin spaces (Figure 3). This change is an indicator for manifestations of microangiopathy. These animal experiments showed that antibodies for α1-AR induced macrovascular and microvascular impairment to vessels of rat brain. We therefore assume that antibodies for α1-AR participate in the pathogenesis and progression of diseases such as dementia.

6. CLINICAL FINDINGS

It could be shown in initial smaller clinical studies that the removal of agonistic autoantibodies with the help of immunoadsorption led to an improvement in clinical outcomes. Left ventricular ejection fraction (LVEF) was improved for patients with dilated cardiomyopathy and positive agAAB for β1-AR (21). Patients with DCM who were treated with immunoadsorption that removed only the β1-antibodies by means of one specific adsorber (Core Affin) had a survival rate of 89% after five years in contrast to 69% for the experimental subjects treated with unspecific immunoadsorption (22). In patients with therapeutically refractory hypertension, it is not possible to achieve satisfactory blood pressure level with multiple administrations of anti-hypertensive medications. Experimental subjects who tested positive for agAAB experienced a long-term reduction in blood pressure through administration of immunoadsorption
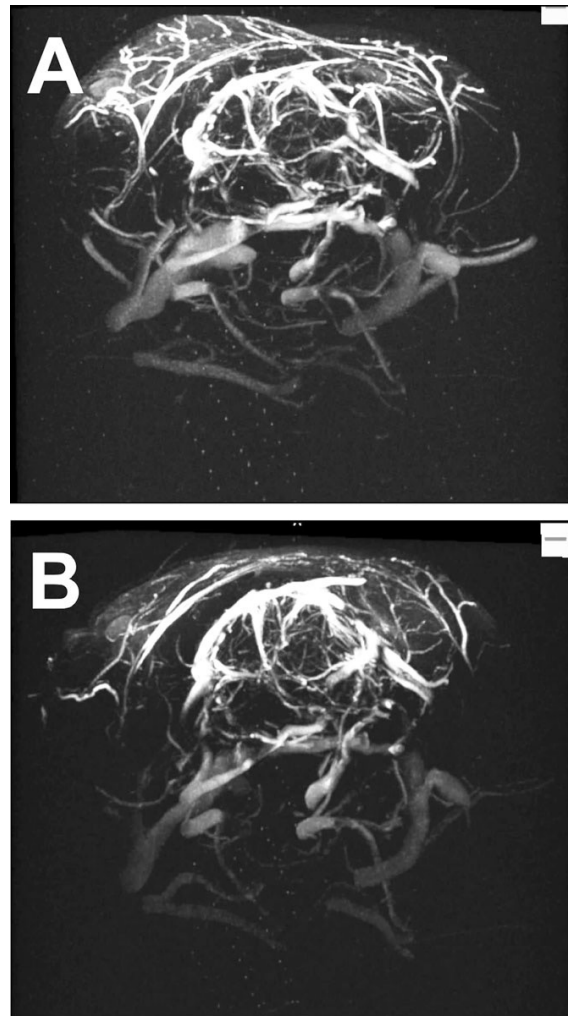

Figure 1. TOF-MRA of rat brain. Three-dimensional representation of the lateral view of the frontal brain segment. Angiographs of the same animal were recorded when an α1-AR-specific peptide was administered (A) and eight months later (B). Massive lesions after 8 months of antibody exposure are obvious (17).

(13). In patients with thromboangiitis obliterans (TAO), additional amputations were no longer observed following removal of the agAAB (23).

Our findings from in-vitro and animal-model studies on the effect of antibodies for α1-AR suggest investigating what effect the removal of the agAAB has upon the course of the disease in dementia patients positive for agAAB. As a result of the experience noted above, immunoadsorption suggested itself as a process. A cohort of patients was selected for this purpose having mild-to-moderate Alzheimer's-type dementia (MMSE between 18 and 26) and positive for agAAB for α1-AR as well as the antibodies. The immunoadsorption was carried out using Immunosorba® (Fresenius Medical Care Deutschland GmbH). The treatment took place over four days. The goal was to stabilize cognition level. The patients
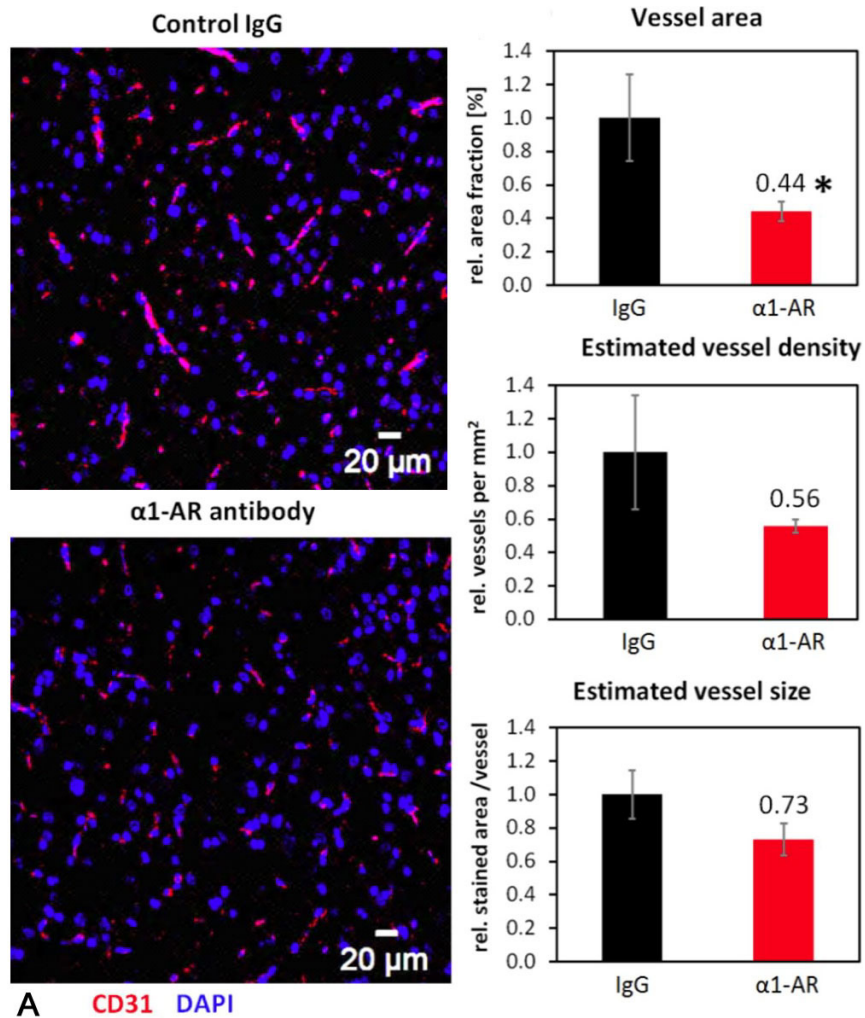
Figure 2. Immunofluorescent dye of blood vessels in sections of rat brain with antibodies for CD31 (A). The CD31 signals (red) were sharply reduced in the cortex of the animals that were administered the α1-adrenoceptor (α1- AR) antibodies. The nuclei of the cells are dyed blue with DAPI (4',6-diamidino-2-phenylindol). (B, C, D) Quantitative analysis of the immunofluorescence images of IgG-treated control animals (black) and α1-AR antibody-treated animals (red). Asterisk indicates a statistically significant difference ($p < 0.0.5$) between both groups (18).
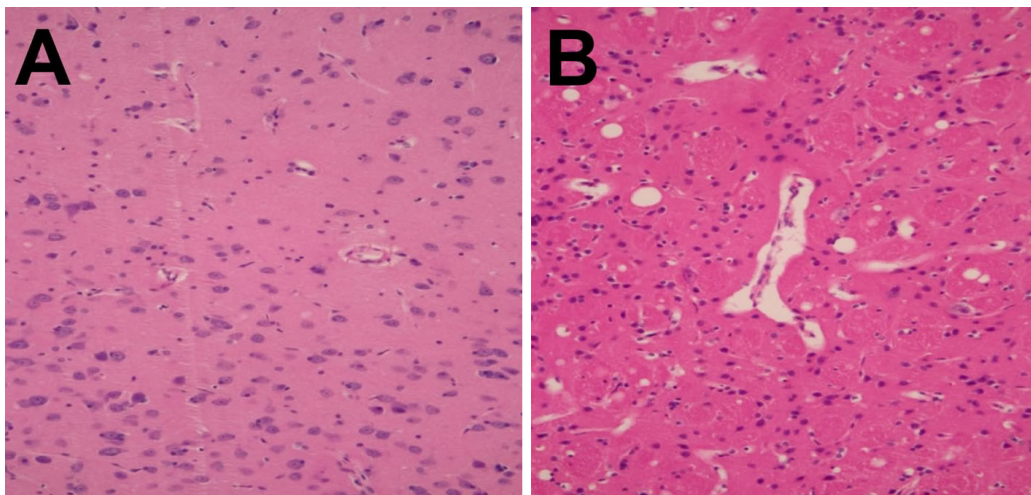

Figure 3. Optical microscopy of Virchow-Robin spaces in hematoxylin-eosin-dyed sections of rat brain. In the cerebral sections of the animals administered the α1-adrenoceptor (α1-AR) antibodies, a clearly increased dilatation of the Virchow-Robin spaces was seen.
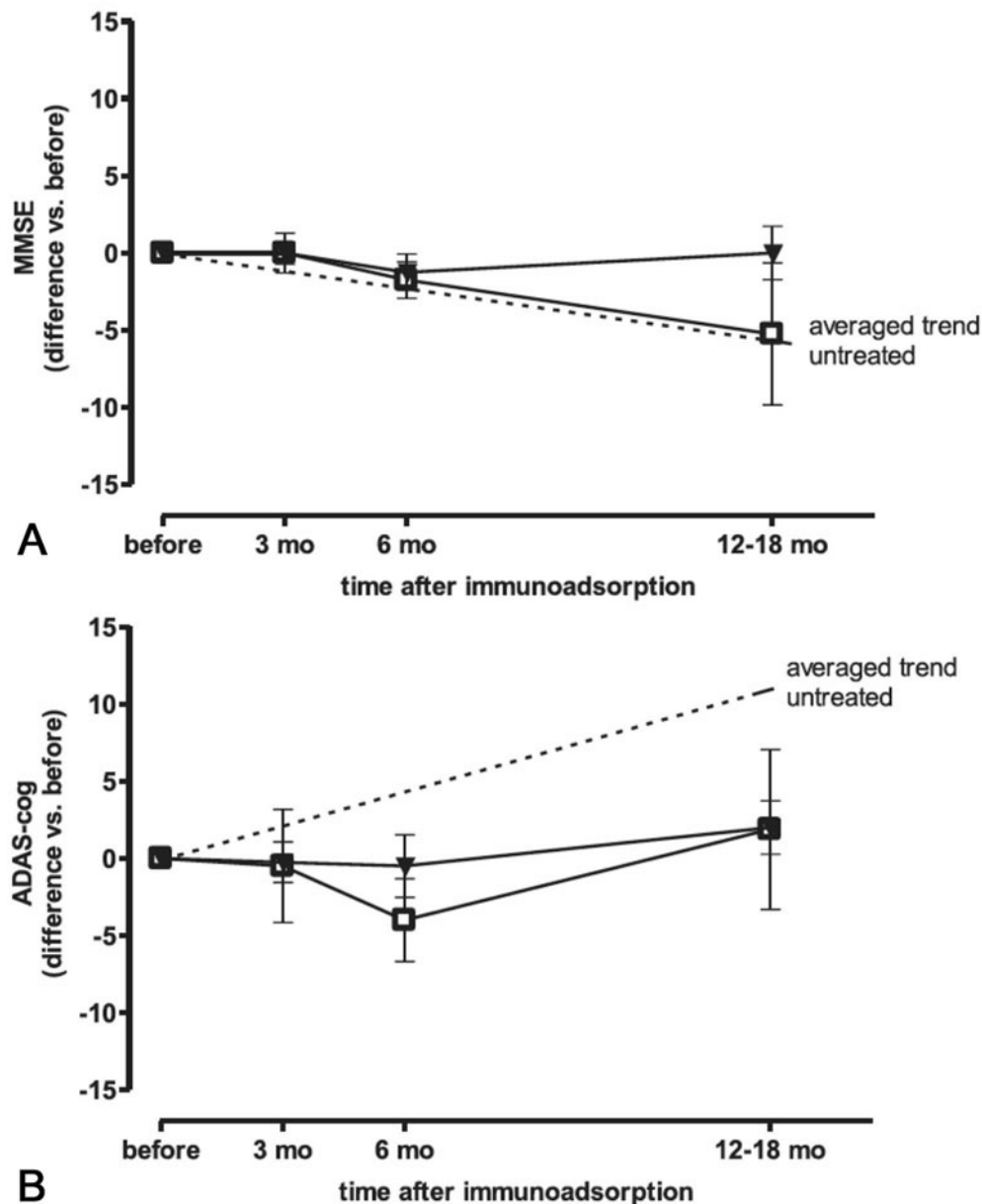
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Figure 4. Cognitive course in dementia patients after IA. Evaluation of Alzheimer's Disease Assessment Scale: (A) Mini-Mental State Examination (MMSE) and (B) ADAScog scores in patients with mild-to-moderate Alzheimer's and/or vascular dementia before and after immunoadsorption over 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 (22).

received immunoadsorption treatment on each of four sequential days. The plasma volumes were processed 2-2.5. times daily. IVIG was administered subsequently (24). No renewed occurrence of the antibodies was observed in the follow-up examination of the experimental subjects 12-18 months following the complete removal of the agAAB. During a subsequent observation period of 12-18 months, stabilization of cognitive parameters MMSE and ADAScog was observed (Figure 4 AB).

7. CONCLUSIONS

In numerous studies over the last 20 years on treatment of dementia patients using anti-dementia medications, the group of acetylcholinesterase-inhibitors, Aricept® (Donepezil), has been unable to achieve any long-term stabilization of memory ability (25). The anti-dementia medications were only applied over a period of six months in many studies. The interaction with other medications is problematic in

administering anti-dementia formulations. Similarly, all studies on reduction of amyloid-ß have lacked any promise of success. This includes the randomized study by the pharmaceutical concern Lilly. The anti-amyloid-beta antibody slanezumab was not shown to be effective against mild Alzheimer's disease (26). As well, a study with bapineuzumab (27) did not show the desired effect. These findings suggest that the reduction of amyloid-ß cannot be the sole therapeutic goal.

The Inverse Warburg Hypothesis for Alzheimer's-type dementia postulates a dysfunction of the mitochondria and a metabolic problem, abandoning the amyloid hypothesis (28). It may be that agAAB with its persistent and prolonged activation of GPCR triggers this phenomenon, which can lead finally to demise of the cell through apoptosis. The demise of the cell through the persistent and prolonged activation of the receptor by agAAB would be an explanation for the reduction in the density of intact vessels and the shrinking of the brain in dementia patients.

As a result of the findings described, it can be suggested that there is a relationship of agonistic autoantibodies for α1-AR with patients suffering from Alzheimer's disease. The stabilization of cognitive function over a longer period correlates with the complete removal of the antibodies. For this reason, immunoadsorption over a period of five days is recommended. Renewed occurrence of the antibodies was observed in the follow-up examination of the experimental subjects 12-18 months following the complete removal of the agAAB. Because older experimental subjects are involved who present poor vascular condition, patients should be admitted to hospital as regular in-patients and treated via a central IV line. In this initial small study, the experimental subjects were ambulatory and treated without a central IV line. This led to premature termination of immunoadsorption in a few cases, and notably, to incomplete removal of α1-AR autoantibodies and the tendency towards worsened mental parameters. (24).

It is advantageous that immunoadsorption has no side effects and no interactions with other medications. The blood pressure of the experimental subjects must be monitored if they take anti-hypertensive medications. The removal of the agAAB may sharply reduce blood pressure if this is caused by agAAB.

The findings of the study attest to the neuropathological effect of agAAB for α1-AR in patients with Alzheimer's disease or vascular dementia. The effective removal of the agAAB by immunoadsorption represents a very promising procedure for eliminating the influence of these vascularly harmful components on the progression of dementia. In order to verify these findings, an additional study is running currently on immunoadsorption in patients suffering from Alzheimer's-type dementia who are positive for agAAB, and in whom further neurological, radiological and biochemically parameters are being examined. Furthermore, studies of other groups on autoimmunity towards α1-AR in Alzheimer's dementia are necessary to confirm the present data.

8. ACKNOWLEDGEMENTS

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