MAYO CLINIC

ORIGINAL ARTICLE

Ganglionic Antibody Level as a Predictor of Severity of Autonomic Failure

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Abstract

Objective: To assess antibody level as a test of autonomic failure (AF) associated with ganglionic nicotinic acetylcholine receptor antibody (AChR-Ab) autoimmunity.

Patients and Methods: We searched the Mayo Clinic laboratory database of 926 ganglionic AChR-Ab–seropositive patients seen at our institution between October 1, 1997, and April 1, 2015, for initial level of 0.05 nmol/L or higher and contemporaneous autonomic reflex screen (standardized evaluation of adrenergic, cardiovagal, and sudomotor functions) from which Composite Autonomic Scoring Scale (CASS) scores could be calculated.

Results: Of 289 patients who met inclusion criteria, 163 (56.4%) were women, median age was 54 years (range, 10-87 years), median antibody level was 0.11 nmol/L (range, 0.05-22.10 nmol/L), and median CASS total score was 2.0 (range, 0-10). Using receiver operating characteristic curve analysis, a level above 0.40 nmol/L predicted severe AF (CASS score, ≥7) with 92% specificity and 56% sensitivity. For at least moderate AF (CASS score ≥4 and anhidrosis ≥25%), a level of at least 0.20 nmol/L had 80% specificity and 59% sensitivity. Levels below 0.20 nmol/L were not predictive of the presence or absence of AF. For predicting orthostatic hypotension, ganglionic AChR-Ab level had excellent specificity above 0.4 nmol/L but lacked sensitivity. Autoantibodies to additional targets were present in 61 patients (21.1%).

Conclusion: Ganglionic AChR-Ab level of at least 0.40 nmol/L is a moderately sensitive and highly specific marker for severe AF, as is a level of at least 0.20 nmol/L for moderate AF if CASS score is coupled with anhidrosis of 25% or more, among patients with suspected ganglionic AChR-Ab autoimmune autonomic ganglionopathy. Antibody levels of less than 0.20 nmol/L have little clinical importance in the absence of clinical AF.

 ■ Mayo Clin Proc. 2018;■■(■):1-8

Autoimmune autonomic ganglionopathy (AAG) is an antibody-mediated disease that classically manifests with widespread autonomic failure (AF) involving sympathetic, parasympathetic, and enteric functions.[1-3] One target of the pathogenic antibodies is the α3 subunit of the ganglionic nicotinic acetylcholine receptor antibody (AChR-Ab) in autonomic ganglia.[4] More severe AF has been found to occur with higher α3-AChR-Ab (ganglionic AChR-Ab; ganglionic Ab) level.[3,5] In single case reports and small series, limited phenotypes with milder autonomic dysfunction have also been described, including isolated gastrointestinal dysmotility,[6] postural tachycardia syndrome,[7] pure AF,[8] distal small fiber neuropathy,[7] chronic idiopathic anhidrosis,[7] cognitive impairment,[9,10] psychiatric symptoms,[11] and QT prolongation and ventricular tachycardia.[12] It has also been reported that many patients harboring antibodies against the ganglionic AChR-Ab have neither dysautonomia nor neurologic disease.[13]

Limited AAG phenotypes generally are associated with lower ganglionic AChR-Ab levels, although it remains unclear if a strict correlation exists between level and severity or distribution of autonomic dysfunction. With the widespread availability and ordering of this test, a key question is whether low antibody levels are meaningful. The goal of the current study was to determine what an

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abnormal ganglionic AChR-Ab antibody means and when it is reliably associated with AF. We sought to correlate, in the first large cohort with detailed autonomic testing, the degree of AF associated with ganglionic antibody level.

PATIENTS AND METHODS

This study was approved by the Institutional Review Board of Mayo Clinic, Rochester, Minnesota (IRB 14-009546).

Study Population

The Mayo Clinic Rochester Neuroimmunology Laboratory database was queried for serum samples that contained ganglionic AChR-Ab at a level of 0.05 nmol/L or greater ("positive") from patients seen between October 1, 1997, and April 1, 2015. Patients were excluded if there was no autonomic reflex screen (ARS) within 1 month in the Mayo Clinic Rochester Autonomic Laboratory database or if the level from their earliest sample was less than 0.05 nmol/L (only the initial level was used for analysis if multiple samples were available from a single patient). The indication for testing ganglionic AChR-Ab, which is included in a service paraneoplastic autoantibody panel, was not used for screening eligible patients, nor was the reason for performing the ARS.

Autoantibody Measurements

A radioimmunoprecipitation assay was used to detect autoantibodies binding to the α3 subunit of the acetylcholine receptor, as previously described.[14] Testing for this α3-AChR-Ab, referred to as ganglionic AChR-Ab in this article, is most often performed in our neuroimmunology laboratory as part of a paraneoplastic autoimmunity profile screening for neuronal nuclear or cytoplasmic antibodies (including amphiphysin antibody; antineuronal nuclear antibody types 1, 2, and 3; Purkinje cell 1, 2, and Tr antibodies; collapsin response mediator protein 5 antibody; antiglial or neuronal nuclear antibody; and glutamic acid decarboxylase isoform 65 antibody), neuronal voltage-gated cation channel antibodies (P/Q- and N-type calcium channel antibodies and potassium channel complex antibody), striational antibodies, and muscle (α1) nicotinic AChR-Ab, as previously described.[15-18]

Autonomic Testing

The quantitative sudomotor axon reflex test was used to evaluate postganglionic sympathetic sudomotor nerves at 4 routine sites (forearm, proximal leg, distal leg, and foot). Control values were derived from studies on 357 healthy individuals aged 10 to 83 years.[19] For patients with autonomic testing later than 2010, quantitative sudomotor axon reflex test (Q-Sweat; WR Medical Electronics Co., Maplewood, MN) was used. Heart rate variation to deep breathing and the Valsalva ratio were used to quantify cardiovagal function, with results compared with normative data from 376 (heart rate response to deep breathing) and 425 (Valsalva ratio) healthy subjects aged 10 to 83 years.[19] Blood pressure and heart rate responses to the Valsalva maneuver and head-up tilt were used to examine cardiovascular adrenergic function.[20] Together, these tests constitute the ARS. Sudomotor function was also assessed with the thermoregulatory sweat test (TST), from which the distribution and percentage of anterior body surface anhidrosis was determined.[21]

The Composite Autonomic Scoring Scale (CASS) quantifies severity and distribution of AF from the ARS.[22] The 10-point CASS total score is the sum of 3 subdomains: sudomotor (CASS-sudomotor range, 0-3), cardiovagal (CASS-cardiovagal range, 0-3), and adrenergic (CASS-adrenergic range, 0-4). Higher CASS scores indicate more severe AF. Each score is normalized for the confounding effects of age and sex.[19] The percent anhidrosis on TST also grades severity of sudomotor failure. One of the authors (J.K.C.-G.) reviewed all ARS and TST data and assigned CASS scores. Moderate AF was defined as a CASS score of 4 through 6 or TST anhidrosis of 25% to 50%, and severe AF was defined as a CASS score of 7 or higher or TST anhidrosis of 50% or more. Orthostatic hypotension (OH) was defined as a decrease in systolic blood pressure of 30 mm Hg or more or mean blood pressure decrease of 20 mm Hg or more during head-up tilt.

Statistical Analyses

We used Spearman rank correlation analysis to test the correlation between ganglionic