Autoimmune Autonomic Ganglionopathy With Reversible Cognitive Impairment

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Background: Autoimmune autonomic ganglionopathy (AAG) is a rare disorder of antibody-mediated impaired transmission across the autonomic ganglia resulting in severe autonomic failure. Some patients with AAG report cognitive impairment of unclear etiology despite treatment of autonomic symptoms.

Objective: To investigate the relationship between orthostatic hypotension, antibody titers, and cognitive impairment in patients with AAG.

Design: Prospective cohort.

Setting: Academic medical center.

Participants: Three patients with AAG underwent neuropsychological testing before and after cycles of plasma exchange in both the seated and standing positions.

Main Outcome Measures: Patients’ responses to neuropsychological tests were measured by percentage change from baseline in the seated and standing positions before and after plasma exchange to determine the effects of orthostatic hypotension and antibody titers on cognition.

Results: Orthostatic hypotension and elevated antibody titer were associated independently with neuropsychological impairment (P<.05), particularly in domains of executive function, sustained attention, and working memory. Cognitive dysfunction improved, even in the seated normotensive position, after plasmapheresis and consequent reduction in antibody levels.

Conclusion: Reversible cognitive impairment is independently associated with both orthostatic hypotension and elevated nicotinic acetylcholine receptor autoantibodies, thereby expanding the clinical spectrum of autonomic ganglionopathy and, in so doing, providing an additional treatable cause of cognitive impairment.


AUTOIMMUNE AUTONOMIC ganglionopathy (AAG) is a rare disorder characterized by immune-mediated disruption of fast synaptic transmission across the peripheral autonomic ganglia. Patients present with severe orthostatic hypotension that requires both symptomatic, therapeutic interventions with multiple agents and immunomodulatory therapy of the underlying disease. Other sequelae of AAG include sudomotor abnormalities, gastrointestinal and bladder dysfunction, dry eyes, dry mouth, and pupillary dysfunction. Previous studies have demonstrated correlations between antibody titers and decreases in systolic blood pressure with standing or upright tilt table test. Higher antibody titers are also associated with reduced heart rate variability during a Valsalva maneuver and tests of paced breathing.

These symptoms, signs, and test abnormalities reverse after immunomodulating therapy and concomitant antibody reduction. Despite substantial resolution of autonomic symptoms, we have observed that patients have ongoing cognitive impairment and are not able to return to their prior occupations. While dementia is a recognized concomitant feature of central autonomic neurodegenerative disorders such as Parkinson disease, Lewy body disease, and multiple system atrophy, impaired cognition has not been reported previously in peripheral autonomic disorders to our knowledge.

Pathophysiological mechanisms that may underlie cognitive impairment in AAG include transient, intermittent, reduced cerebral perfusion due to orthostatic hypotension or chronic cerebral effects of repeated episodes of severe orthostatic hypotension. Central effects of the nicotinic acetylcholine receptor

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(AChR) antibody also may be responsible. Encephalopathy and other central features have been reported in a patient with elevated peripheral α-3 and central α-4 and α-7 antibody levels, and an immunotherapy-responsive dementia has been associated with elevated nicotinic AChR antibody levels. In addition, cortical and neuropsychiatric manifestations may be present in up to 10% of patients with elevated peripheral α-3 nicotinic AChR antibody levels.

We hypothesized that the cognitive impairment was due to transient decreased cerebral perfusion caused by antibody-mediated orthostatic hypotension. To test this hypothesis, we studied 3 patients with AAG before and after plasma exchange (with corresponding high and low antibody titers) and varying degrees of orthostatic hypotension. All studies were performed in the seated and upright positions.

METHODS

The study was approved by the institutional review board at Beth Israel Deaconess Medical Center, Boston, Massachusetts. Three individuals with AAG receiving immunomodulatory maintenance therapy with prednisone and mycophenolate mofetil were studied. These subjects were treated periodically with plasma exchange when symptomatic orthostatic hypotension worsened in association with an increase in antibody titers. There was no history of cognitive dysfunction, traumatic brain injury, psychiatric illness, or other central nervous system disorders. All subjects with AAG had orthostatic hypotension with variable severity depending on antibody titer (ranging from systolic blood pressure decreases of 10-100 mm Hg with antibody titers <1 nmol/L to >2 nmol/L; see Table 1 in the article by Gibbons and Freeman).

MEASURES

A battery of neuropsychological tests was administered in the seated and standing positions during a 1-year period before and/or after cycles of plasma exchange. Blood pressures and antibody titers were measured at each visit. The neuropsychological test order varied across subjects, visits, and positional change. To avoid confounding effects of the sleep-wake cycle on cognition, all testing prior to plasmapheresis began within 1 hour of 9 AM and all testing subsequent to plasmapheresis began within 1 hour of 1 PM for all subjects. Subjects refrained from eating for 90 minutes prior to testing. The test battery included measures of visual search, motor speed, processing speed, immediate and working memory, executive function, and spontaneous verbal fluency. Test selection was guided by hypothesized deficits within the domains of attention, activation/retrieval, and working memory; appropriate difficulty level; brevity of administration; and availability of alternate forms for resistance to test-retest effects. The test battery required approximately 10 minutes to complete in each position. Premorbid level of functioning was determined with the Wechsler Test of Adult Reading.

Visuomotor tracking and attention were assessed using the Trail Making Test Part A. In this test, the patient is asked to draw a continuous line connecting circled numbers in sequence. Executive functioning was assessed using the Trail Making Test Part B, in which both circled numbers and circled letters are connected in alternating sequence. Set-shifting ability and working memory were determined by subtracting the time to complete Trail Making Test Part B from the time to complete Trail Making Test Part A. The Digit Span Test (forward and backward) was used to measure immediate (forward) and working (backward) memory. In this test, the patient is asked to repeat a string of digits of increasing length. Phonemic fluency and activation/retrieval were assessed with the Controlled Oral Word Association Test, in which patients are asked to generate as many words as possible according to a first-letter criterion, using the letters F, A, and S and the alternate forms B, H, and R. A computerized version of the Stroop Color Word Test was used to measure mental speed, attention, and response inhibition (executive function). The Stroop Color Word Test requires the patient to determine whether the text color of a word is the same color as the presented word. The Ruff Test of Selective Attention, a serial search and number cancellation task, was used to measure sustained attention, selective attention, and graphomotor speed. In this test, the patient is asked to visually search a series of digit strings and identify and mark all occurrences of 2 target digits. In the automatic condition, the target digits are embedded among letter distractors. In the controlled condition, the target digits are embedded among number distractors.

Blood pressure and heart rate were measured with a standardized automated oscillometric device 3 times during each battery (6 times per testing session). Antibodies binding to neuronal ganglionic AChR were detected by a radioimmunoprecipitation assay. This assay uses a solubilized AChR from a human neuroblastoma cell line (IMR-32) that is labeled with a high-affinity radioligand, iodine 125 (125I)-labeled epibatidine. The antigen-binding capacity of serum is expressed in nanomoles of 125I-epibatidine–receptor complexes precipitated per liter of serum. The upper limit of the reference range in serum is 0.05 nmol/L. Antibody titer levels were drawn before and after plasmapheresis. One subject underwent lumbar puncture to determine whether antibodies were present within the cerebrospinal fluid.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 15 statistical software (SPSS Inc.). Results are expressed as mean (SD) unless otherwise specified. The mean baseline condition (seated pre–plasmapheresis) was determined. Results while standing or after plasmapheresis were reported as percentage change from the baseline condition for graphical representation. Raw data scores were used to calculate statistical significance. One-way analyses of variance with Tamhane T2 post hoc tests were used to determine differences between prespecified conditions (seated, standing, prepheresis and postpheresis). The total number of completed testing cycles (1 cycle refers to testing before and after pheresis in both seated and standing positions) was used to determine statistical significance, set at P < .05.

RESULTS

All subjects were female, aged 52, 54, and 57 years. The duration since diagnosis of AAG ranged from 4 to 7 years. Symptoms in the youngest 2 patients were clearly identifiable with a sudden onset of severe dysautonomia. Symptoms in the oldest patient appear to have developed gradually for 10 or more years prior to final diagnosis of AAG. A total of 10 complete testing cycles were analyzed for the 3 subjects (5 rounds of testing for patient 1, 3 rounds for patient 2, and 2 rounds for patient 3). All subjects tested within the average range of estimated premorbid intelligence. No notable motor or lan-
guage deficits were observed, and all subjects were able to follow task instruction without repetitions or clarifications. All intelligence estimations aligned with self-reported educational history and did not differ from occupational attainment or behavioral observations. On physical examination, all patients had normal cranial nerve, strength, coordination, reflex, and sensory findings. There was no evidence of nystagmus, ataxia, dysarthria, parkinsonism, or long-tract signs. Gait was normal when systolic blood pressures were greater than 90 mm Hg.

ORTHOSTATIC HYPOTENSION

Before plasma exchange, the mean (SD) blood pressure of subjects with AAG was 144/88 (36/19) mm Hg while seated and 101/69 (29/17) mm Hg while standing. After plasma exchange, the mean (SD) blood pressure of subjects with AAG was 122/74 (18/14) mm Hg while seated ($P < .05$ vs before pheresis while seated) and 109/66 (12/9) mm Hg while standing. The patients did not report orthostatic symptoms while standing despite the orthostatic hypotension.

ANTIBODY TITERS

The mean (SD) antibody titer directed against the $\alpha$-3 nicotinic AChR prior to plasma exchange for the subjects with AAG was 6.7 (6.6) nmol/L (range, 2.3-15.7 nmol/L). The mean (SD) antibody titer after plasma exchange was 0.4 (0.2) nmol/L (range, 0.1-0.7 nmol/L) ($P < .001$). Antibodies directed against the $\alpha$-4 or $\alpha$-7 AChRs were not detected. One subject with AAG had a cerebrospinal fluid sample tested for ganglionic AChR antibodies, and it revealed no detectable antibodies. A serum sample drawn at the same time had antibody levels of 3.2 nmol/L.

TESTS OF COGNITION

A summary of all test results are outlined in Figure 1 and Figure 2. Following a change in position from seated to standing and accompanied by orthostatic hypotension, performance on Trail Making Test Part A, Trail Making Test Part B, the difference between Trail Making Test Part B and Trail Making Test Part A, the Controlled Oral Word Association Test, and the incongruent form of the Computerized Stroop Test worsened ($P < .05$). Following plasmapheresis, performance in the seated position improved on all forms of the Trail Making Test, the Controlled Oral Word Association Test, and both forms of the Computerized Stroop Test ($P < .05$, all tests) but did not change in the backward condition of the Digit Span Test. After plasmapheresis, position change from seated to standing had no effect on cognition on any test.

COMMENT

Autoimmune autonomic ganglionopathy is a rare disorder consisting of generalized autonomic failure due to ganglionic nicotinic AChR antibodies. Cognitive impairment is not a characteristic feature of the disorder. Prompted by patient reports of cognitive difficulties, we carried out a structured neuropsychological assessment in the seated and upright positions before and after plasmapheresis. The major findings of our study are as follows: (1) postural hypotension in the presence of high nicotinic AChR antibody levels prior to plasma exchange resulted in impaired cognition characterized by deficits in executive function, sustained attention, and working memory; (2) cognitive impairment associated with postural hypotension resolved with improvement in orthostatic hypotension after plasma exchange and consequent reduction of antibody levels; (3) cognitive dysfunction was present in the seated, normotensive position prior to plasma exchange, and (4) cognitive dysfunction present in the seated position improved after plasmapheresis and consequent reduction in antibody levels.

These data suggest that orthostatic hypotension, in association with elevated nicotinic AChR antibody levels, results in cognitive impairment. These data also demonstrate that elevated nicotinic AChR antibody levels alone are associated with cognitive impairment. The study design did not allow us to determine the relative contribution of these factors.

Several potential mechanisms exist whereby orthostatic hypotension and nicotinic AChR antibody levels alone or in combination lead to cognitive impairment. Both orthostatic hypotension and cholinergic system dysfunction have associations with cognitive impairment. Several reports have drawn attention to the association of orthostatic hypotension and/or low blood pressure with chronic cognitive impairment in elderly individuals. The mechanism whereby hypotension impairs cognition in older individuals is not fully understood but is most likely related, at least in part, to impaired cerebral perfusion. In support of this mechanism, white matter lesions and silent cerebral infarcts are often associated with orthostatic hypotension in elderly individuals.

The central autonomic neurodegenerative disorders of multiple system atrophy, Parkinson disease, and Lewy body dementia are frequently accompanied by severe orthostatic hypotension, also may have substantial cognitive impairment. However, the presence of central neurodegeneration in these disorders provides an additional, confounding cause of cognitive impairment. Nevertheless, there are reports of chronic cognitive impairment in the peripheral autonomic degenerative disorder of pure autonomic failure, lending support to the notion that chronic cognitive impairment is associated with decreased cerebral perfusion in some patients with orthostatic hypotension without central neurodegeneration. However, in our study, the improvement in cognitive scores after plasma exchange in both upright and seated positions suggests that the cognitive impairment is reversible and that factors in addition to orthostatic hypotension are implicated in the cognitive abnormalities.

Cortical manifestations have been associated with elevated nicotinic AChR antibody levels. We therefore tested the hypothesis that cognitive impairment was a consequence of centrally acting nicotinic AChR antibodies.
Figure 1. Changes in cognitive performance by position, before and after plasma exchange. The results are shown for the individual cognitive tests (mean [SD] of 10 cycles of testing across the 3 patients). The direction of improvement is test specific. There were differences between the seated and standing tests before pheresis (ie, associated with orthostatic hypotension) with all 3 Trail Making Tests and the Controlled Oral Word Association Test. There were differences between seated tests before and after pheresis (ie, associated with changes in antibody titer) with all tests except the backward Digit Span Test. *P<.05. Tests of significance between standing before and after pheresis are not shown for ease of view but were significant in all tests except Trail Making Test Part A and Digit Span Test backward.
directed against the α-4 and α-7 AChRs, as was noted in 1 prior patient with encephalopathy and central features that included nystagmus, ataxia, dysarthria, long-tract signs, and positive Babinski reflexes.9 Nicotinic AChRs are prominent in central nervous system regions that play a role in attention, learning, and memory such as the cerebral cortex, hippocampus, thalamus, and limbic system.23 Furthermore, nicotine and nicotine agonists enhance working memory in rodents and nonhuman primates, while nicotine antagonists impair cognition in these models.24-28 Similar effects are present in humans.27,29-31 In addition, there is degeneration of basal forebrain neurons and a consequent decrease in cortical AChR density and function [Trail Making Tests and Controlled Oral Word Association Test] worsened due to orthostatic hypotension); and white circles, change in performance in the seated position after vs before plasma exchange (ie, change due to antibody removal; after plasma exchange, significant improvements on all neuropsychological tests were noted except on the backward Digit Span Test). *P<.05.

Figure 2. Mean (SD) changes in cognitive performance due to orthostatic hypotension and antibody removal. The change in the cognitive test result is expressed as a percentage relative to the seated, pre-plasma exchange baseline result. A negative percentage change denotes worsening of the test result; a positive percentage change, improvement. The dotted line represents performance prior to plasma exchange in the seated position (baseline condition, no orthostatic hypotension); black circles, change in performance in the standing vs sitting position prior to treatment (ie, change due to orthostatic hypotension); note that results on tests of executive function [Trail Making Tests and Controlled Oral Word Association Test] worsened due to orthostatic hypotension); and white circles, change in performance in the seated position after vs before plasma exchange (ie, change due to antibody removal; after plasma exchange, significant improvements on all neuropsychological tests were noted except on the backward Digit Span Test). *P<.05.

the rarity of this disorder. Second, cerebrospinal fluid studies were performed on only 1 patient. Third, although the tests chosen have demonstrated resistance to practical effects, were randomized across position and treatment states, and were presented as alternate forms during each testing session, some task-specific familiarity existed when patients returned to the clinic for treatment. Therefore, test-retest, order, and learning effects may have played some role in the test results. Fourth, placebo effects may have also contributed to improvement; sham plasma exchange was not performed. Finally, the study design did not allow us to examine the role of orthostatic hypotension on cognition in the absence of nicotinic AChR antibodies in patients or control subjects. Despite these limitations, the data presented in this study convincingly demonstrate reversible cognitive impairment, thereby expanding the clinical spectrum of autonomic ganglionopathy and, in so doing, providing an additional treatable cause of cognitive impairment.

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