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High but not Low Level of Ganglionic Antibody Predicts 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 (ganglionic AChR Ab) autoimmunity.

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

Results: Of 289 patients who met inclusion criteria, 163 (56%) were women, median age was 54 years (range 10–87), median antibody level was 0.11 nmol/L (range 0.05–22.1), and median CASS-total was 2.0 (range 0–10). Using ROC analysis, a level above 0.40 nmol/L predicted severe AF (CASS ≥ 7) with 92% specificity and 56% sensitivity. For at least moderate AF (CASS ≥ 4 and anhidrosis ≥ 25%), a level above 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%).

Conclusion: Antibody level above 0.40 nmol/L is a moderately sensitive and highly specific test for severe AF, as is level above 0.20 nmol/L for moderate AF if CASS score is coupled with anhidrosis ≥ 25%, among patients with suspected ganglionic AChR Ab AAG autoimmunity. Antibody levels less than 0.2 nmol/L have little significance in the absence of clinical AF.

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Author Disclosures

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Keywords

Autoimmune autonomic ganglionopathy; Ganglionic nicotinic acetylcholine receptor; Composite Autonomic Scoring Scale; Autonomic failure; Autoantibodies

Introduction

Autoimmune autonomic ganglionopathy (AAG) is an antibody-mediated disease that classically manifests with widespread autonomic failure involving sympathetic, parasympathetic, and enteric functions.^{1–3} One target of the pathogenic antibodies is the $\alpha 3$ subunit of the nicotinic acetylcholine receptor (ganglionic AChR Ab) in autonomic ganglia.⁴ More severe autonomic failure (AF) has been shown to occur with higher $\alpha 3$ -AChR antibody (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 autonomic failure,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 shown 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, though 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 is to determine what an abnormal ganglionic AChR Ab antibody means and when it reliably is associated with autonomic failure. We sought to correlate, in the first large cohort with detailed autonomic testing, the degree of AF associated with ganglionic Ab level.

Methods

This study was approved by the institutional review board of Mayo Clinic, Rochester, Minnesota (IRB 14–009546).

Patients

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”) 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 given 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 $\alpha 3$ -AChR, as previously described.¹⁴ Testing for this $\alpha 3$ -AChR Ab, referred to as ganglionic AChR Ab in this publication, 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 [ANNA]-1, 2, 3; Purkinje cell 1, 2, and Tr antibodies; collapsin response-mediator protein [CRMP]-5 antibody; antiglial or neuronal nuclear antibody [AGNA]; and glutamic acid decarboxylase 65-isoform [GAD65] antibody), neuronal voltage-gated cation channel antibodies (P/Q- and N-type calcium channel antibodies and potassium channel complex antibody), striational antibodies, and muscle ($\alpha 1$) nicotinic acetylcholine receptor antibodies, as previously described.^{15–18}

Autonomic testing

The quantitative sudomotor axon reflex test (QSART) was used to evaluate postganglionic sympathetic sudomotor nerves at four routine sites (forearm, proximal leg, distal leg, and foot). Control values were derived from studies on 357 healthy subjects aged 10 to 83 years.¹⁹ For patients with autonomic testing later than 2010, 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 to normative data from 376 (HR_{DB}) and 425 (VR) 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 three subdomains: sudomotor (CASS-sudomotor, range 0–3), cardiovagal (CASS-card iovagal, range 0–3), and adrenergic (CASS-adrenergic, 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 us (J.K.C-G.) reviewed all ARS and TST data and assigned CASS scores. Moderate AF was defined as CASS 4–6 or TST anhidrosis 25–50%, and severe AF as CASS ≥ 7 or TST anhidrosis $\geq 50\%$. Orthostatic hypotension (OH) was defined as a drop in systolic blood pressure of ≥ 30 mmHg or mean blood pressure of ≥ 20 mmHg during head-up tilt.

Statistical analysis

We used Spearman rank analysis to test the correlation between ganglionic AChR Ab level and various measures of AF, including CASS-total and subdomain scores, presence of OH, and percent anhidrosis on TST. We then used receiver operator characteristic (ROC) curves to assess the sensitivity and specificity of ganglionic AChR Ab level for moderate AF, severe AF, and OH.

Results

Patients and autoantibody levels

Of 926 serum samples positive for ganglionic AChR Ab, 637 were excluded for lack of contemporaneous ARS or because they were not the patient's initial sample, leaving 289 patients for analysis (Supplemental Figure). The study cohort included slightly more women (n=163, 56%) than men. The median age was 54 years, with a wide range extending from 10 to 87 years. The range of ganglionic AChR Ab levels was also wide, from the predefined minimum of 0.05 nmol/L to 22.10 nmol/L. The overwhelming majority of levels were less than 1.00 nmol/L (n=266, 92%), and the median level was 0.11 nmol/L (Table 1). Additional antibodies were sought in all patients and discovered in 61 (21%), most often at low level against GAD65, skeletal muscle antigens, or voltage-gated calcium or potassium channels (Supplemental Table). Ganglionic AChR Ab level was not correlated with the presence of additional antibodies ($p=.25$, Spearman $\rho = -0.068$). These additional autoantibodies were present at low level and similar frequency in patients with low or high levels of ganglionic AChR Ab; VGKC and CRMP-5 antibodies were only found in patients with low levels of ganglionic AChR Ab. Eleven patients had multiple coexisting autoantibodies.

Autonomic failure

By design, all 289 patients had undergone ARS that allowed CASS scoring of autonomic impairment. Patients' CASS-total scores ranged from 0 to 10, with median 2.0, corresponding to only mild AF. Similarly, CASS subdomain scores ranged from normal to severe AF: CASS-sudomotor range 0 to 3 (median 1.0), CASS-cardiovagal range 0 to 3 (median 0.0), and CASS-adrenergic range 0 to 4 (median 0.0) (Table 1). Visual inspection of CASS-total and all subdomains suggested that high ganglionic AChR Ab level was associated with high scores (severe AF), but low levels could be associated with the full spectrum from no autonomic impairment to severe AF (Figure 1); this inspection helped guide our selection of statistical tests. OH was detected in 61 patients, among whom ganglionic AChR Ab level ranged from 0.05 to 22.1 nmol/L (median, 0.14 nmol/L). A majority of patients (n=175, 61%) also had TST as part of the initial evaluation. The percent anhidrosis spanned the full range from 0 to 100%, with median 2.0% (Table 1).

Spearman rank analysis

Statistically significant correlations existed between rising ganglionic-AChR Ab level and rising CASS scores, including CASS-total ($p=.02$) and all three subdomains (sudomotor, $p=.04$; cardiovagal, $p=.003$; adrenergic, $p=.02$). Correlations were also significant between level and OH ($p=.001$) and percent anhidrosis on TST ($p=.005$). The Spearman coefficients for all of these correlations were poor (<0.25 in all cases; Table 2).

ROC analysis

ROC analysis showed that ganglionic AChR Ab level of 0.4 nmol/L predicted severe AF (CASS ≥ 7) with 92% specificity and 56% sensitivity. With severe AF defined as the combination of CASS ≥ 7 and anhidrosis $\geq 50\%$, specificity remained high at 88% and sensitivity improved to 65% (Figure 2A). Lower levels were less specific, and higher levels

lost sensitivity without significant gains in specificity (Table 3). For at least moderate AF defined as CASS ≥ 4 , a level of 0.2 nmol/L had 81% specificity but only 36% sensitivity. The specificity was essentially the same (80%) and sensitivity was somewhat improved (59%) by incorporating percent anhidrosis (moderate AF as CASS ≥ 4 and anhidrosis $\geq 25\%$; Figure 2B). Levels less than 0.20 nmol/L were not predictive of the presence or absence of AF (Table 3). For predicting OH, ganglionic AChR Ab level had excellent specificity above 0.40 nmol/L but lacked sensitivity (Table 3, Figure 2C).

Discussion

The key finding of this study is that ganglionic AChR Ab level is a moderately sensitive and highly specific test for severe autonomic failure above 0.40 nmol/L. It is similarly sensitive and specific for moderate autonomic failure above 0.20 nmol/L if an additional requirement of anhidrosis $\geq 25\%$ on TST is imposed, likely reflecting the importance of cholinergic failure with this antibody. It is even more sensitive but utterly non-specific for severe AF above 0.10 nmol/L, highly specific but insensitive for orthostatic hypotension above 0.2 nmol/L, and a very poor test for mild or moderate autonomic impairment at any value. The significance of low ganglionic AChR Ab level is dictated by clinical context. Hence a level above 0.40 nmol/L in a patient with suspected AAG is predictive of AAG with severe autonomic failure.

The strengths of this study are its large size and the detailed autonomic testing performed in every patient. Previous series of AAG relied on clinical phenotypes or included relatively few patients.^{3,8,23–28} A previous large retrospective series from our institution included 155 patients seropositive for ganglionic AChR Ab (many of whom are included in the present study), but detailed autonomic testing was not reported.¹³ Our study confirms prior reports associating higher level with more severe AF.^{3,5,8,13,25,29,30} This correlation was observed in all three subdomains of the CASS score – adrenergic, cardiovascular, and sudomotor – and reflects the presence of the ganglionic AChR Ab in all types of autonomic ganglia.³¹

Our study and that of Li et al (2015)³⁰ also shows that high ganglionic AChR Ab level is not required for severe AF (i.e., low level can be associated with more than mild or moderate autonomic impairment). This distinction from earlier reports is likely due to the different methods of case ascertainment. Whereas others have started with patients with the clinical phenotype of AAG and then demonstrated the presence of ganglionic AChR Ab (not surprisingly at high level), we started with serum samples harboring the antibody of interest and then correlated level with the results of autonomic tests. Our approach likely underestimates the value of the test. For patients with low level of antibody and severe AF, there is often a good clinical explanation. Nine patients had severe autonomic failure (high CASS) despite low ganglionic AChR Ab level (<0.10 nmol/L). Most of these had another explanation for AF (2 post-infectious autonomic neuropathy, 1 each of diabetes, and familial amyloid, 1 with multiple system atrophy). We did not examine the change in ganglionic AChR Ab level after treatment, which has previously been shown to reflect disease activity.^{9,23,24,32,33}

The presence of additional autoantibodies in a significant minority (21%) of ganglionic AChR Ab–seropositive patients suggests that ganglionic AChR Ab may sometimes be a non-specific marker of autoimmunity. This possibility is further supported by the finding of ganglionic AChR Ab at low level in patients with myasthenia gravis⁴ or celiac disease³⁴ without autonomic symptoms and in 14% of patients in the previous Mayo series who had autoimmune neurologic or systemic disorders without autonomic impairment.¹³

Low levels of ganglionic AChR Ab were present in patients with celiac disease but no autonomic symptoms except sicca complex.³⁴ Low positive antibody values (ganglionic AChR Ab and other antibodies detected by radioimmunoprecipitation assays) can be detected in some patients with cancer but no neurological disease, or may be detected as false positives in patients with monoclonal or polyclonal hypergammaglobulinemia.^{13,35} It is also possible that in some cases other autoantibodies have pathogenic relevance to autonomic dysfunction. Kimpinski and colleagues reported three patients with antibodies targeting the N-type voltage-gated calcium channel among a series of 49 patients with clinical AAG but no evidence of ganglionic AChR Ab autoimmunity.³⁶

The chief limitation of our study is the fact that the CASS does not capture many of the prominent symptoms of AAG, including sicca complex, pupil dysfunction, gastrointestinal dysmotility, or urinary retention. Sandroni and colleagues previously showed that abnormal pupillary responses, dry eyes and dry mouth, and lower gastrointestinal tract symptoms were all more likely in ganglionic AChR Ab–seropositive than seronegative patients when AAG was defined by clinical phenotype.³⁷ Nevertheless, CASS is a validated measure of autonomic failure that summarizes several of the most commonly used clinical autonomic tests that are used to diagnose and measure treatment response in AAG. Since AAG phenotype is typically characterized as generalized autonomic failure, CASS should provide a reasonable index of autonomic failure. Another limitation is that tests of sensitivity/specificity applies only to the prespecified conditions of the study.

Conclusion

Antibody level above 0.40 nmol/L is a moderately sensitive and highly specific test for severe AF among patients with ganglionic AChR Ab AAG autoimmunity. Level above 0.2 nmol/L correlates with moderate AF when paired with anhidrosis 25%. Low levels are usually of little significance in the absence of clinical features of AF. Future research should correlate ganglionic AChR Ab level with autonomic symptoms and other clinical features not captured by CASS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations:

AF	autonomic failure
AChR	acetylcholine receptor
CASS	composite autonomic scoring scale
ROC	receiver operating characteristic curve
AAG	autoimmune autonomic ganglionopathy
ganglionic AChR Ab	ganglionic AChR antibody
ARS	autonomic reflex screen
Q-Sweat	quantitative sudomotor axon reflex test
HR_{DB}	heart rate response to deep breathing
VR	Valsalva ratio
TST	thermoregulatory sweat test
OH	orthostatic hypotension
GAD65	glutamic acid decarboxylase antibody directed against the 65 kd isoform
VGKC	voltage gate potassium channel
CRMP5	collapsing response mediator protein 5

References

1. Young RR, Asbury AK, Adams RD, Corbett JL. Pure pan-dysautonomia with recovery. *Trans Am Neurol Assoc* 1969;94:355–357. [PubMed: 5374487]
2. Vernino S, Adamski J, Kryzer TJ, Fealey RD, Lennon VA. Neuronal nicotinic ACh receptor antibody in subacute autonomic neuropathy and cancer-related syndromes. *Neurology* 1998;50(6):1806–1813. [PubMed: 9633732]
3. Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. *N Engl J Med* 2000;343(12):847–855. [PubMed: 10995864]
4. Vernino S, Lindstrom J, Hopkins S, Wang Z, Low PA. Characterization of ganglionic acetylcholine receptor autoantibodies. *J Neuroimmunol* 2008;197(1):63–69.
5. Gibbons CH, Freeman R. Antibody titers predict clinical features of autoimmune autonomic ganglionopathy. *Auton Neurosci* 2009;146(1–2):8–12. [PubMed: 19144572]
6. Flanagan EP, Saito YA, Lennon VA, et al. Immunotherapy trial as diagnostic test in evaluating patients with presumed autoimmune gastrointestinal dysmotility. *Neurogastroenterol Motil* 2014;26(9):1285–1297. [PubMed: 25039328]
7. Sandroni P, Low PA. Other autonomic neuropathies associated with ganglionic antibody. *Auton Neurosci* 2009;146(1–2):13–17. [PubMed: 19058765]
8. Klein CM, Vernino S, Lennon VA, et al. The spectrum of autoimmune autonomic neuropathies. *Ann Neurol* 2003;53(6):752–758. [PubMed: 12783421]

9. Gibbons CH, Centi J, Vernino S, Freeman R. Autoimmune autonomic ganglionopathy with reversible cognitive impairment. *Arch Neurol* 2012;69(4):461–466. [PubMed: 22158721]
10. Baker SK, Morillo C, Vernino S. Autoimmune autonomic ganglionopathy with late-onset encephalopathy. *Auton Neurosci* 2009;146(1–2):29–32. [PubMed: 19028442]
11. Hayashi M, Ishii Y. A Japanese case of autoimmune autonomic ganglionopathy (AAG) and a review of AAG cases in Japan. *Auton Neurosci* 2009;146(1–2):26–28. [PubMed: 19195935]
12. Cheshire WP. Cardiovascular antibodies and orthostatic hypotension. *Auton Neurosci* 2015;192:14.
13. McKeon A, Lennon VA, Lachance DH, Fealey RD, Pittock SJ. Ganglionic acetylcholine receptor autoantibody: oncological, neurological, and serological accompaniments. *Arch Neurol* 2009;66(6):735–741. [PubMed: 19506133]
14. Vernino S, Lennon V, A. Neuronal ganglionic acetylcholine receptor autoimmunity. *Ann N Y Acad Sci* 2003;998:211–214. [PubMed: 14592878]
15. Pittock SJ, Kryzer TJ, Lennon VA. Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. *Ann Neurol* 2004;56(5):715–719. [PubMed: 15468074]
16. Graus F, Vincent A, Pozo-Rosich P, et al. Anti-glial nuclear antibody: marker of lung cancer-related paraneoplastic neurological syndromes. *J Neuroimmunol* 2005;165(1–2):166–171.
17. Pittock SJ, Yoshikawa H, Ahlskog JE, et al. Glutamic acid decarboxylase autoimmunity with brainstem, extrapyramidal, and spinal cord dysfunction. *Mayo Clin Proc* 2006;81(9):1207–1214. [PubMed: 16970217]
18. Keegan BM, Pittock SJ, Lennon VA. Autoimmune myelopathy associated with collapsin response-mediator protein-5 immunoglobulin G. *Ann Neurol* 2008;63(4):531–534. [PubMed: 18306241]
19. Low PA, Denq JC, Opfer-Gehrking TL, Dyck PJ, O'Brien PC, Slezak JM. Effect of age and gender on sudomotor and cardiovascular function and blood pressure response to tilt in normal subjects. *Muscle Nerve* 1997;20(12):1561–1568. [PubMed: 9390669]
20. Low PA, Opfer-Gehrking TL. The autonomic laboratory. *Am J Electroneurodiagnostic Technol* 1999;39(2):65–76. [PubMed: 11542437]
21. Fealey RD, Low PA, Thomas JE. Thermoregulatory sweating abnormalities in diabetes mellitus. *Mayo Clin Proc* 1989;64(6):617–628. [PubMed: 2747292]
22. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. *Mayo Clin Proc* 1993;68(8):748–752. [PubMed: 8392653]
23. Gibbons C, Vernino S, Freeman R. Combined immunomodulatory therapy in autoimmune autonomic ganglionopathy. *Arch Neurol* 2008;65(2):213–217. [PubMed: 18268189]
24. Iodice V, Kimpinski K, Vernino S, Sandroni P, Fealey RD, Low PA. Efficacy of immunotherapy in seropositive and seronegative putative autoimmune autonomic ganglionopathy. *Neurology* 2009;72(23):2002–2008. [PubMed: 19506222]
25. Kimpinski K, Iodice V, Sandroni P, Fealey RD, Vernino S, Low PA. Sudomotor dysfunction in autoimmune autonomic ganglionopathy. *Neurology* 2009;73(18):1501–1506. [PubMed: 19884578]
26. Low PA, Dyck PJ, Lambert EH, et al. Acute panautonomic neuropathy. *Ann Neurol* 1983;13(4):412–417. [PubMed: 6301359]
27. Parize P, Gaultier JB, Badet F, et al. Autoimmune autonomic ganglionopathy: a case series of six patients and literature review. *Rev Med Interne* 2010;31(7):476–480. [PubMed: 20493594]
28. Suarez GA, Fealey RD, Camilleri M, Low PA. Idiopathic autonomic neuropathy: Clinical, neurophysiologic, and follow-up studies on 27 patients. *Neurology* 1994;44(9):1675–1682. [PubMed: 7936295]
29. Mukherjee S, Vernino S. Dysfunction of the pupillary light reflex in experimental autoimmune autonomic ganglionopathy. *Auton Neurosci* 2007;137(1–2):19–26. [PubMed: 17613283]
30. Li Y, Jammoul A, Mente K, et al. Clinical experience of seropositive ganglionic acetylcholine receptor antibody in a tertiary neurology referral center. *Muscle Nerve* 2015;52(3):386–391. [PubMed: 25557122]
31. Vernino S Neuronal acetylcholine receptor autoimmunity. *Ann N Y Acad Sci* 2008;1132:124–128. [PubMed: 18567861]

32. Fischer PR, Sandroni P, Pittock SJ, Porter CB, Lehwald LM, Raj SR. Isolated sympathetic failure with autoimmune autonomic ganglionopathy. *Pediatr Neurol* 2010;43(4):287–290. [PubMed: 20837310]
33. Imrich R, Vernino S, Eldadah BA, Holmes C, Goldstein DS. Autoimmune autonomic ganglionopathy: treatment by plasma exchanges and rituximab. *Clin Auton Res* 2009;19(4):259–262. [PubMed: 19399547]
34. Briani C, Doria A, Ruggero S, et al. Antibodies to muscle and ganglionic acetylcholine receptors (AChR) in celiac disease. *Autoimmunity* 2008;41(1):100–104. [PubMed: 18176871]
35. Zalewski NL, Lennon VA, Lachance DH, Klein CJ, Pittock SJ, Mckeon A. P/Q-and N-type calcium-channel antibodies: Oncological, neurological, and serological accompaniments. *Muscle Nerve* 2016;54(2):220–227. [PubMed: 26789908]
36. Kimpinski K, Iodice V, Vernino S, Sandroni P, Low PA. Association of N-type calcium channel autoimmunity in patients with autoimmune autonomic ganglionopathy. *Auton Neurosci* 2009;150(1–2):136–139. [PubMed: 19541551]
37. Sandroni P, Vernino S, Klein CM, et al. Idiopathic autonomic neuropathy: comparison of cases seropositive and seronegative for ganglionic acetylcholine receptor antibody. *Arch Neurol* 2004;61(1):44–48. [PubMed: 14732619]

Figure 1: Ganglionic AChR Ab level versus degree of autonomic failure as measured by Composite Autonomic Scoring Scale.

Higher CASS scores indicate more severe autonomic failure. Higher antibody levels were generally associated with more severe AF, but there were exceptions. Occasional high levels (>1.00 nmol/L) were seen in patients with no or only mild autonomic impairment, and several patients with severe AF had low levels (<0.20 nmol/L). Ganglionic AChR Ab indicates antibodies to $\alpha 3$ subunit of nicotinic ganglionic acetylcholine receptor; CASS, composite autonomic scoring scale.

Figure 2. ROC curves for Ganglionic AChR Ab antibody level as test of (A) severe autonomic failure, (B) moderate autonomic failure, and (C) orthostatic hypotension.

Ganglionic AChR Ab level of 0.40 nmol/L predicted severe AF by CASS alone with 92% specificity and 56% sensitivity. Sensitivity was somewhat better with severe AF defined as the combination of CASS ≥ 7 and anhidrosis $\geq 50\%$ (A). Antibody level poorly predicted moderate AF (B). Antibody level above 0.40 nmol/L predicted OH with excellent specificity (91%) but poor sensitivity (38%, C). Ganglionic AChR Ab indicates antibodies to $\alpha 3$ subunit of nicotinic ganglionic acetylcholine receptor; AUC, area under curve; CASS,

composite autonomic scoring scale; ROC, receiver operator characteristic; TST, thermoregulatory sweat test.

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Table 1.

Distribution of Ganglionic AChR Ab level and measures of autonomic failure.

Finding	Frequency (%)
Ganglionic AChR Ab level, nmol/L (n=289)	median 0.11
0.05–0.19	215(74)
0.2–0.39	29(10)
0.4–0.99	22(8)
1.0	23(8)
CASS-total (n=289)	median 2.0
0–3	201(70)
4–6	47(16)
7–10	41(14)
CASS-sudomotor (n=289)	median 1.0
0	122(42)
1	72(25)
2	36(12)
3	59(20)
CASS-cardiovagal (n=289)	median 0.0
0	164(57)
1	49(17)
2	47(16)
3	29(10)
CASS-adrenergic (n=289)	median 0.0
0	165 (57)
1	41(14)
2	27(9)
3	27(9)
4	29(10)
TST anhidrosis, % (n=175)	median 2.0%
0	52(30)
1–24	84(48)
25–49	15(9)
50	24(14)

Abbreviations: Ganglionic AChR Ab, antibodies to $\alpha 3$ subunit of nicotinic ganglionic acetylcholine receptor; CASS, composite autonomic scoring scale; TST, thermoregulatory sweat test

Table 2.

Spearman rank analysis.

Multivariate Correlation^a	<i>p</i> value	Spearman coefficient
Level vs. CASS-total	.02	0.144
Level vs. CASS-sudomotor	.04	0.123
Level vs. CASS-cardiovagal	.003	0.172
Level vs. CASS-adrenergic	.02	0.138
Level vs. OH	.001	0.199
Level vs. TST anhidrosis %	.005	0.213

Abbreviations: Ganglionic AChR Ab, antibodies to $\alpha 3$ subunit of nicotinic ganglionic acetylcholine receptor; CASS, composite autonomic scoring scale; OH, orthostatic hypotension; TST, thermoregulatory sweat test

^aLevel refers to Ganglionic AChR Ab level in all cases.

Table 3.

Ganglionic AChR Ab level versus autonomic failure.

Clinical Condition	AUC	$\alpha 3$		
		Sensitivity	Specificity	Level
<i>Severe autonomic failure</i>				
CASS 7 (n=41)	0.76	0.10	0.76	0.51
		0.20	0.56	0.81
		0.40	0.56	0.92
		1.00	0.46	0.98
TST 50% (n=24)	0.67	0.10	0.71	0.49
		0.20	0.54	0.78
		0.40	0.50	0.88
		1.00	0.33	0.94
CASS 7 + TST 50% (n=17)	0.78	0.10	0.88	0.49
		0.20	0.65	0.78
		0.40	0.65	0.88
		1.00	0.47	0.95
<i>Moderate autonomic failure</i>				
CASS 4 (n=88)	0.58	0.10	0.58	0.49
		0.20	0.36	0.81
		0.40	0.30	0.92
		1.00	0.22	0.98
TST 25% (n=39)	0.69	0.10	0.69	0.50
		0.20	0.51	0.78
		0.40	0.49	0.90
		1.00	0.36	0.96
CASS 4 + TST 25% (n=32)	0.75	0.10	0.78	0.50
		0.20	0.59	0.80
		0.40	0.56	0.90
		1.00	0.44	0.96
<i>Orthostatic hypotension</i>				
SBP drop 30 mmHg or mean BP drop 20 mmHg (n=61)	0.66	0.10	0.66	0.50
		0.20	0.43	0.81
		0.40	0.38	0.91
		1.00	0.30	0.98

Abbreviations: Ganglionic AChR Ab, antibodies to $\alpha 3$ subunit of nicotinic ganglionic acetylcholine receptor; AUC, area under curve; CASS, composite autonomic scoring scale; SBP, systolic blood pressure; TST, thermoregulatory sweat test