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Sudomotor dysfunction in autoimmune autonomic ganglionopathy: a follow-up study

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Abstract

Objective—We have previously shown that sudomotor dysfunction in autoimmune autonomic ganglionopathy is severe, widespread, and predominantly post-ganglionic. However, the long-term changes in sudomotor function have not been studied in detail. Our objective was to characterize the long-term changes in sudomotor dysfunction in patients with autoimmune autonomic ganglionopathy.

Methods—Changes in sudomotor function were compared in a cohort of nine α3 nAChR antibody positive autoimmune autonomic ganglionopathy patients over an approximate 5-year period. Standard measurements of sudomotor function were used including the thermoregulatory sweat test and quantitative sudomotor axon reflex test.

Results—Total body anhidrosis on thermoregulatory sweat testing showed improvement in four of nine patients. Quantitative sudomotor axon reflex testing for both forearm and foot sites was variable with four of nine patients showing improvement in total sweat output. Distribution of sudomotor dysfunction at follow-up was post-ganglionic in seven of nine patients at the foot site and three of nine patients at the forearm site. Overall, sudomotor dysfunction was post-ganglionic in seven of nine patients throughout the follow-up period (62.4 ± 19.4 months).

Interpretation—Sudomotor dysfunction in autoimmune autonomic ganglionopathy was severe and widespread throughout the follow-up period for the majority of patients studied. Sudomotor dysfunction was predominantly post-ganglionic throughout the follow-up period.

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Keywords

Sudomotor function; Autoimmune autonomic ganglionopathy; Anhidrosis; Preganglionic; Post-ganglionic

Introduction

Autoimmune autonomic ganglionopathy (AAG) is characterized by dysfunction in multiple autonomic domains [13]. In addition to common features such as orthostatic hypotension and gastrointestinal hypomotility, sudomotor dysfunction has been shown to be severe and widespread in this condition [5]. Ganglionic α3 nicotinic acetylcholine receptor (nAChR) antibodies occur in approximately half of patients with the disease and have been shown to correlate with autonomic dysfunction in multiple autonomic domains [6, 11]. More recently, studies show that the severity of sudomotor dysfunction increases with higher ganglionic α3 AChR antibody levels [5].

We have previously taken advantage of clinical methods to evaluate sudomotor function including quantitative sudomotor axon reflex testing (QSART) and the thermoregulatory sweat test (TST). QSART and TST allow for localization of dysfunction to either the preganglionic (abnormal TST but normal QSART) or post-ganglionic (abnormal QSART) sudomotor pathways [8]. Using these methods, sudomotor dysfunction in AAG was found to be predominantly post-ganglionic and that this post-ganglionic dysfunction increased with higher ganglionic α3 AChR antibody levels [5].

However, little is known regarding changes in sudomotor function in AAG over time. We have previously reported the initial sudomotor findings in a cohort of 21 patients with AAG [5]. It was our objective to study those patients who had undergone repeat autonomic investigations to determine whether the severity and distribution of sudomotor abnormalities change with follow-up.

Methods

Patients

Patients with ganglionic nAChR antibody levels of >0.05 nmol/L were identified from prior records (Mayo Clinic, Rochester). Antibody levels were obtained on all patients at the onset of diagnosis with AAG and correspond to the initial autonomic testing. Patients with abnormalities in either adrenergic, cardiovagal, or sudomotor function on standard clinical autonomic testing and a positive antibody levels (>0.05 nmol/L) were deemed to have antibody-positive AAG. Patients were required to have undergone both QSART and TST on at least two separate occasions. A total of nine patients met the above criteria and were included in the study.

All patients had extensive investigations to rule out other causes of autonomic dysfunction. All patients were negative for other paraneoplastic and neuronal antibodies on standard paraneoplastic antibody panels (Mayo Clinic, Rochester, MN). Patients with multiple system atrophy, diabetes, amyloidosis, rheumatologic disorders, malignancy, or other cause of autonomic dysfunction were eliminated from the study.

All patients provided written permission to use their medical records for research purposes using the standard institutional research authorization protocols. The Mayo Clinic Institutional Review Board approved this study.

Autoantibody measurements

Previously described, standard methods were used to determine ganglionic nAChR antibody levels [15]. Antibody levels of >0.05 nmol/L were considered positive.

Sudomotor testing

Post-ganglionic sympathetic sudomotor function was measured using the quantitative sudomotor axon reflex test (QSART). Sites tested included the left forearm, proximal leg, distal leg, and foot. Based on standard protocols, a 10% acetylcholine solution was iontophoresed for 5 min (2 mA) and recorded for an additional 5 min using standard multi-compartmented sweat cells [10]. Whether the obtained result was normal or abnormal at each individual QSART site was based on control data from 223 healthy individuals [9].

The thermoregulatory sweat test (TST) measures total body sweating. The TST was performed as per standard protocols using a sweat cabinet (43–46°C air temperature, 35–40% relative humidity) in order to raise oral temperature by 1.0°C or to an overall body temperature of 38.0°C [3]. An indicator powder consisting of alizarin red, corn starch, and sodium carbonate was used which changes color with sweating. The % anhidrosis (100% indicates complete anhidrosis) over the anterior surface of the subject was determined using standard digital imaging software [2].

Determination of pre- versus post-ganglionic sudomotor function

Pre- versus post-ganglionic sudomotor deficits were determined as previously described [5]. Briefly, the lesion is considered to be preganglionic if TST shows anhidrosis (for the site) and QSART is normal (recorded over the identical site). Since QSART is a very sensitive test (and may detect sweating when TST reads anhidrosis), to avoid the situation where TST shows anhidrosis while QSART shows a low (but still normal value, e.g., 7th percentile), we have insisted that the QSART site would only be considered normal if it is>25th percentile. This criterion of 25th percentile is solely used to designate a preganglionic lesion. When TST shows anhidrosis and QSART is reduced (below 25th percentile) for the identical site, then a post-ganglionic lesion was determined for that specific site [8].

If the majority of the designated QSART sites (i.e., 3 of 4 sites) was either pre- or post-ganglionic for an individual patient, then that patient was designated as such. If an individual patient had at least one abnormal QSART site with the remainder of sites being normal, the patient was designated as either being pre- or post-ganglionic based on the single abnormal QSART site. If a patient had a mixture of abnormal QSART sites with less than three sites being either pre- or post-ganglionic, then that individual was designated as having a mixed lesion. QSART and TST have previously been described for several autonomic disorders including pure autonomic failure and multiple system atrophy [8, 9].

Composite autonomic severity score (CASS)

The CASS score is a previously validated, objective and quantitative measure to characterize the degree of abnormality on standard autonomic reflex screening [7]. The CASS score is a 10-point total scale. It is divided into three subscores: sudomotor (CASS-sudomotor; range 0–3), cardiovagal (CASS-cardiovagal; range 0–3), and adrenergic (CASS-adrenergic; range 0–4). CASS scores are normalized for both effects of age and gender. Grading for autonomic failure is follows: 1–3 mild; 4–6 moderate; 7–10 severe.

Statistical analyses

Descriptive statistics are presented as mean values with their corresponding standard deviation (mean ± SD).

Results

Patient characteristic are described in Table 1. Ganglionic nAChR antibody and norepinephrine levels were evaluated at the initial assessment. Follow-up ganglionic nAChR antibody levels were available in three patients. Patient 6 had an initial antibody level of 0.07 nmol/L, normal QSART and minimal anhidrosis (13%) on TST. At 1-year follow-up, the nAChR antibody level was 0.01 nmol/L, QSART was again normal and mild improvement on TST (9% anhidrosis). Patient 3 had an initial antibody level of 0.99 nmol/L with absent QSART response at all 4 sites and 85% anhidrosis on TST. Follow-up levels at 2 and 6 years post onset were 11.92 and 1.74 nmol/L, respectively. Patient 7 had an initial antibody level of 0.35 nmol/L, normal QSART and minimal anhidrosis (13%) on TST. At the 4-year follow-up point, the nAChR antibody level was 0.53 nmol/L. There was no corresponding autonomic testing data for follow-up antibody levels in either patient 3 or 7.

TST results were variable with respect to total body anhidrosis (Table 2). Four of nine patients showed significant improvement (decreased % anhidrosis), while only two patients showed an increase in total body anhidrosis over a follow-up period of 62.4 ± 19.4 months. The remaining three patients had modest anhidrosis on TST which was marginally improved at follow-up assessment. Similarly, QSART measurement of post-ganglionic sudomotor fiber integrity showed variable results (Table 2). For both forearm and foot QSART sites there was improvement in four of nine patients (both forearm and foot sites) with respect to total sweat volume over a 70.9 ± 20.6 month follow-up period. Overall the majority of patients (6 of 9) had severe sudomotor abnormalities on either TST or QSART consistent with a ganglionic neuropathy.

In total seven of nine patients exhibited overall post-ganglionic sudomotor dysfunction (Table 3). Interestingly the remaining two patients initially showed preganglionic dysfunction at initial assessment but sudomotor function in these patients normalized by the final follow-up assessment (Table 3). Analysis of specific QSART sites, showed post-ganglionic sudomotor dysfunction in three of nine patients at the forearm site and seven of nine patients at the foot site (Table 2). For both QSART sites, none of the nine patients revealed preganglionic dysfunction at final follow-up. The sudomotor function in the remaining patients by QSART site normalized for both the forearm (6 of 9) and foot sites (2 of 9). Taken together this sudomotor dysfunction in our patients was predominantly post-ganglionic in distribution.

Discussion

In this study, we have further characterized the unique sudomotor dysfunction in AAG over an approximate 5-year period. The relevant conclusions are: (i) sudomotor dysfunction was generally severe and widespread; (ii) sudomotor dysfunction continued to be primarily post-ganglionic in distribution at follow-up. We have previously defined the sudomotor abnormalities in ganglionic AChR antibody positive AAG as severe, widespread, and predominantly post-ganglionic in distribution at initial presentation [5]. Our current study shows the same severity and pattern of sudomotor abnormality is demonstrated through the follow-up period.

We have previously shown that the severity of autonomic dysfunction including sudomotor dysfunction and the post-ganglionic distribution is proportional to increasing ganglionic AChR antibody levels [5, 11, 16]. However, the patients included here were evaluated primarily on the basis of their clinical symptoms and abnormalities seen on standardized autonomic testing at follow-up time points. Several patients were also evaluated prior to our full understanding of how the AChR antibody levels related to autonomic dysfunction. As a

result, our study is limited in that we did not obtain ganglionic AChR antibody levels for the majority of the follow-up assessments. Only one patient has ganglionic nAChR antibody levels and corresponding autonomic testing at both onset and follow-up. While there was a reduction in the antibody levels corresponding to improved sudomotor function, this improvement was mild and difficult to draw further conclusions from. Further studies with ganglionic AChR antibody levels at later time points would be of interest. Based on our prior studies, we would speculate that changes in the severity and post-ganglionic distribution of sudomotor dysfunction in AAG would correlate with antibody levels over a prolonged duration [4, 5].

The question of long-term treatment for antibody-positive AAG and the resulting effects on sudomotor function remains to be determined and was not addressed in this study. We have previously shown that immunomodulatory therapy including intravenous immunoglobulin (IVIg) and plasma exchange (PLEX) reduced total body anhidrosis on TST and increased total sweat volume on QSART in three of four patients in a treatment trial of AAG [4]. The prior study was conducted over a follow-up period of less than 18 weeks, but further long-term treatment trials in AAG are planned [4]. We have limited data regarding treatment in these patients. Several factors account for this. First, the majority of patients (7 of 9) in the study had very gradual onset disease (see Table 1). Secondly, the majority of patients (5 of 9) presented for evaluation (at Mayo) greater than 4.5 years after onset (see Table 1). As a result only two patients (patients 2 and 3) were treated with a combination of intravenous immunoglobulin and plasma exchange around the time of this study at outside hospitals. The effect of this treatment did not alter the distribution of sudomotor dysfunction and had variable effects on severity. The effect of long-term treatment with IVIg, PLEX, or other immunomodulatory therapies would be of interest to further elucidate the effect on the severity and distribution of autonomic dysfunction and AChR antibody levels in AAG.

It was interesting that two of the seven patients that showed initial preganglionic dysfunction at onset both improved to reveal no sudomotor dysfunction at the final follow-up period (see Table 3, patients 6 and 9). These patients in general had lower ganglionic AChR antibody levels than those patients with more severe disease. This preganglionic dysfunction could potentially be a result of nAChR antibodies inhibiting acetylcholine from binding to corresponding receptors on the surface of the post-ganglionic cell body [1, 12, 14, 17, 18]. The post-ganglionic dysfunction in seven of the patients presented here may represent more significant physiological derangement of the post-ganglionic neuron or potentially some degree of neuron/axon loss and tended to be associated with higher ganglionic AChR antibody levels [17]. Therefore, post-ganglionic dysfunction may represent a more significant impairment of the corresponding cell body and/or axon and could be related to higher ganglionic AChR antibody levels.

In conclusion sudomotor dysfunction in AAG was severe, widespread, and predominantly post-ganglionic in distribution. The severity and post-ganglionic distribution was unchanged over the duration of the study. This study provides the first long-term systematic investigation of sudomotor function in AAG.

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Table 1

Patient characteristics

Patient	Sex	Age	Disease onset[a]	Antibody level (nmol/L)[b]	Time to initial evaluation (years)	CASS score	NE level Supine (nmol/L)	NE level Standing (nmol/L)
1	M	68	Gradual	6.73	10	7	81	210
2	F	75	Subacute	0.45	0.25	9	115	167
3	F	45	Gradual	0.99	0.16	9	38	52
4	F	66	Gradual	9.70	2	10	30	219
5	F	58	Subacute	0.17	1	7	n/a	n/a
6	M	55	Gradual	0.07	5	6	n/a	n/a
7	F	65	Gradual	0.35	40	5	111	170
8	M	65	Gradual	0.09	4.5	7	215	203
9	F	48	Gradual	0.13	5	0	170	369

CASS score Composite autonomic severity score, *n/a* not available

[a] Subacute ≤6 weeks; gradual >6 weeks

[b] Ganglionic α3 nicotinic acetylcholine receptor antibody

Table 2

Initial and follow-up assessments of sudomotor function by QSART, TST, and distribution

Patient	Sudomotor abnormalities										Duration (months)[d]
			Foot site				Forearm site				
	TST[a]		QSART[b]		Pre- versus post-ganglionic[c]		QSART		Pre- versus post-ganglionic		
	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final	
1	97	59	0.00	0.00	Post	Post	0.15	0.00	Post	Post	62
2	43	96	0.00	0.00	Post	Post	0.00	0.46	Post	Normal	152
3	85	10	0.00	0.21	Post	Post	0.18	0.06	Post	Post	9
4	78	39	0.00	0.00	Post	Post	0.00	0.17	Post	Post	194
5	61	27	0.00	0.08	Post	Post	0.00	0.43	Post	Normal	42
6	13	9	1.51	1.05	Normal	Normal	1.69	0.81	Pre	Normal	14
7	11	8	0.50	0.16	Pre	Post	0.81	0.43	Normal	Normal	52
8	7	4	0.36	0.58	Post	Post	4.54	1.53	Normal	Normal	52
9	4	13	0.42	0.69	Pre	Normal	0.43	2.57	Normal	Normal	61

QSART Quantitative sudomotor axon reflex testing, *TST* thermoregulatory sweat testing

[a] Data is expressed as % anhidrosis, see “Methods”

[b] Data is expressed as total sweat volume in μL

[c] Sudomotor abnormalities are designated as pre- or post-ganglionic. Please refer to “Methods”

[d] Follow-up duration between the initial and final QSART testing

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Table 3

Sudomotor abnormalities for individual patients at initial and final assessment

Patient	Sudomotor abnormalities[a]					
	Initial assessment	1st follow-up	2nd follow-up	3rd follow-up	4th follow-up	5th follow-up
1	Post-ganglionic	Post-ganglionic				
2	Post-ganglionic	Post-ganglionic	Post-ganglionic	Post-ganglionic	Post-ganglionic	
3	Post-ganglionic	Post-ganglionic				
4	Post-ganglionic	Post-ganglionic	Post-ganglionic	Post-ganglionic	Post-ganglionic	Post-ganglionic
5	Post-ganglionic	Post-ganglionic				
6	Preganglionic	Normal				
7	Preganglionic	Post-ganglionic	Post-ganglionic			
8	Post-ganglionic	Post-ganglionic	Post-ganglionic	Post-ganglionic	Post-ganglionic	
9	Preganglionic	Mixed	Normal			

[a]Sudomotor abnormalities are designated as pre- or post-ganglionic. Please refer to “Methods”. Time between the initial and final assessments is the same as that listed in Table 2