

Influence of Anticholinergic Activity in Serum on Clinical Symptoms of Alzheimer's Disease

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Key Words

Alzheimer's disease · Serum anticholinergic activity · Clinical symptoms · Behavioral and psychological symptoms of dementia

Abstract

Alzheimer's disease (AD) is well known as a disease characterized by degeneration of cholinergic neuronal activity in the brain. It follows that patients with AD would be sensitive to an 'anticholinergic burden', and also that medicine with anticholinergic properties would promote various clinical symptoms of AD. Despite the relevance of this important phenomenon to the clinical therapeutics of AD patients, few reports have been seen concerning the relationship between anticholinergic burden and clinical AD symptoms. Therefore, we wished to investigate the relationship between serum anticholinergic activity (SAA) and the severity of clinical symptoms of AD patients. Twenty-six out of 76 AD patients referred by practitioners to our hospital were positive for anticholinergic activity in their serum, and the remaining 50 patients were negative. Cognitive and psychiatric symptoms in AD patients were compared between the positive SAA (SAA+) group and the negative SAA (SAA-)

group. The SAA+ group showed a significantly ($p < 0.05$) lower total score on the Mini-Mental State Examination, and significantly ($p < 0.05$) higher scores on the Functional Assessment Staging and the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). In particular, certain subscales of the BEHAVE-AD, i.e. the items of paranoid and delusional ideation, hallucinations and diurnal rhythm disturbances, had higher scores in the SAA+ group. Moreover, it was shown that many more psychotropic medicines were prescribed to the SAA+ group. By means of logistic regression analysis, the items of paranoid and delusional ideation and diurnal rhythm disturbances in the BEHAVE-AD were positively correlated with SAA in patients. We hypothesized that SAA in AD patients would be associated with clinical symptoms, especially delusion and diurnal rhythm disturbances.

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Introduction

Tune and Coyle [1] developed a radioreceptor assay technique to measure serum anticholinergic activity (SAA), and reported that there is an inverse correlation

between the presence of extrapyramidal side effects due to neuroleptics and SAA in patients. Moreover, Tune et al. [2] consider that the appearance of SAA is a consequence of multiple psychotropic medicines. Mulsant et al. [3] detected SAA-positive (SAA+) subjects in certain community dwellings, and found that the activity comes from taking both prescribed and over-the-counter medicines. SAA is detected in some Alzheimer's disease (AD) patients even at first admission to hospital because they have already been prescribed cognitive enhancers together with antipsychotics to prevent behavioral and psychotic symptoms of dementia (BPSD) [4, 5]. In contrast to the cognitively intact subjects, patients with central-cholinergic-deficiency-related dementia are exceptionally vulnerable to anticholinergic burdens [6, 7]. AD is well known as a disease with degeneration of cholinergic neuronal activity in the brain. Therefore, especially when SAA is detected in AD patients at first admission to hospital, we should scrutinize medicines and reduce or exchange medicines with less anticholinergic burden in order to lessen this burden. Moreover, we should discuss the relationship between SAA and demographic data, global cognitive function and BPSD to consider the degree of cognitive and behavioral impairment in these patients. To our knowledge, however, there have been only a few reports describing the relationship between anticholinergic burden and clinical symptoms of dementia, i.e. BPSD, in AD patients. Therefore, in this study we have evaluated SAA and BPSD in AD patients referred by practitioners and admitted to our hospital in order to investigate the relationship of SAA to global cognitive function and BPSD.

Patients and Methods

Seventy-six patients with AD who regularly visited the National Shimofusa Hospital (Chiba, Japan) from May 1, 2003, to March 31, 2005, were enrolled in this study. All subjects met the diagnostic criteria for probable AD assessed by a scale developed by a working group of the National Institute of Neurological and Communicative Disorders and Stroke in collaboration with the Alzheimer's Disease and Related Disorders Association [8]. Patients diagnosed with other psychiatric disorders (such as drug abuse) before the onset of dementia, as well as those with cerebral hemorrhage or infarction, were excluded from the study. We also excluded patients with active physical symptoms or with severe physical illnesses.

We evaluated demographic data (sex, educational level, age at dementia onset, age at the time of test, and severity of dementia), cognitive function, BPSD, the number of different kinds of prescribed psychotropic medicine taken (the number of prescribed psychotropic medicines) and prescribed nonpsychotropic medi-

Table 1. Demographic data in the SAA+ and SAA- groups

	SAA+	SAA-	p
Number	26 (12/14)	50 (20/30)	0.7867
Educational level, years	9.96 (3.84)	10.26 (4.00)	0.7553
Age at dementia onset years	75.3 (8.3)	73.4 (7.9)	0.3323
Test age, years	78.9 (7.2)	77.9 (7.1)	0.5460
MMSE score	8.89 (8.40)*	13.16 (8.27)	0.0367
FAST score	5.46 (1.21)*	4.78 (0.98)	0.0096
Number of psychotropic medications	1.3 (2.0)*	0.5 (1.1)	0.0234
Number of nonpsycho- tropic medications	1.8 (2.9)	1.0 (1.8)	0.1456

Data are given as means with SD in parentheses, except for the number of patients, where numbers in parentheses denote male/female ratios. Number of prescribed psychotropic medicines: number of different kinds of prescribed psychotropic medicines taken. Number of prescribed nonpsychotropic medicines: number of different kinds of prescribed nonpsychotropic medicines taken. * $p < 0.05$.

cine taken (the number of prescribed nonpsychotropic medicines). The severity of dementia was evaluated by Functional Assessment Staging (FAST) [9]. Cognitive function was evaluated by the Mini-Mental State Examination (MMSE) [10], and BPSD were assessed by the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) [11], which measures behavioral and psychological symptoms in 7 symptom domains such as paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbance, and anxieties and phobias. The BEHAVE-AD is scored on a 4-point scale according to the severity of disease. We used the total score for each symptom domain of the BEHAVE-AD, except for diurnal rhythm disturbances, which is treated as a single item. All clinical data were collected at the first visit to our hospital (at study entry).

Blood samples were collected at study entry for evaluation of anticholinergic activity. The samples, which were clotted at room temperature, were centrifuged at 3,000 rpm for 15 min, and the obtained serum samples were stored at -80°C until the assay. To avoid diurnal changes in SAA, the blood samples were collected approximately at the same time, between 10.00 a.m. and 12.00 noon. Patient information was omitted from the samples. SAA was assayed according to the receptor-binding assay protocol by Tune and Coyle [1] at Mitsubishi Chemical Medicine Corporation, Kazima, Japan. This assay is based upon the fact that the potent muscarinic receptor antagonist [^3H]radiolabeled quinuclidinyl benzilate ([^3H]QNB) binds specifically and avidly to muscarinic receptors. In each assay run, a standard displacement curve was made, adding various concentrations of atropine to the serum of young healthy volunteers taking no medicines. The level of SAA was expressed as atropine equivalents, picomoles of atropine equivalents per milliliter serum (nM), according to the [^3H]QNB counts in the patient's serum.

Table 2. List of medicines prescribed to the patients in the SAA+ and SAA- groups

a Psychotropic medicines

	SAA+	SAA-
Benzodiazepines and hypnotics	bromazepam brotizolam diazepam etizolam triazolam zopiclone quazepam (2) nitrazepam	alprazolam etizolam flunitrazepam oxazolam triazolam (2) rilmafafone zopiclone
Antiparkinsonian agents	biperiden levodopa	biperiden levodopa
Antidementia agents	donepezil (4) nicergoline	donepezil (4)
Antidepressants	fluvoxamine paroxetine (2) trazodone (2)	fluvoxamine imipramine
Antiepileptics	sodium valproate carbamazepine	sodium valproate
Antipsychotics	haloperidol (3) quetiapine (2) risperidone (2) tiapride (2) olanzapine perospirone	risperidone (2) sulpiride (2) propericiazine tiapride vegetamin B

b Nonpsychotropic medicines

SAA+	SAA-
alfacalcidol ambroxol hydrochloride amlodipine besylate benproperine phosphate bufferin calcium lactate candesartan cilexetil (2) carbocisteine cinal digoxin furosemide fursultiamine ibudilast magnesium oxide methotrexate nifedipine (3) nitrendipine potassium L-aspartate (2) pravastatin sodium prednisolone propiverine hydrochloride rebamipide sennoside seven EP tamsulosin hydrochloride ticlopidine hydrochloride tocopherol acetate verapamil hydrochloride	alacepril allopurinol senna (2) amlodipine besylate (2) arotinolol hydrochloride aspirin atenolol bezafibrate bufferin cefadroxil chlorpheniramine maleate digitoxin doxazosin mesylate famotidine (2) furosemide (2) glycyron magnesium oxide marzulene-S mecobalamin (2) naftopidil nicorandil (2) nifedipine (2) nitroglycerin oxitropium bromide oxybutynin hydrochloride senna (2) sennoside (3) simvastatin spironolactone tamsulosin hydrochloride temocapril hydrochloride teprenone theophylline tiopronin tocopherol nicotinate ubidecarenone valsartan

Numbers of patients prescribed this medicine are provided in parentheses.

We compared SAA levels between the SAA+ group and the SAA- group. The statistical analysis comparing group means was conducted using Student's t test. Items that were significantly different between the 2 groups became candidate variables for logistic regression analysis. $p < 0.05$ was accepted as a statistically significant value. The data were analyzed by the statistical software package SPSS-12.0J (Statview Inc., Tokyo, Japan).

We obtained informed consent from all study subjects or their proxies before conducting the study. This study was approved by the ethical committee of the National Shimofusa Hospital.

Results

The relationship between atropine concentration (the amount of atropine in standard solution, given in nanomoles per liter) and [³H]QNB counts (radiolabeled tritiated QNB counts, given in disintegrations per minute, dpm) is linear from 1.95 to 25 nM. Any SAA level over the detection limit is defined as SAA+. Among the 76 AD patients in this study, 26 patients were SAA+ and 50 patients

Table 3. Mean total scores for each BEHAVE-AD symptom domain in the SAA+ and SAA- groups

	SAA+	SAA-	p
Delusion	3.4 (1.3)*	1.2 (1.7)	<0.0001
Hallucination	1.9 (1.0)*	0.7 (1.0)	<0.0001
Activity disturbance	2.3 (2.2)	2.1 (2.2)	0.7162
Aggressiveness	1.9 (2.1)	1.1 (1.7)	0.0714
Rhythm disturbance	1.7 (0.7)*	0.6 (0.8)	<0.0001
Affection	0.6 (0.8)	1.0 (1.2)	0.1590
Anxiety	1.7 (1.8)	1.4 (1.8)	0.6278

Data are given as means with SD in parentheses. Delusion = Paranoid and delusional ideation; rhythm disturbance = diurnal rhythm disturbances; affection = affective disturbances; anxiety = anxieties and phobias. * $p < 0.05$ (Student's *t* test).

were SAA-. The mean SAA value \pm SD in the SAA+ group was 4.14 ± 2.70 nM.

Table 1 shows the demographic data, the total score of MMSE, the number of psychotropic medicines taken and the number of nonpsychotropic medicines taken, both in the SAA+ and the SAA- groups. Table 2 shows the lists of medicines prescribed to patients in the SAA+ and the SAA- groups. Nine medicines in the SAA+ group and 3 medicines the SAA- group were not elucidated. The prescribed psychotropics were antipsychotics, antidepressants, antiparkinsonian drugs, benzodiazepines and hypnotics, antidementia agents and antiepileptics. The prescribed nonpsychotropics were mostly cardiovascular medicines (Ca²⁺ antagonists, β -blockers, angiotensin II antagonists, angiotensin-converting enzyme inhibitors, etc.), antipulmonary disease agents and antiprosthetic hyperplastic agents. SAA+ AD patients have a tendency to be prescribed many antidepressants and antipsychotics. Especially the number of patients who took antipsychotics was as high as 9 in the SAA+ group (9/26 patients), compared with 6 in the SAA- group (6/50 patients; χ^2 test: $p = 0.0315$). Similarly, the rates of prescribed antidepressants in SAA+ and SAA- patients were 5/26 and 1/50, respectively (χ^2 test: $p = 0.0161$). Moreover, SAA+ patients were prescribed more antipsychotics that possess potent anticholinergic activity, such as olanzapine, quetiapine and risperidone. The rates of prescribed antiparkinsonian drugs, benzodiazepines and hypnotics in the SAA+ and SAA- groups were mostly equivalent. The rates of prescribed nonantipsychotic medicines in the SAA+ and SAA- groups were mostly equivalent. The numbers of nonpsychotropic medicines were equally prescribed to

patients both in the SAA+ and the SAA- group; however, the highest number of prescribed nonpsychotropic medicines to one patient was 10, and the patient was in the SAA+ group. AD patients have a tendency to be prescribed many nonpsychotropic medicines.

Table 3 shows the scores of each item on the BEHAVE-AD for the 2 groups. There were no significant differences in sex distribution, educational level, age at onset of dementia and age at the time of test between the SAA+ group and the SAA- group. The total mean MMSE scores, however, were lower in the SAA+ group than in the SAA- group, while the FAST score, the scores for paranoid and delusional ideation, hallucinations and diurnal rhythm disturbances on the BEHAVE-AD as well as the number of prescribed psychotropic medicines were significantly ($p < 0.05$) higher in the SAA+ group than in the SAA- group.

We performed a logistic regression analysis using SAA as the dependent variable, and significant univariate values of FAST scores, total MMSE score, total scores for paranoid and delusional ideation, hallucinations and diurnal rhythm disturbances on the BEHAVE-AD and total number of psychotropic medicines as the independent variables, and the logistic regression analysis revealed that there were significant ($p < 0.05$) correlations between SAA and the total scores for paranoid and delusional ideation, and the diurnal rhythm disturbances of the BEHAVE-AD, respectively.

Discussion

When we detected SAA in AD patients at first admission to our hospital, 26 out of 76 AD patients (34.2%) were found to be SAA+. Our detected rate of SAA+ patients was lower than that reported by Mulsant et al. [3] in community dwellings, which was 180 out of 201 subjects (89.6%). We found about one third of the AD patients to be SAA+ at first admission to hospital, and the mean value of SAA was 4.14 ± 2.70 nM. Tune et al. [12] reported that SAA at 7.5 nM and higher concentrations in postoperative nondemented patients was associated with a higher risk of delirium. On the other hand, Tune and Coyle [1] commented that SAA at 3.5 nM and higher concentrations was required to show a beneficial effect in schizophrenic patients taking antipsychotics in order to avoid extrapyramidal side effects, striking a balance between dopaminergic and acetylcholinergic neuronal activity. Our detected mean concentration of SAA of 4.14 ± 2.70 nM is lower than that which risks causing delirium in

postoperative nondemented patients, and somewhat higher than the lower limit to avoid extrapyramidal side effects in schizophrenic patients reported by Tune and Coyle [1]. It is quite probable, however, that even low values of SAA could affect cognition and BPSD in AD patients (although having no effect on cognition in nondemented patients) [6, 7]. Anticholinergic activity easily deteriorates the AD symptoms.

The number of prescribed psychotropic medicines was significantly ($p < 0.05$) higher in the SAA+ group. This result confirms previous expectations. Most psychotropic medicines have anticholinergic activity and are known to cause cognitive dysfunctions [2, 13, 14]. However, we commented that even if each medicine has little anticholinergic activity, a positive SAA could be the consequence of cumulatively prescribed medicines [2]. In fact, in the SAA+ group the rates of patients prescribed with antipsychotics or antidepressants were significantly higher than those in SAA- group; however, the numbers of antiparkinsonian drugs, benzodiazepines and hypnotics with potent anticholinergic activity in the SAA+ and SAA- groups were mostly equivalent, and the rates of prescribed antipsychotics and antidepressants were relatively low. We emphasized that the anticholinergic activity in the serum is caused by the cumulatively prescribed medicines, even though each medicine has no, or no prominent, anticholinergic activity [2]. Therefore, the more kinds of psychotropic medicine we prescribe, the more the SAA tends to be positive. Some of our patients who showed BPSD were prescribed psychotropic medicines and thus showed positive SAA even at study entry. Moreover, psychotropic medicines have prominent anticholinergic activity and are known to cause cognitive dysfunctions, especially in AD patients [6, 7]. Accordingly, the more kinds of nonpsychotropic medicine we prescribe, the more SAA tends to be positive because many nonpsychotropic medicines for cardiac disorders, urinary tract disorders, gastrointestinal disorders and other disorders have prominent anticholinergic properties [2]. However, regarding nonpsychotropic medicines, because patients with active physical symptoms or with severe physical illnesses were not referred, there was no significant difference in the number of nonpsychotropic medicines between the SAA+ group and the SAA- group. In fact, one patient who was prescribed with 10 nonpsychotropic medicines, without any psychotropic medicine, showed positive SAA. We considered that the higher the number of nonpsychotropic medicines prescribed was, the more the SAA would tend to be positive, as with psychotropic medicines. However, we avoided any de-

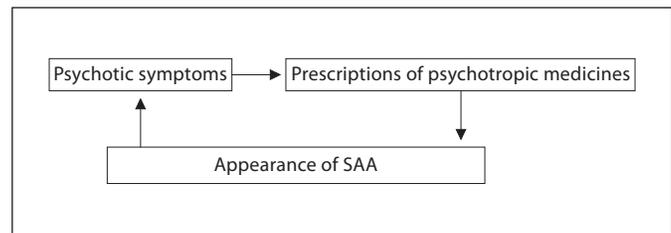


Fig. 1. SAA is induced by prescribed psychotropic medicines, and this anticholinergic activity causes clinical symptoms, especially psychiatric symptoms. Moreover, we prescribe psychotropic medicines to prevent clinical symptoms, mainly psychiatric symptoms of aggressiveness, plus hallucinations and delusions. We considered that these 3 factors (appearance of SAA, psychotic symptoms and prescription of psychotropic medicines) participated in the loop. We refer to this loop relationship as the 'vicious circle of anticholinergic activity in AD'. However, because our report was a cross-sectional one, we could not elucidate the causal relationships among these factors (appearance of SAA, psychotic symptoms and prescription of psychotropic medicines). Therefore, this hypothesis should be experimentally tested.

finite conclusion because not all prescribed medicines were elucidated. Of course, the prescribed medicines were not the only cause of anticholinergic burden. For example, Flacker and Lipsitz [15] commented that SAA might reflect a nonspecific stress response to illness in elderly people. In fact, 9 patients in the SAA+ group were prescribed with no medicine. However, prescribed medicines, especially psychotropic medicines, were one of the main causes of positive SAA in AD patients.

Although there were no significant differences in sexual distribution, educational level, age at onset of dementia and age at the time of test between the SAA+ group and the SAA- group, the total MMSE score was significantly ($p < 0.05$) lower in SAA+ group than in the SAA- group, while the FAST score and BEHAVE-AD score involving the items of paranoid and delusional ideation, hallucinations and diurnal rhythm disturbances were significantly ($p < 0.05$) higher in SAA+ group. Moreover, logistic regression analysis revealed that there were significant ($p < 0.05$) correlations between SAA and the total scores for paranoid and delusional ideation, and the diurnal rhythm disturbances of the BEHAVE-AD, respectively. These results indicate that SAA in AD patients is associated with cognitive dysfunction, disturbances of the diurnal rhythm as well as paranoid delusion and hallucination. Tune et al. [12], Flacker and Lipsitz [15] and Mach Jr. et al. [16] reported that elevated SAA in elderly patients is associated with higher rates of delirium. It is

conceivable that cognitive reduction, delusions, hallucinations and diurnal rhythm disturbances (similar to symptoms of delirium) were consequences of anticholinergic activity. Cummings [17] and Lemstra et al. [18] commented that central cholinergic deficiency was clinically characterized by neuropsychiatric symptoms rather than by cognitive impairments. Our findings are that delusions and diurnal rhythm disturbance are more strongly affected by SAA than cognitive function, and they support the comments by Cummings [17] and Lemstra et al. [18]. Similar results were also found by Mulsant et al. [19], who reported that a higher value of anticholinergic activity was associated with higher scores on the Neuropsychiatric Inventory, especially for delusion.

From our results, the clinical symptoms (cognitive dysfunction and BPSD) and the prescription of psychotropic medicines were factors related to SAA, especially hallucination and disturbed diurnal rhythm. Because our report was a cross-sectional study, we could not elucidate the causal relationships among these factors (the clinical symptoms, the prescription of psychotropic medicines and SAA). However, we speculated that there might be cyclic relationships among these three factors – we termed this the ‘vicious cycle of anticholinergic activity in AD’ (fig. 1) – and that there might be an endogenous anticholinergic factor. Medicines with potent anticholinergic activity or the prescription of many kinds of medicine cause positive SAA, and anticholinergic activity worsens clinical psychiatric symptoms. However, in general we prescribe psychotropic medicines for the clinical psychiatric symptoms of agitation and psychosis in AD [20, 21]. Therefore, the relationship among prescribed psychotropic medicines, SAA and clinical symptoms, es-

pecially hallucination and disturbed diurnal rhythm, might be a cyclic one.

Secondly, there is a high probability that the pathogenesis of AD concerns neuronal degeneration by oxidative stress [22], and it has been shown that amyloid- β peptide might have the ability to generate free radicals. On the other hand, an endogenous ligand of the muscarinic receptor in the AD brain has been detected, more than in the nondemented control brain, and the endogenous ligand of the muscarinic receptor seems to be a low-molecular substance of 100–1,000 Da which has been catalyzed by oxidation [23]. It is possible that SAA does not always derive from prescribed psychotropic medicines, but also from endogenous oxidative products [15].

Therefore, psychiatrists should first treat with medicines which activate cholinergic neuronal activity and reduce oxidative stress, then treat with psychotropic medicines with weak or no anticholinergic activity. Of course, because our report was a cross-sectional one, no causal relationships could be established, and this hypothesis should be experimentally tested. It is, however, important to realize that – whether there are cyclic relationships among these three factors or not, and whether SAA is exogenous or endogenous – SAA plays a role in the psychiatric symptoms of AD.

The limitations of this study included a small sample size, absence of control subjects, and that this study was a cross-sectional one, with no longitudinal course of SAA. Further investigations using longitudinal observations of large samples would be necessary to delineate a more precise relationship between SAA and clinical symptoms (especially BPSD) in AD.

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