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A Unique Manifestation of Pupillary Fatigue in Autoimmune Autonomic Ganglionopathy

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Abstract

Objective—To demonstrate a unique abnormality of the pupillary light reflex in patients with Autoimmune Autonomic Ganglionopathy (AAG).

Design—Case series

Setting—Autonomic clinics at two university hospitals (University of Texas Southwestern Medical Center and Beth Israel Deaconess Medical Center)

Participants—Seven patients with antibody positive AAG.

Intervention—All patients with AAG underwent either monocular or binocular infrared pupillometry using a standard 2 second light stimulus at a defined intensity. Findings were compared to healthy controls and patients with other autonomic disorders. The light stimulus used in this study was selected to eliminate the normal phenomenon of pupil escape.

Main Outcome measure—The time to onset of redilation was the main outcome measure. Other indices of pupillary constriction to light stimulus were also measured.

Results—Patients with AAG exhibited premature pupillary redilation (1.02 ±0.20 seconds) compared to healthy control subjects (2.24±0.10 seconds) and other patients with autonomic disorders (2.3±0.12 seconds; $P<0.0001$). In healthy control subjects and patients with other autonomic disorders pupillary redilation always followed the termination of the light stimulus while in AAG patients redilation consistently occurred during the light stimulus. In one patient, serial repetitive light stimulation further decreased the time to onset of redilation.

Conclusion—Premature redilation of the pupil is a unique physiological feature seen only in patients with AAG. This phenomenon appears to be a manifestation of pupillary fatigue, a clinical

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Study concept and design: Muppidi, Gibbons, and Vernino. *Acquisition of data*: Muppidi, Vernino, Scribner, Spaeth and Gibbons. *Analysis and interpretation of data*: Muppidi, Scribner, Gibbons, Spaeth, Adams-Huet, Vernino. *Drafting of the manuscript*: Muppidi, Adams-Huet, and Vernino. *Critical revision of the manuscript for important intellectual content*: Muppidi, Scribner, Gibbons, Spaeth, Adams-Huet, Vernino. *Statistical expertise:* Adams-Huet *Obtained funding*: None. *Administrative, technical, and material support*: *Study supervision*: Muppidi, Gibbons, and Vernino.

correlate of defective synaptic transmission at the level of autonomic ganglia in antibody positive AAG.

Introduction

Patients with autoimmune autonomic ganglionopathy (AAG), a disorder characterized by antibodies against the nicotinic acetylcholine receptor of the autonomic ganglia, present with symptoms of diffuse autonomic failure. AAG is pathophysiologically similar to myasthenia gravis as both disorders are caused by antibody against nicotinic acetylcholine receptors. In AAG, the antibody targets the acetylcholine receptor at the autonomic ganglia, rather than the neuromuscular junction. Major clinical features of AAG include orthostatic hypotension, gastrointestinal dysmotility, anhidrosis, bladder dysfunction and sicca complex.[1] Impaired pupillary light reflexes are often seen in AAG[2] and may help differentiate AAG from other autonomic disorders.

In cases of subacute severe autonomic failure, a diagnosis of AAG can be confirmed by the presence of antibodies against the ganglionic acetylcholine receptor. However, the disease may go unrecognized if the onset of autonomic failure is insidious or atypical. In these instances, AAG may be misdiagnosed as a pure autonomic failure or multiple system atrophy, both of which are neurodegenerative conditions without significant pupillary involvement. This distinction is vitally important, as AAG is a potentially reversible disorder that responds to immunotherapy.[3]

Fixed, dilated pupils on clinical examination can indicate pupillary involvement. However, milder deficits of pupillomotor function may be difficult to detect on routine clinical examination. Additionally, pupillomotor dysfunction in AAG may be difficult to distinguish from impaired pupillary reflexes due to intracranial pathology, oculomotor nerve problems, medication effects, or normal aging.

Infrared pupillometry provides quantitative assessment of the pupillary reaction to light, including magnitude of pupillary constriction and constriction velocity [4]. Since myasthenia gravis is characterized by muscle fatigue, we hypothesized that AAG might be associated with fatigue in autonomic function. In an experimental model of AAG (EAAG) in rabbits, a unique pupillary abnormality suggestive of pupillary fatigue was seen [5]. The current study was performed to determine if pupillary fatigue may be detected in antibody positive AAG patients using dynamic pupillometry.

Methods

Subjects

We identified seven patients with AAG at our two centers (Table 1). All patients provided informed consent for this research study and all were evaluated with a standard battery of autonomic tests. Autonomic testing included Quantitative Sudomotor Axon Reflex Test (QSART), assessment of heart rate variability during deep breathing and Valsalva, and continuous blood pressure recording during Valsalva and 70° head-up tilt table test. The diagnosis of AAG was defined by symptoms and signs consistent with AAG, objective evidence of diffuse autonomic failure, and presence of serum ganglionic acetylcholine receptor antibodies. All patients were receiving immunomodulatory and symptomatic treatment at the time of the pupillometry study. None of the AAG patients were taking medications that could interfere with cholinergic function. Acetylcholinesterase inhibitor therapy was discontinued for at least 12 hours prior to testing. None of the AAG patients reported any known ocular disease apart from correctable refractive error.

Pupillometry was performed with six healthy control subjects to define the optimal testing parameters. Between July 2010 to June 2011,110 consecutive patients referred for autonomic evaluation had infrared pupillometry. The institutional review board at our institutions approved collection of the data for this study.

Infrared Pupillometry

Either binocular or monocular infrared pupillometry was used for data collection (Neuroptics Inc, San Clemente, CA) with a digital image capture rate at 30 Hz. Pupil diameter was detected by threshold detection of the dark pupil and corrected for distance from the camera. The calibrated light stimulus was presented to one or both eyes using a circumferential array of white LEDs. We used a 28 μW light intensity and 2 second duration stimulus for binocular testing at UTSW and a 50μW light intensity and 2 second duration for the monocular testing at BIDMC. The healthy controls were tested with identical monocular and binocular stimulation protocols. Non-AAG patients referred to us for autonomic testing had binocular pupillometry testing using the same protocol. Raw dynamic pupil diameter data was recorded in real time and analyzed offline using automated algorithms to determine baseline pupil diameter, maximum constriction velocity, relative constriction amplitude (a ratio of change in pupillary diameter to baseline pupil diameter) and time to onset of redilation. Pupillary light stimulation was done in a darkened room. Only direct pupillary light responses were analyzed. To avoid the phenomenon of pupil escape (a normal pupil redilation which may occur during low intensity unilateral light stimulus of prolonged duration), we chose a higher light intensity and bilateral stimulus in this study. [6] Using this protocol, we did not observe pupil escape in any of the non-AAG subjects.

Statistics

Statistical analysis was performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). Results were compared by one way ANOVA, with significance set at $P<0.05$.

Results

AAG Patients

By inclusion criteria, all AAG patients had severe diffuse autonomic dysfunction and serological evidence of ganglionic acetylcholine receptor antibody. Table 1 summarizes the demographic and clinical data including the duration of AAG. Pupillometry data from the seven AAG patients is summarized in Table 2. Patients 1 to 4 were tested with binocular pupillometry, and patients 5 to 7 were tested using monocular pupillometry. Normal data was obtained from healthy controls for each technique. The baseline dark-adapted pupillary diameter was within normal range in AAG patients. The pupillary constriction parameters, especially relative constriction amplitude, were decreased compared to controls ($P = 0.03$). More importantly, the time to redilation was less than 2 seconds (with 2-second light stimulus) in all AAG patients except in the left eye of patient 1, which was normal. Patient 1 also had the lowest antibody titer and lowest Composite Autonomic Severity Score (CASS). Figure 1 is a composite image of pupillometric waveforms from the seven AAG patients and healthy controls.

One AAG patient (patient 2 in Table 1) also had testing of the pupil light reflex using the 2-second duration light stimuli repeated every 10 to 20 seconds for 2.5 minutes. Figure 2 reveals that the time to redilation gradually decreased with repeated stimulation. We analyzed pupillometry data from healthy controls and from 110 consecutive patients with other autonomic disorders. Healthy controls and non-AAG autonomic patients were tested with the same binocular pupillary light stimulation of 2 second duration as the 4 patients with AAG at UTSW. The mean time to redilation was 2.24 (± 0.10) seconds in healthy

controls, 2.30 (± 0.12) seconds in patients with autonomic diseases other than AAG, and 1.02(± 0.2) seconds in patients with AAG (P<0.0001, Figure 3). Only patients with AAG showed premature redilation of the pupil with time to redilation less than 2 seconds.

Comment

Our study demonstrates that 1) Premature pupil redilation is seen in patients with AAG similar to the phenomenon described in the experimental AAG rabbit model [5]; 2) Using this light stimulation protocol we did not see premature redilation, indicating fatigue of pupillary constriction, in healthy controls or in patients with other autonomic diseases such as diabetes; and 3) Pupillary fatigue is demonstrable with either monocular or binocular pupillometry.

Pupillary abnormalities in antibody positive AAG are well known, but this is the first report to demonstrate the phenomenon of pupillary constriction fatigue in humans with AAG. Our study also highlights that pupillary diameter alone cannot reliably distinguish AAG patients from healthy controls. The normal pupil size in AAG is likely a consequence of concomitant sympathetic and parasympathetic impairment. Although significant parasympathetic failure is noted in AAG patients, similar parasympathetic dysfunction is seen in other autonomic disorders too, such as diabetes mellitus [7]. Therefore, dark-adapted pupillary diameter and pupillary constriction measures (maximum constriction velocity, relative constriction amplitude) are not conclusive in differentiating AAG patients from other autonomic disorders.

We used two different pupillometry techniques (binocular and monocular) in AAG patients. It would have been ideal to perform both techniques in all AAG patients; however, the monocular and binocular techniques in healthy controls provided similar results. Our group of non-AAG patients had a variety of diagnoses including diabetic autonomic neuropathy, Parkinson disease, postural orthostatic tachycardia and others. While the lack of uniformity in this group is a possible limitation, it supports the unique nature of pupillary fatigue in AAG, as similar findings were not seen in any of the non-AAG patients, even those that had evidence of pupil dysfunction.

This brief report highlights the unique phenomenon of pupillary constriction fatigue in AAG. We believe that pupillary fatigue represents a clinical expression of defective synaptic transmission at the level of autonomic ganglia in antibody positive AAG. As infrared pupillometry is non-invasive and relatively easy to perform, this technique offers a new diagnostic testing method to distinguish AAG patients from all others with autonomic dysfunction. Further studies are needed to investigate whether the severity of pupillary fatigue correlates with antibody titers, disease severity, or is responsive to acute or chronic immunomodulatory treatment. We plan to pursue similar studies in antibody negative AAG patients in future, as this could potentially help differentiate antibody negative AAG from other chronic progressive autonomic disorders.

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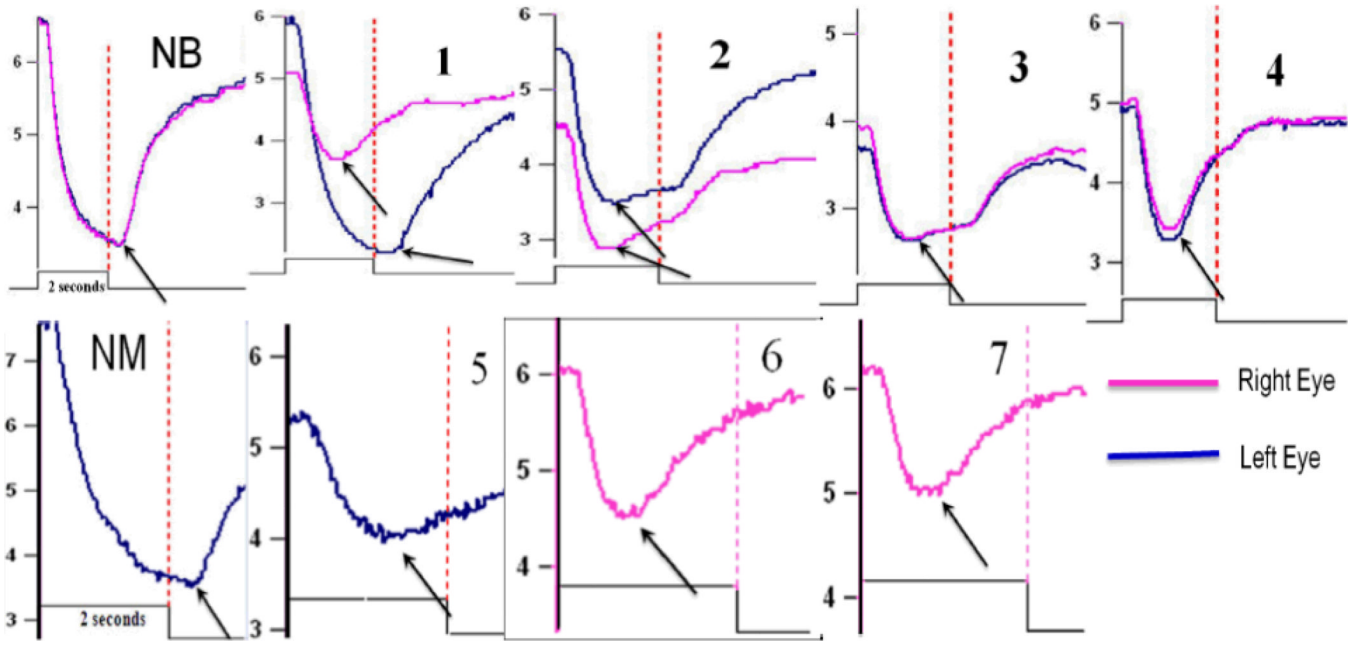

Figure 1.

NB- Binocular Pupillometry in a healthy control. NM- Monocular Pupillometry in a healthy control. Arrow points to the time of onset of redilation which follows the cessation of the light stimulus in healthy controls. Images 1 to 4 show binocular pupillometry in patients 1 to 4. Note patient 1 had an unaffected left eye and the onset of redilation was after the end of the 2-second light stimulus. Images 5 to 7 show monocular pupillometry in patients 5 to 7. In all AAG patients, there was at least one eye with premature pupillary redilation. All light stimuli were of 2-second duration and the dotted red line indicates the 2-second point. X-axis: Time in seconds; and Y-axis: pupil diameter in mm.

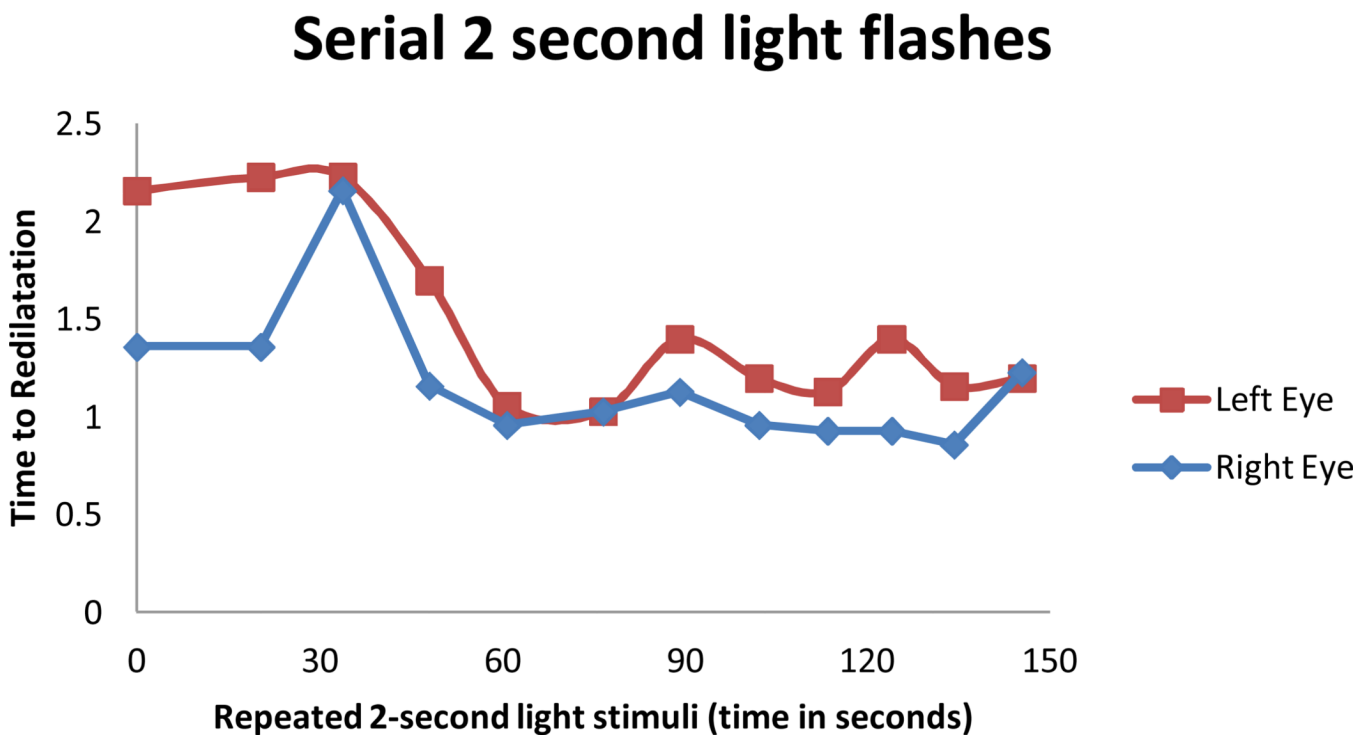

Figure 2.
Each point refers to data from one light stimulus. Note the time to onset of redilation gradually decreased. X- axis: Time in seconds. Y-axis: Time to Redilation in seconds.

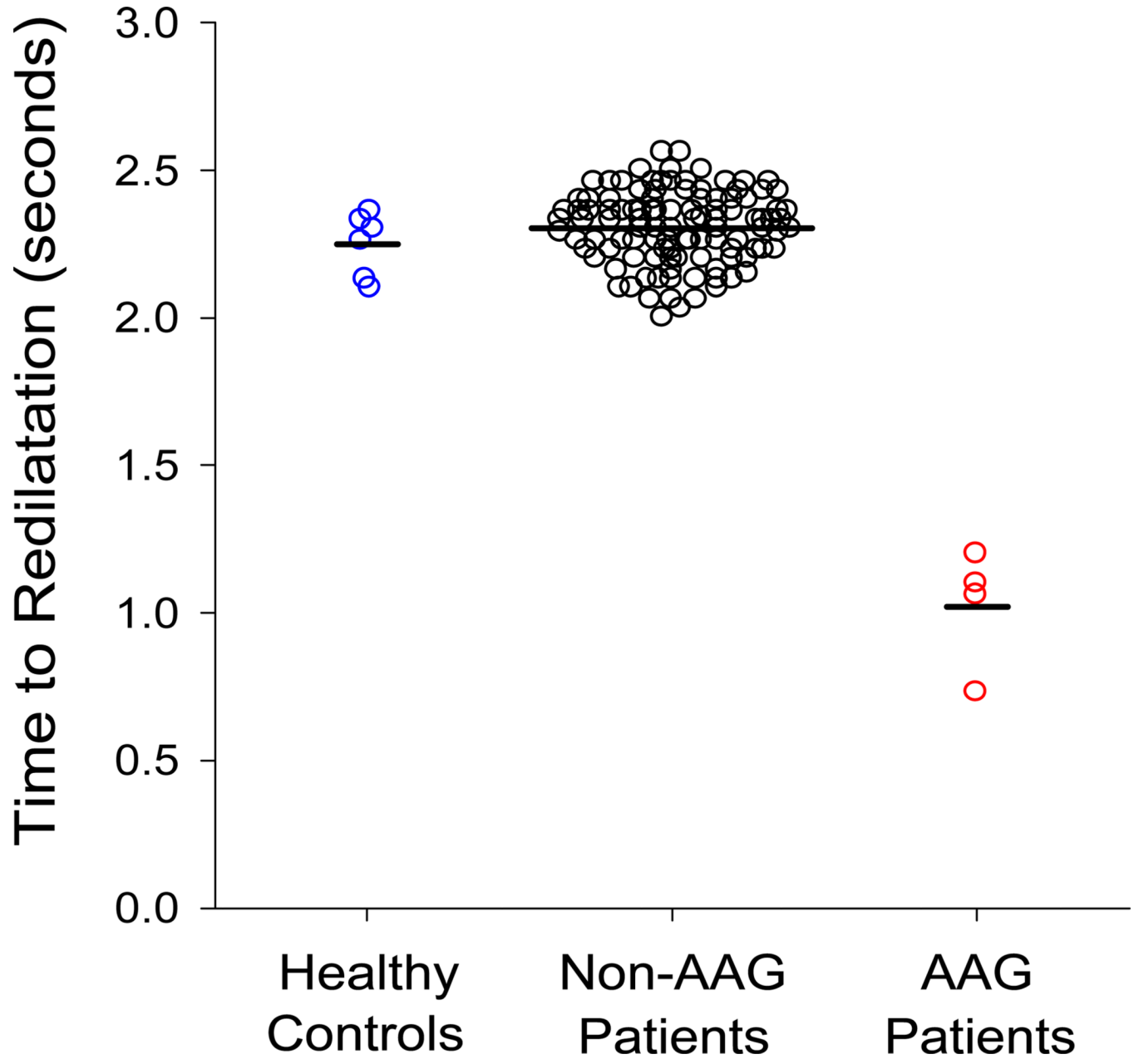

Figure 3.
One way ANOVA testing with binocular pupillometry between the 3 groups revealed that the mean time to redilation in the AAG group was significantly lower than other groups (P<0.0001). The horizontal line represents the mean for each group. Y- Axis represents the time to redilation. Only the 4 AAG patients who had the binocular had binocular pupillometry were included in this analysis.

Table 1

Demographic data and severity of autonomic dysfunction in seven AAG patients

Patient number	Age/Sex	Duration of AAG (in years)	gnAChR Ab (nmol/L)	GI involvement (Yes or No)	HRDB range (bpm)	QSART (Normal or Abnormal)	BP Supine	BP 3 min Head up Tilt	CASS
1	37/M	3	0.50	No	6.0	N/A *	131/82	73/43	5/7 *
2	54/M	1	1.10	Yes	2.1	Abnormal	128/70	85/50	9/10
3	63/M	1.5	0.80	Yes	1.1	Abnormal	121/66	65/36	10/10
4	57/M	2	4.08	Yes	2.3	Abnormal	130/72	78/43	10/10
5	53/F	6	2.30	Yes	2.1	Abnormal	142/86	64/40	10/10
6	54/F	5	5.70	Yes	1.8	Abnormal	142/92	64/42	10/10
7	38/F	4	7.10	Yes	1.1	Abnormal	152/82	60/38	10/10

gnAChR, Ganglionic acetylcholine receptor antibody (normal < 0.05 nmol/L). GI involvement refers to gastrointestinal symptoms of either constipation, vomiting or early satiety. HRDB range, Heart Rate Deep Breathing range (a measure of parasympathetic vagal baroreflex function, normal >10 bpm). QSART, Quantitative Sudomotor Axon Reflex Testing. CASS, Composite Autonomic Severity Score. CASS [8] of 10 indicates severe autonomic failure and 0 is normal.

* QSART was not completed and this was not included in CASS analysis.

Table 2

Pupillometry data in seven patients with AAG.

AAG Patient #	Eye	Baseline dark adapted pupil diameter (in mm)	Maximum Constriction Velocity (mm/sec)	Relative constriction amplitude (%)	Time to Redilation (sec)
1	L	6.3	4.15	65.8	2.53
	R	4.96	1.55	14.4	1.00
2	L	5.52	4.65	37.5	1.16
	R	4.5	4.11	36.1	0.86
3	L	4.06	3.38	42.7	1.75
	R	4.38	4.62	45.2	1.56
4	L	4.93	3.26	36.8	1.03
	R	5.11	3.31	35.6	1.10
Normal Binocular (Mean/Range)	Both	5.87(4.03 –7.22)	5.26(3.78 –7.03)	53.2(49 –60.6)	2.26(2.1–2.4)
5	L	5.14	1.68	18.1	1.39
6	R	6.21	4.12	25.2	0.90
7	R	6.16	3.29	19.3	0.82
Normal Monocular (Mean/Range)	L or R	6.63(4.94 –7.78)	5.07(3.37 –6.32)	44.48(33.3 –55.3)	2.36(1.99 –2.8)

Patients 1 to 4 were tested with a binocular pupillometer and patients 5–7 were tested with a monocular pupillometer. Normative data was obtained from healthy controls. Maximum constriction velocity was calculated from the steepest part of the downslope during the pupillary constriction. Relative constriction amplitude is the ratio of change in pupillary diameter and baseline pupil diameter. Note that the left eye of patient 1 did not reveal any abnormalities, but all others tested were abnormal.