

Serum Anticholinergic Activity in a Community-Based Sample of Older Adults

Relationship With Cognitive Performance

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Background: Serum anticholinergic activity (SAA), as measured by a radioreceptor assay, quantifies a person's overall anticholinergic burden caused by all drugs and their metabolites. In several small geriatric patient groups, SAA has been associated with cognitive impairment or frank delirium. To our knowledge, there has not yet been any systematic study of the prevalence of SAA and its effect on cognition in a community-based population.

Methods: Serum anticholinergic activity was measured in 201 subjects who were randomly selected among the participants in an epidemiological community study, based on their age and sex. Cognitive performance was assessed with use of the Mini-Mental State Examination. The association between SAA and cognitive performance was examined using a univariate analysis and a multiple logistic regression model, adjusting for age, sex, educational level, and number of medications.

Results: Serum anticholinergic activity was detectable in 180 (89.6%) participants (range, 0.50-5.70 pmol/mL). Univariate testing showed a significant association between SAA and Mini-Mental State Examination scores. Logistic regression analysis indicated that subjects with SAA at or above the sample's 90th percentile (ie, SAA \geq 2.80 pmol/mL) were 13 times (odds ratio, 1.08-152.39) more likely than subjects with undetectable SAA to have a Mini-Mental State Examination score of 24 (the sample's 10th percentile) or below.

Conclusions: To our knowledge, this is the largest analysis of SAA and the first to examine its extent and relationship with cognitive performance in a community sample. Its results suggest that SAA can be detected in most older persons in the community and confirm that even low SAA is associated with cognitive impairment.

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FOR MORE THAN 100 years, clinicians have recognized that drugs with anticholinergic properties are associated with an acute and reversible confusional state, eg, what we now call delirium, particularly in older patients.¹⁻³ The centrally acting cholinomimetic agent physostigmine salicylate has been used to treat anticholinergic delirium since the mid 1800s,¹ and conversely, scopolamine hydrobromide, a powerful anticholinergic drug, has been used to induce and study these confusional states experimentally.⁴⁻⁷ Drugs that have high central anticholinergic effects, ie, those that have a high propensity to antagonize muscarinic receptors, are particularly likely to be implicated in these confusional states.⁸⁻¹¹

Since the early 1980s, a radioreceptor assay has been available to quantify a person's overall anticholinergic burden caused by all drugs and their metabolites, referred to as serum anticholinergic activity (SAA).¹¹⁻¹⁴ This measure of SAA has

been shown to correlate with the measurable anticholinergic effects of specific drugs.¹⁴⁻¹⁶ Conversely, its availability has also led to the realization that patients can present with detectable SAA even when the drugs they are taking are not identified as typically having a substantial anticholinergic effect.^{11,17} In younger patients, the relationship between SAA and cognition has been inconsistent.¹⁸⁻²⁵ By contrast, with one exception,²⁶ SAA has consistently been shown to be associated with cognitive impairment or frank delirium in at least 11 studies^{4,10,15,17,27-33} involving older patients. This association between SAA and cognitive impairment is independent of the burden of physical illness in patients who are medically stable, ie, SAA does not merely reflect a worse physical status resulting in the prescription of a higher number of anticholinergic drugs.³¹ To date, all the published studies of SAA have been performed in small groups, typically 10 to 40, of younger patients with schizophrenia or older patients with preexisting cog-

nitive impairment or “at risk” for cognitive impairment or delirium (eg, inpatients in a surgery unit, an intensive care unit, or a geropsychiatry program). To our knowledge, there has not yet been any systematic study of the prevalence of detectable SAA and its effect on cognition in a community-based geriatric population. Therefore, we assessed the prevalence and extent of SAA in a subsample of the Monongahela Valley Independent Elders Survey (MoVIES) cohort, a community-based epidemiological study, and examined its relationship with cognitive performance.

METHODS

SUBJECTS AND MATERIALS

The MoVIES project was a prospective epidemiological community study conducted from April 1, 1987, to April 30, 2002, in the mid Monongahela Valley, a rural, formerly industrial, region of southwestern Pennsylvania. Details of its overall objectives, sampling, recruitment, and data collection methods have been described previously.³⁴⁻³⁶ The study cohort described herein represents survivors of an age-stratified random sample of 1422 individuals and 259 volunteers, recruited from the community between April 1, 1987, and October 20, 1989.³⁷ Inclusion criteria included age 65 years or older, fluency in English, having at least a sixth-grade education, and not being in an institution at the time of study entry. The MoVIES cohort has been followed up prospectively since that time in a series of biennial data collection waves. At each wave, subjects were assessed with various instruments, including the Mini-Mental State Examination (MMSE).³⁸ Information about regular medication use was obtained by self-report and by examining medication bottle labels for prescription drugs³⁹ and over-the-counter products.⁴⁰ At certain waves, venous blood specimens were drawn for different laboratory studies. All study procedures were carried out with written informed consent obtained according to protocols approved by the Institutional Review Board at University of Pittsburgh.

For the present analyses, serum specimens had been collected between March 8, 1995, and September 9, 1997, and stored at -20°C . From 703 available specimens, we randomly selected 201 specimens, based on the age and sex (at the time of blood draw) of the participants, so as to be representative of the age and sex distribution of the US population in 1996 according to the US Census estimates. The age and sex distribution of the sample is shown in **Table 1**. Serum anticholinergic activity was measured as previously described,^{31,41} using a radioreceptor assay developed by Tune and Coyle.¹¹⁻¹³ Briefly, tritiated quinuclidinyl benzilate has a high and specific affinity for the 5 subtypes of muscarinic receptors.¹² Anticholinergic drugs competitively inhibit tritiated quinuclidinyl benzilate binding to these muscarinic receptors. Therefore, displacement of tritiated quinuclidinyl benzilate bound to a homogenate of rat forebrain can be used to quantify SAA. Serum anticholinergic activity is reported in picomoles of atropine equivalents per milliliter (ie, picomoles per milliliter or nanomolar), based on the amount of tritiated quinuclidinyl benzilate displacement that would have been caused by a standard amount of atropine in a 200- μL sample. Serum anticholinergic activity is thought to reflect the cumulative anticholinergic effect of all exogenous substances taken by the subject (ie, medications and supplements) and their metabolites. In our laboratory, the limit of detection for this assay is 0.25 pmol/mL, with a standard linear curve ($r=0.99$) from 0.50 to 25.00 pmol/mL and good interassay and intra-assay reproducibility for these concentrations (ie, coefficient of variations $<12\%$).

Table 1. Baseline Characteristics of 201 Participants*

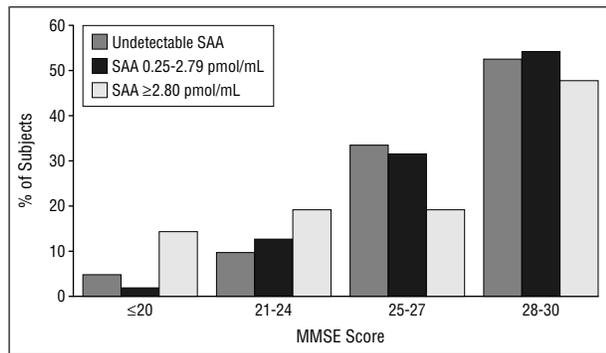
| Variable | Female (n = 122 [60.7%]) | Male (n = 79 [39.3%]) | All (N = 201 [100%]) |
|------------------------------------|--------------------------------|-----------------------------|----------------------------|
| Age, y | | | |
| Mean (SD) | 78.5 (5.3) | 77.6 (5.0) | 78.2 (5.2) |
| Median (range) | 77.0 (71-94) | 76.0 (72-95) | 77.0 (71-95) |
| Educational level | | | |
| <High school | 36.9 | 40.5 | 38.3 |
| \geq High school | 63.1 | 59.5 | 61.7 |
| No. of medications | | | |
| Mean (SD) | 5.6 (3.5) | 4.5 (3.2) | 5.2 (3.4) |
| 0-3 | 28.7 | 45.6 | 35.3 |
| 4-6 | 39.3 | 30.4 | 35.8 |
| >6 | 32.0 | 24.1 | 28.9 |
| No. of anticholinergic medications | | | |
| Mean (SD) | 0.88 (1.00) | 0.96 (1.53) | 0.91 (1.23) |
| 0 | 44.3 | 55.7 | 48.8 |
| >0 | 55.7 | 44.3 | 51.2 |
| MMSE score | | | |
| Mean (SD) | 26.9 (4.0) | 26.6 (2.4) | 26.8 (3.5) |
| Median (range) | 28.0 (2-30) | 27.0 (17-30) | 28.0 (2-30) |
| ≤ 24 | 10.7 | 7.6 | 9.5 |
| >24 | 89.3 | 92.4 | 90.6 |
| SAA, pmol/mL | | | |
| Mean (SD) | 1.50 (1.25) | 1.30 (1.25) | 1.45 (1.10) |
| Median (range) | 1.35 (0-4.80) | 1.05 (0-5.70) | 1.25 (0-5.70) |
| Undetectable | 8.2 | 13.9 | 10.5 |
| 0.25-2.79 | 79.5 | 78.5 | 79.1 |
| ≥ 2.80 | 12.3 | 7.6 | 10.5 |

Abbreviations: MMSE, Mini-Mental State Examination; and SAA, serum anticholinergic activity.

*Data are given as percentages unless otherwise indicated. Some percentages do not sum to 100 because of rounding.

STATISTICAL ANALYSES

Descriptive statistics were calculated for age, sex, educational level, number of medications, MMSE scores, and SAA. To test the association between SAA and cognitive performance, first we examined the univariate association between SAA and MMSE scores, using Pearson χ^2 tests. Because the SAA and MMSE scores have skewed distributions in this nonclinical community-based sample, we treated them as categorical rather than continuous variables, using 3 categories for SAA: undetectable SAA (ie, SAA <0.25 pmol/mL), detectable SAA of less than 2.80 pmol/mL, and SAA of 2.80 pmol/mL or higher, with 2.80 being the 90th percentile value and 0 being the 10th percentile value for SAA. We dichotomized MMSE scores by using the score at the 10th percentile of the study sample as a cutpoint: lower MMSE (ie, ≤ 24) vs higher MMSE (ie, >24) scores. To further adjust for other factors that might be potential confounders, we modeled lower MMSE score (ie, ≤ 24) as an outcome, using logistic regression analysis with SAA as a covariate, adjusting for age, sex, educational level, and number of prescription and non-prescription medications (categorized as 0-3, 4-6, or >6). Previous studies^{42,43} have shown that the number of medications taken by older people is correlated with global burden of physical illness, assessed by the number of active medical problems or with a validated scale. In the logistic regression analysis, we treated SAA in 2 ways: as a categorical variable (using the 3 categories for SAA already mentioned) and as a continuous variable. Goodness of fit was examined by using Hosmer and Lemeshow goodness-of-fit statistics. For descriptive purposes, a report was also generated of the prescription and over-the-



Distribution of Mini-Mental State Examination (MMSE) scores in each serum anticholinergic activity (SAA) group.

counter drugs being taken by the subjects in each SAA group. The number of drugs that have possible or definite central anticholinergic effects was determined in each of the 3 groups, following a published method.²⁷

RESULTS

The distribution of age, sex, educational level, number of medications, number of medications with possible or definite central anticholinergic effects, MMSE scores, and SAA for the study sample ($n=201$) is summarized in Table 1. The mean (SD) age was 78.2 (5.2) years; 60.7% of the subjects were women. The median educational level was high school graduate. The mean (SD) number of medications was 5.2 (3.4) (median, 5; range, 0-16), with a mean (SD) number of anticholinergic medications of 0.91 (1.23) (median, 1; range, 0-8). The mean (SD) MMSE score was 26.8 (3.5) (median, 28; range, 2-30) and a 10th percentile score of 24. Serum anticholinergic activity was detectable in 180 (89.6%) participants; the mean (SD) SAA value was 1.45 (1.10) pmol/mL (median, 1.25; range, 0.50-5.70 pmol/mL) and a 90th percentile value of 2.80 pmol/mL.

The **Figure** presents the distribution of MMSE scores in subjects with undetectable SAA, detectable SAA of less than 2.80 pmol/mL, and SAA of 2.80 pmol/mL or higher. Univariate testing showed a significant association between SAA and MMSE scores (Pearson $\chi^2=10.18$, $P=.006$). The MMSE scores were low (ie, ≤ 24) in 4.8% of the subjects with undetectable SAA, 7.6% of those with detectable SAA below 2.80 pmol/mL, and 28.6% of those with SAA of 2.80 pmol/mL or higher, suggesting that subjects with higher SAA have lower MMSE scores. Treating SAA as a categorical variable, the result of a logistic regression analysis indicated that subjects with SAA of 2.80 pmol/mL or higher had a significantly higher probability of having an MMSE score of 24 or below compared with subjects with undetectable SAA (odds ratio [OR], 12.81; 95% confidence interval [CI], 1.08-152.39; $P=.04$). Similarly, when SAA was treated as a continuous variable, the association between SAA and low MMSE score was also significant (OR, 16.71; 95% CI, 2.02-138.29; $P=.009$) (**Table 2**). Tests of goodness of fit indicated that there was no significant lack of fit for the 2 models.

One or more subjects were taking 1 of the following medications with definite central anticholinergic ef-

Table 2. Logistic Regression Analyses With Lower MMSE Score (≤ 24) as the Dependent Variable*

| Variable | SAA as Categorical Variable | SAA as Continuous Variable |
|--------------------|-----------------------------|----------------------------|
| Age, y | 1.19 (1.08-1.31) | 1.20 (1.09-1.32) |
| Sex | | |
| Male | 1.00 (Reference) | 1.00 (Reference) |
| Female | 1.05 (0.33-3.32) | 1.15 (0.37-3.57) |
| Educational level | | |
| <High school | 1.00 (Reference) | 1.00 (Reference) |
| \geq High school | 0.41 (0.13-1.26) | 0.39 (0.13-1.21) |
| No. of medications | | |
| 0-3 | 1.00 (Reference) | 1.00 (Reference) |
| 4-6 | 1.30 (0.33-5.04) | 1.46 (0.39-5.44) |
| >6 | 1.18 (0.28-4.96) | 1.21 (0.29-5.05) |
| SAA, pmol/mL | | |
| Undetectable | 1.00 (Reference) | 16.71 (2.02-138.29) |
| 0.25-2.79 | 2.01 (0.22-18.53) | |
| ≥ 2.80 | 12.81 (1.08-152.39) | |

Abbreviations: MMSE, Mini-Mental State Examination; SAA, serum anticholinergic activity.

*Data are given as odds ratio (95% confidence interval).

fects: amitriptyline hydrochloride ($n=1$ subject in the group with SAA of ≥ 2.80 pmol/mL, 0 subjects in the group with detectable SAA of < 2.80 pmol/mL, and 0 subjects in the group with undetectable SAA); chlorpheniramine polistirex ($n=2$, 2, and 0, respectively); diphenhydramine ($n=1$, 8, and 0); hydroxyzine ($n=0$, 1, and 0); hyoscyamine ($n=2$, 0, and 0); ipratropium bromide inhaler ($n=1$, 3, and 0); or meclizine hydrochloride ($n=1$, 2, and 0). Among the same 3 SAA groups already defined, 1 or more subjects were taking one of the following medications with possible central anticholinergic effects: alprazolam ($n=0$, 1, and 0, respectively); brompheniramine maleate ($n=0$, 1, and 0); bupropion hydrochloride ($n=0$, 1, and 0); captopril ($n=1$, 4, and 2); chlorthalidone ($n=0$, 2, and 1); cimetidine hydrochloride ($n=1$, 3, and 1); clorazepate ($n=0$, 3, and 0); colchicine ($n=1$, 2, and 0); diazepam ($n=0$, 3, and 0); digoxin ($n=6$, 23, and 2); dipyridamole ($n=0$, 5, and 0); disopyramide phosphate ($n=0$, 1, and 0); furosemide ($n=3$, 13, and 2); hydralazine ($n=0$, 2, and 0); hydrocortisone ($n=0$, 2, and 0); isosorbide ($n=0$, 20, and 2); nifedipine ($n=1$, 5, and 1); prednisone ($n=0$, 4, and 0); quinidine ($n=1$, 2, and 1); ranitidine ($n=2$, 10, and 0); theophylline sodium glycinate ($n=1$, 8, and 0); triamterene ($n=1$, 5, and 0); or warfarin sodium ($n=2$, 7, and 3). Among subjects with SAA of 2.80 pmol/mL or higher, the mean (SD) number of medications with possible or definite central anticholinergic effects was 1.3 (1.9) (range, 0-8), with 11 (52%) of 21 taking at least 1 such drug. Among the subjects with detectable SAA less than 2.80 pmol/mL, the mean (SD) number of anticholinergic medications was 0.9 (1.1) (range, 0-5), with 84 (53%) of 159 taking at least 1 such drug. Finally, among the subjects with undetectable SAA, the mean (SD) number of anticholinergic medications was 0.7 (1.2) (range, 0-4), with 8 (38%) of 21 taking at least 1 such drug. These means and proportions did not differ significantly ($P>.20$). However, there was a trend for the proportion of subjects who

were taking a drug with definite central anticholinergic effects to differ among the 3 groups: 4 (19%) of 21 subjects with SAA of 2.80 pmol/mL or higher, 13 (8%) of 159 subjects with detectable SAA of less than 2.80 pmol/mL, and 0 of 21 subjects with undetectable SAA (Cochran-Armitage trend test, $P=.05$). Therefore, to determine whether the observed association between SAA and cognition was solely because of the higher proportion of subjects with SAA of 2.80 pmol/mL or higher taking drugs with definite central anticholinergic effects, we added to our 2 logistic regression models (treating SAA as a categorical or as a continuous variable) a dichotomous variable to control for the intake of drugs with definite central anticholinergic effects. In both models, the association between SAA and low MMSE score remained significant and similar to the association observed without controlling for the intake of definite anticholinergic drugs (SAA as a categorical variable: OR, 13.40; 95% CI, 1.13-159.49; $P=.04$; and SAA as a continuous variable: OR, 19.12; 95% CI, 2.15-169.85; $P=.008$).

COMMENT

An analysis of SAA in a representative community sample of 201 older subjects revealed that SAA could be detected in most subjects. Although SAA was modest in this community sample (median, 1.25 pmol/mL; range, 0.50-5.70 pmol/mL), it was strongly and significantly associated with cognitive impairment. Participants with SAA higher than the sample's 90th percentile were 13 times (OR, 1.08-152.39) more likely to have an MMSE score below the sample's 10th percentile than participants with undetectable SAA.

To our knowledge, this is the largest analysis of SAA and the first to examine the prevalence of detectable SAA and its relationship with cognitive performance in a community sample. It confirms and extends results obtained in several small clinical groups and supports that even low SAA (ie, <5 pmol of atropine equivalents per milliliter) is associated with cognitive impairment in older persons.³¹ Several limitations of our study should be considered when interpreting its results. First, although our sample size was 3 times larger than the sample size of the largest study²⁷ of SAA published so far, it remains small in epidemiological terms; thus, our CIs are wide. Also, our subjects were selected so that their age and sex would be representative of the US older populations, but all subjects were from a rural blue-collar community. In a previous analysis, social variables (eg, educational level and income) were strongly associated with the use of prescription and over-the-counter medications.^{39,40} For instance, more educated older persons were more likely to use over-the-counter drugs in general⁴⁰ and diphenhydramine in particular.⁴⁴ Therefore, our results need to be replicated in other community samples drawn from various geographic and social groups. Finally, in this study, cognitive performance was assessed globally with use of the MMSE. It is possible that we would have found a different association by assessing specific cognitive domains.⁴⁵ However, it is likely that an association between SAA and cognition could also have been demonstrated using instruments

that assess specific cognitive functions, as has been done in other studies.^{4,10,15,22,24,31}

Notwithstanding these possible limitations, our results strongly support that even low SAA is associated with cognitive impairment in older persons. Although this association can be considered well established, it does not necessarily imply causality, and the mechanism underlying it is not clear. It is assumed that SAA is the result of medications and their metabolites, although potentially endogenous sources of SAA may exist.^{26,27,46} Nevertheless, SAA correlates with directly measured serum concentrations of typical anticholinergic drugs.^{15,41} Furthermore, although SAA is measured in serum and it is not known to what degree it correlates with actual central antimuscarinic blockade,¹⁰ in one small study⁴ SAA and CSF anticholinergic activity were significantly correlated ($r=0.69$) and both were associated with cognitive impairment.

The absence in our study and others of an association between SAA and number of medications or even number of possible anticholinergic drugs is similar to the absence in large epidemiological studies^{47,48} of an association between use of anticholinergic drugs and a clinical diagnosis of delirium. This apparent puzzling lack of association between SAA (or delirium) and anticholinergic drugs can be attributed to several factors. First, only a few medications (eg, tertiary tricyclic antidepressants, diphenhydramine, and low potency neuroleptics) have been clearly identified as having central anticholinergic effects and as putting older patients at risk for confusion or frank delirium.⁴⁹ Their use has been discouraged in older patients,^{50,51} and they were used only by a few of our subjects. As expected, these subjects were among those with the highest SAA. More important, a growing number of medications frequently prescribed to older patients but not typically thought of as being anticholinergic (eg, warfarin, digoxin, isosorbide, and prednisone) have been shown to have measurable anticholinergic effects.^{11,14} We considered these medications as having possible anticholinergic effects. However, it has been estimated that more than 600 other medications may have unrecognized anticholinergic effects.^{1,2} Older persons are disproportionately liable to take several of these medications (as well as different herbal and other supplements).⁴⁰ Although one of these medications taken alone may not result in significant central or peripheral anticholinergic effects in most individuals, the concurrent use of several of these medications may result in significant "cumulative" SAA and associated cognitive impairment. Also, it is likely that pharmacologically active metabolites of many drugs have unrecognized anticholinergic effects. Finally, there are considerable individual differences in absorption, distribution, rate of metabolism, formation, and excretion of pharmacologically active metabolites.⁵² For instance, serum levels of benzotropine mesylate have been reported to vary nearly 100-fold among young individuals receiving the same dosage.¹² Assessing anticholinergic activity based on administered drugs does not account for this intersubject variability and gives a poor estimate of true exposure in a particular individual.^{10,47} Therefore, because of the incomplete elucidation of which medications have

anticholinergic effects and because of individual variability, measurement of SAA appears the most promising way to detect, and potentially prevent or correct, pharmacological cognitive toxicity from subclinical impairment to frank delirium. However, additional studies to simplify and standardize the measurement of SAA and to establish its accuracy in other community samples are needed before it becomes practical in the clinical setting. In the meantime, the results of this and previous studies provide the clinician with yet another reason to scrutinize the medications taken by their older patients and to judiciously eliminate or replace selected medications.⁵³

For the researchers who are studying cognitive performance in late life and the determinants of its variability, our results suggest that systematic measurement of SAA should be considered in all such studies, because SAA may be a covariate as important as age or sex. Our understanding of the nature and severity of the cognitive decrements associated with normal aging may be distorted by the effects of prescribed and over-the-counter medications with anticholinergic effects. The presence of varying SAA levels in older individuals could help to account for some of the remarkable heterogeneity that exists in the cognitive performance of older persons. After age 65, there is a marked increase in the mean magnitude of these cognitive impairments and in individual variability, with some older persons showing a substantially greater cognitive decline than others. The number of older persons with medical conditions requiring medications also rises sharply in this age group. Studies of cognitive toxicity carried out in the drug approval process rarely look beyond whether a medication produces severe cognitive deficits such as confusion or frank delirium. Therefore, current procedures for drug approval may fail to recognize milder adverse cognitive effects that are specific to older persons,⁵⁴ especially when one considers the potential for a cumulative effect from multiple medications. If anticholinergic medications produce a substantial portion of the cognitive impairment typically attributed to the normal aging process, this has major implications for the risk-benefit equation of many medications commonly taken by older persons.

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Correction

Error in Text. In the Special Article titled "The Interplay of Nature, Nurture, and Developmental Influences: The Challenge Ahead for Mental Health," published in the November issue of the ARCHIVES (2002;59:996-1000), the sentence at the end of the right-hand column on page 996 should have read as follows: "It is necessary to take into account stochastic effects¹⁰ and developmental influences (possibly including endocrine influences on genetic effects). In addition, gene-environment correlations and interactions mean that some variance is accounted for by the joint coaction of genetic and environmental effects."