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Association of N-type calcium channel autoimmunity in patients with autoimmune autonomic ganglionopathy

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Abstract

The nicotinic acetylcholine receptor (nAChR) antibody directly contributes to the autonomic dysfunction in Autoimmune Autonomic Ganglionopathy (AAG). The pathological mechanism leading to autonomic dysfunction in seronegative AAG is unclear. We evaluated patients with presumed antibody negative AAG (n=49) to determine whether there was an association with other autoantibodies. Three patients met the clinical criteria and were positive for N-type calcium channel antibodies. All patients had severe autonomic dysfunction characterized by orthostatic hypotension and gastrointestinal involvement. Autonomic testing revealed severe impairment of sudomotor, cardiovagal, and adrenergic domains. These findings raise the possibility that other autoantibodies may contribute to the pathogenesis of AAG.

Keywords

autonomic failure; autoimmune ganglionopathy; calcium channel antibodies

Introduction

Autoimmune autonomic ganglionopathy is characterized by dysfunction of the sympathetic, parasympathetic, and enteric nervous systems. It is most often associated with orthostatic hypotension, anhidrosis, and gastrointestinal hypomotility (Suarez et al., 1994). Approximately 50% of individuals diagnosed with AAG are positive for ganglionic $\alpha 3$ nicotinic acetylcholine receptor (nAChR) antibodies (Vernino and Lennon, 2003). Higher ganglionic antibody levels correlate with more severe disease (Klein et al., 2003; Sandroni et al., 2004).

A direct role of the ganglionic antibody in the pathogenesis of AAG is supported by data from animal experiments. Rabbits immunized with $\alpha 3$ nAChR fusion protein developed ganglionic auto antibodies and secondary autonomic dysfunction (Vernino et al., 2003). The severity of the autonomic dysfunction correlated with antibody titer (Vernino et al., 2003; Lennon et al., 2003). Failure of ganglionic transmission through sympathetic ganglia in the same animal

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model confirmed a post synaptic channelopathy (Lennon et al., 2003). Furthermore, adopted transfer of mice with rabbit ganglionic $\alpha 3$ nAChR antibodies or IgG from human AAG patients resulted in severe autonomic dysfunction (Vernino et al., 2004).

The pathogenesis in ganglionic nAChR seronegative AAG remains unclear. However, autoimmune processes due to other autoantibodies may play a role given the clinical similarity to seropositive AAG, and the response of some seronegative patients to immunomodulatory therapies. In this study, we retrospectively evaluated consecutive patients seen at the Mayo Clinic (Rochester, Minnesota) with the clinical diagnosis of seronegative AAG to determine whether there is an association with other autoantibodies.

Materials and Methods

Patients

All patients referred to the Mayo Clinic (Rochester) with the diagnosis of AAG after 1997 were retrospectively evaluated (n=49). Patients were included in the study if they met the clinical criteria for AAG, were negative for the ganglionic $\alpha 3$ nAChR antibody and had undergone the paraneoplastic autoantibody comprehensive panel performed by Mayo Medical Laboratories (Rochester MN).

The criteria for the diagnosis of antibody negative AAG included a ganglionic $\alpha 3$ nAChR antibody level of < 0.05 nmol/L (prior to treatment). In addition, patients were required to have the following clinical characteristics to be considered antibody-negative AAG: 1. Orthostatic hypotension, defined as a systolic blood pressure reduction of ≥ 30 mmHg or mean blood pressure reduction of ≥ 20 mmHg occurring within 3 minutes of head-up tilt; 2. Significant gastrointestinal symptoms with predominant upper gastrointestinal dysmotility; 3. Severe autonomic dysfunction on standardized autonomic testing (Composite Autonomic Severity Score ≥ 7 , see below). Additional criteria suggestive of seronegative AAG but not required include impaired pupillary light responses and a prior antecedent event (i.e., viral illness). Onset was defined as the time to peak autonomic dysfunction (subacute < 3 months, gradual > 3 months).

Comprehensive clinical, hematologic, biochemical, and serological assessments of all patients were performed at baseline. Patients with known causes of autonomic failure including multiple system atrophy, diabetes, amyloidosis, rheumatologic disorders, and known malignancies were excluded. All patients were negative for any other neuronal autoantibodies on a standard comprehensive paraneoplastic antibody panel (Mayo Clinic, Rochester, MN) other than P/Q and N-type Calcium Channels antibodies specified. This study was approved by the Mayo Clinic Institutional Review Board.

Autoantibody measurements

Autoantibodies binding to neuronal ganglionic acetylcholine receptors ($\alpha 3$ nAChR), P/Q type and N-type calcium channels were detected by immunoprecipitation assays as previously described (Pittock et al., 2003; Vernino and Lennon, 2003). The normal ranges in serum for both antibodies are < 0.05 nmol/L ($\alpha 3$ nAChR) and < 20 pmol/L (P/Q and N-type calcium channels). All patients underwent the paraneoplastic autoantibody comprehensive panel performed by Mayo Medical Laboratories (Rochester MN). Antibodies tested include anti-neuronal nuclear antibodies type 1 (anti-Hu) and type 2 (anti-Ri), amphiphysin antibody, type 1 Purkinje cell cytoplasmic antibody (PCA-1), AChR binding antibody, striated muscle antibody and collapsin response-mediator protein (CRMP)-5 in addition to N-type and P/Q-type calcium channel antibodies. For a recent description of this autoantibody panel please refer to McKeon et al. (2009).

Autonomic Testing

Autonomic Reflex Screening (ARS) was performed as previously described (Low and Opfer-Gehrking, 1999; Low, 2003). The quantitative sudomotor axon reflex test (QSART) evaluates the postganglionic sympathetic sudomotor axon. The resulting sweat response was recorded routinely from four sites (forearm, proximal leg, distal leg, and foot). Results were compared to normative data derived from studies on 223 healthy subjects aged 10–83 years (Low et al., 1997). Cardiovascular function was assessed using heart rate response to deep breathing and Valsalva ratio. Results were compared to normative data derived from 157 healthy subjects aged 10–83 years (Low et al., 1997). Cardiovascular adrenergic function was evaluated by measuring blood pressure and heart rate responses to Valsalva maneuver and head-up tilt (Low and Opfer-Gehrking, 1999; Low, 2003). Thermoregulatory Sweat Test (TST) was performed as previously described (Fealey et al., 1989). The TST provides a quantitative measure of total body sweating. The percentage of anhidrosis on the anterior body surface was calculated from the distribution of total body sweating (100% indicates complete anhidrosis).

Composite Autonomic Severity Score (CASS)

The CASS score is a previously validated, objective measure used to quantitate autonomic dysfunction on standard autonomic reflex screening (ARS; Low, 1993). The 10-point total CASS score is divided into three subscores: sudomotor (CASS-sudomotor; range 0–3), cardiovascular (CASS-cardiovascular; range 0–3), and adrenergic (CASS-adrenergic; range 0–4). The CASS score is normalized to account for effects of age and gender. Autonomic failure was graded as follows: 1–3 mild; 4–6 moderate; 7–10 severe.

Results

General

We identified four patients with a clinical diagnosis of AAG who were positive for N-type calcium channel antibodies. All four patients were negative for the α_3 nAChR antibody. Of these four patients, one was eliminated from further study after developing small cell lung cancer two years after the initial diagnosis of AAG. This patient was considered to have paraneoplastic autonomic neuropathy. Of the remaining three patients described below, one was positive for P/Q type calcium channel antibodies (Table 2). Otherwise all three patients had no other associated autoantibodies. In addition, no other associated autoantibodies were detected in the remainder of the antibody negative AAG patients ($n=45$) evaluated in our retrospective study. The following is a brief description of three AAG cases positive for N-type calcium channel antibodies and negative for ganglionic α_3 nAChR antibody.

Case 1

A previously healthy 57-year-old female rapidly developed autonomic symptoms after treatment for a urinary tract infection. Autonomic disturbance included syncopal episodes secondary to orthostatic hypotension, nausea, and severe bloating (Table 1). The Autonomic Reflex Screen showed severe orthostatic hypotension with absent postganglionic sudomotor function (Table 2). The patient was treated with oral hydration, increased salt intake, compression garments, and fludrocortisone (0.1 mg/day). The patient's autonomic symptoms progressed and treatment with several courses of IVIg was initiated without benefit. A combination of plasma exchange, midodrine, and pyridostigmine resulted in minimal improvement of autonomic function. N-type calcium channel antibodies and the corresponding timing of immunotherapy for this patient are shown in Figure 1. The patient has not developed a malignancy in 9 years of follow up. Repeated Computed Tomography Scans of the chest, abdomen and pelvis were negative for malignancy. Approximately five years after diagnosis Magnetic Resonance Imaging was negative for lung, breast or pelvic malignancies.

Case 2

A 42-year-old male developed gradual progressive wide spread autonomic dysfunction with an associated small fiber neuropathy. The patient had a prior medical history of seronegative arthritis previously treated with prednisone and methotrexate. A prior treatment attempt with IVIg improved the rheumatologic disorder but did not result in any change to the autonomic manifestations. The autonomic dysfunction included orthostatic hypotension, neurogenic bladder, bloating, early satiety, severe constipation, and erectile dysfunction (Table 1). The neurological examination was notable for absent pupillary responses to light and a mild loss of temperature and superficial pain sensation bilaterally at the feet. The Autonomic Reflex Screen revealed widespread postganglionic sudomotor, cardiovagal, and adrenergic dysfunction (Table 2). The Thermoregulatory Sweat Test showed 75% total body anhidrosis. The autonomic dysfunction did not respond to IVIg. There was mild improvement in orthostasis with floninef (0.1 mg/day). The patient has not developed a malignancy in 4 years of follow up.

Case 3

This 64-year-old man with a prior 20 year history of ulcerative colitis presented with a four year history of autonomic dysfunction. Autonomic dysfunction included orthostatic hypotension, neurogenic bladder, and severe constipation (Table 1). The neurological examination was notable for moderately asymmetric upper extremity muscle stretch reflexes and a left Babinski's sign. The Autonomic Reflex Screen showed evidence of cardiovagal, cardiovascular, adrenergic, and postganglionic sympathetic sudomotor impairment (Table 2). The Thermoregulatory Sweat Test showed 86% total body anhidrosis. The patient was treated conservatively with fluid hydration, exercise, and compression garments. Pharmacological measures included Midodrine 7.5 mg twice daily. Recent body Positron Emission Tomography and Computed Tomography of the chest, abdomen, and pelvis were negative for malignancy. Magnetic Resonance Imaging of the brain and cervical spine showed cervical stenosis but were negative for malignancy.

Discussion

Given that only three patients were positive for the presence of N-type calcium channels, a clear correlation to the onset or pattern of autonomic dysfunction cannot be made. It is interesting, however, that all patients had significant autonomic symptoms and severe dysfunction on standard autonomic testing (CASS scores 8–9). Our criteria as defined (see Materials and Methods: Patients) is selective for severe autonomic dysfunction in that frank orthostatic hypotension, significant gastrointestinal dysmotility and a CASS score ≥ 7 are required for the definition of seronegative AAG. However, none of the patients retrospectively screened (n=49), including those that did not meet this criteria, were positive for N-type calcium channels. In addition, we have not seen an association of N-type calcium channel antibodies in an additional 15 patients who were identified but were ganglionic antibody positive (data not shown). Given these findings, there is some evidence to support the idea that N-type calcium channel antibodies when present in AAG are associated with more severe autonomic dysfunction.

A fourth patient was identified who met our clinical criteria but was excluded from the study after developing small cell lung cancer (SCLC) approximately two years after the diagnosis of AAG. Interestingly, this patient was positive for both N-type and P/Q type antibodies. Both antibodies have been reported to be associated with SCLC, most often in combination with Lambert Eaton Myasthenic Syndrome (LEMS; Motomura et al., 1997) but also in a wider variety of neurological syndromes (Monstad et al., 2004). Neither this patient nor the three AAG patients described here had evidence of a neuromuscular transmission defect. To date,

all AAG patients described in this study have not developed a malignancy including Case 3 who was also positive for both calcium channel antibodies. In this patient an extensive work up looking for an underlying malignancy was negative. Irrespective, any type of voltage-gated calcium channel antibody, particularly in the context of a neurological syndrome, requires a high suspicion for malignancy.

The insidious onset of wide spread autonomic dysfunction with an impaired standing norepinephrine response does raise the possibility of Pure Autonomic Failure (PAF) in Case 2. It has been established in the published literature that a minority of patients with AAG can have a gradual progression of autonomic dysfunction (Klein et al., 2003; Vernino et al., 2008). This makes the differentiation of AAG from PAF difficult under these circumstances. However, upper gastrointestinal dysmotility, involvement of somatic nerves and absent pupillary responses common to AAG are absent in PAF. These findings in our patient associated with a mild distal sensory neuropathy are consistent with the diagnosis of AAG.

N-type calcium channels are associated with other diseases involving autonomic dysfunction. While neurologic dysfunction in LEMS is predominantly associated with the P/Q-type channel, N-type calcium channel autoantibodies can be found in 31–49% of LEMS cases. The vast majority of these patients have autonomic dysfunction (Lennon et al., 1995; O'Suilleabhain et al., 1998). Our patients are different from LEMS patients in that the autonomic dysfunction was much more severe (CASS scores of 8–9 compared to CASS scores of 2–3 in LEMS patients; O'Suilleabhain et al., 1998). These findings are specific to those patients that were N-type but not P/Q autoantibody positive. In Autoimmune Gastrointestinal Dysmotility, a limited autoimmune dysautonomia is associated with multiple autoantibodies including N-type calcium channels (Dhamija et al. 2008). Of the five patients reported, three did not have a corresponding malignancy. A similar case has been reported with a severe gastroparesis occurring over 15 years with mild autonomic dysfunction including sudomotor deficits, positive for both nAChR and N-type calcium channel antibodies (Pasha et al. 2006). Extensive evaluation did not reveal a malignancy in this patient.

Evidence from animal studies point to an important role for N-type calcium channels in the autonomic nervous system. N-type calcium channels are important for acetylcholine release from both preganglionic sacral parasympathetic and superior cervical ganglionic neurons (Gonzalez et al., 1995; Jobling et al., 2004). Mice lacking the α_{1B} subunit ($Ca_v 2.2$) of N-type calcium channels show sympathetic deficits including a severely reduced baroreflex response (Ino et al., 2001). Omega-conotoxin GVIA, a potent and selective inhibitor of N-type voltage-operated calcium channels, can reduce blood pressure, heart rate, and significantly impair the sympathetic component of the baroreceptor reflex in animal models (Pruneau and Bélitchard, 1992). However, the distribution of autonomic dysfunction in our patients does not appear to be completely explained by the evidence from animal models and further work is needed.

To our knowledge, this is the first description of AAG associated with N-type calcium channel autoantibodies. The question remains as to whether the association of N-type calcium channels with AAG is actually a causal relationship. Conversely N-type calcium channels may not play a pathogenic role but could represent a marker of severe autonomic dysfunction. To establish a direct pathological mechanism in AAG, further investigation, similar to work done with the α_3 nAChR antibody, is required (Lennon et al., 2003; Vernino et al., 2003, 2004).

Abbreviations

nAChR, nicotinic acetylcholine receptor; AAG, autoimmune autonomic ganglionopathy; CASS, Composite Autonomic Severity Score; QSART, quantitative sudomotor axon reflex test; TST, Thermoregulatory Sweat Test.

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Figure 1. N-type calcium channel antibody levels corresponding to Case 1. The relationship over time between N-type calcium channel antibodies and treatment with Intravenous Immunoglobulin (IVIg) and Plasma Exchange (PLEX) are shown. No significant change in autonomic symptoms was seen over the same time period.

Table 1
Clinical features of AAG patients associated with N-type Ca²⁺ autoimmunity.

Clinical Features							
	Onset*	Orthostasis	UGI	LGI†	Pupil	Sicca	Bladder
Patient 1	Subacute	Y	Y	0	N	N	N
Patient 2	Gradual	Y	Y	2	Y	N	Y
Patient 3	Gradual	Y	Y	2	N	N	Y

^{*} Subacute = peak of autonomic failure < 3 months; Gradual = gradual onset with the peak of autonomic failure > 3 months; Y = yes; N = no; UGI, upper gastrointestinal symptoms; LGI, lower gastrointestinal symptoms

[†] 0 = normal, 1 = constipation, 2 = severe constipation, 3 = persistent diarrhea

Table 2
Autonomic reflex screen and laboratory findings in AAG patients associated with N-type Ca²⁺ autoimmunity.

	CASS score				NE level [*]			ab level [‡]
	total	sudo	vagal	adren	supine	standing		
Patient 1	8	3	1	4	16	29	232	
Patient 2	9	3	2	4	18	88	54	
Patient 3 [‡]	8	3	1	4	n/a	n/a	92	

^{*} NE level, norepinephrine level (pg/mL, normal range: supine 70–750 pg/mL, standing 200–1700 pg/mL)

[‡] N-type Ca²⁺ channel level (pmol/L, normal range <20 pmol/L); ab, antibody; CASS, Composite Autonomic Severity Scale: sudo, sudomotor; vagal, cardiovagal; adren, adrenergic; CASS: 1 to 3: mild autonomic failure; 4 to 6: moderate autonomic failure; 7 to 10: severe autonomic failure; n/a not available

[‡] Patient 3 was also positive for P/Q type calcium channel antibodies (59 pmol/L, normal < 20 pmol/L).