

A Unique Manifestation of Pupillary Fatigue in Autoimmune Autonomic Ganglionopathy

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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 2 university hospitals (University of Texas Southwestern Medical Center and Beth Israel Deaconess Medical Center).

Participants: Seven patients with antibody-positive AAG.

Interventions: 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 with those from healthy control subjects 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 Measures: The time to onset of redilation as well as other indices of pupillary constriction to light stimulus.

Results: Patients with AAG exhibited premature pupillary redilation (mean [SD], 1.02 [0.20] seconds) compared with healthy control subjects (mean [SD], 2.24 [0.10] seconds) and other patients with autonomic disorders (mean [SD], 2.30 [0.12] seconds) ($P < .001$). In healthy control subjects and patients with other autonomic disorders, pupillary redilation always followed the termination of the light stimulus; in patients with AAG, redilation consistently occurred during the light stimulus. In 1 patient, serial repetitive light stimulation further decreased the time to onset of redilation.

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

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PATIENTS WITH AUTOIMMUNE autonomic ganglionopathy (AAG), a disorder characterized by the presence of antibodies against the nicotinic acetylcholine receptor of the autonomic ganglia, have symptoms of diffuse autonomic failure. Autoimmune autonomic ganglionopathy is pathophysiologically similar to myasthenia gravis because both disorders are caused by antibodies 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 tract dysmotility, anhidrosis, bladder dysfunction, and sicca complex.¹ Impaired pupillary light reflexes are often seen in pa-

tients with AAG² 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 because AAG is a potentially reversible disorder that responds to immunotherapy.³

Fixed, dilated pupils found during clinical examination can indicate pupillary involvement. However, milder deficits of pu-

Table 1. Demographic Data and Severity of Autonomic Dysfunction in 7 Patients With Autoimmune Autonomic Ganglionopathy

Patient No./ Sex/Age, y	Duration of AAG, y	gnAChR Ab, nmol/L ^a	Gastrointestinal Tract Involvement ^b	HRDB Range, Beats/min ^c	QSART Results	Systolic/Diastolic BP, mm Hg		CASS ^d
						Supine	3-min Head-up Tilt	
1/M/37	3	0.50	No	6.0	NA ^e	131/82	73/43	5/7 ^e
2/M/54	1	1.10	Yes	2.1	Abnormal	128/70	85/50	9/10
3/M/63	1.5	0.80	Yes	1.1	Abnormal	121/66	65/36	10/10
4/M/57	2	4.08	Yes	2.3	Abnormal	130/72	78/43	10/10
5/F/53	6	2.30	Yes	2.1	Abnormal	142/86	64/40	10/10
6/F/54	5	5.70	Yes	1.8	Abnormal	142/92	64/42	10/10
7/F/38	4	7.10	Yes	1.1	Abnormal	152/82	60/38	10/10

Abbreviations: AAG, autoimmune autonomic ganglionopathy; Ab, antibody; BP, blood pressure; CASS, Composite Autonomic Severity Score; gnAChR, ganglionic acetylcholine receptor; HRDB, heart rate deep breathing; NA, not applicable; QSART, Quantitative Sudomotor Axon Reflex Test.

^aReference range is 0 to 0.05 nmol/L.

^bGastrointestinal tract involvement refers to symptoms of constipation, vomiting, or early satiety.

^cThe HRDB range is a measure of parasympathetic vagal baroreflex function (reference range, >10 beats/min).

^dA CASS of 10 indicates severe autonomic failure; 0, normal. The data are expressed as patient's score/maximum possible score.

^eThe QSART was not completed and was not included in the CASS analysis.

pillomotor function may be difficult to detect on routine clinical examination. Additionally, pupillomotor dysfunction in AAG may be difficult to distinguish from impaired pupillary reflexes because of an intracranial pathologic disease process, 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 in rabbits, a unique pupillary abnormality suggestive of pupillary fatigue was seen.⁵ Our study was performed to determine whether pupillary fatigue can be detected in patients with antibody-positive AAG using dynamic pupillometry.

METHODS

SUBJECTS

We identified 7 patients with AAG at our 2 centers at the University of Texas Southwestern Medical Center and Beth Israel Deaconess Medical Center (**Table 1**). All of the patients provided informed consent for this research study and were evaluated with a standard battery of autonomic tests. Autonomic testing included the Quantitative Sudomotor Axon Reflex Test, heart rate variability assessment during deep breathing and the Valsalva maneuver, and continuous blood pressure recording during the Valsalva maneuver 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 the presence of serum ganglionic acetylcholine receptor antibodies. All patients were receiving immunomodulatory and symptomatic treatment at the time of the pupillometry study. No patients with AAG were taking medications that could interfere with cholinergic function. Acetylcholinesterase inhibitor therapy was discontinued for at least 12 hours prior to testing. No patients with AAG reported any known ocular disease apart from correctable refractive error.

Pupillometry was performed with 6 healthy control subjects to define the optimal testing parameters. Between July 2010 and June 2011, 110 consecutive patients who had been re-

ferred for autonomic evaluation underwent infrared pupillometry. The institutional review boards 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) 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 1 or both eyes using a circumferential array of white light-emitting diodes. We used a 28- μ W light intensity and 2-second stimulus for binocular testing at University of Texas Southwestern Medical Center and a 50- μ W light intensity and 2-second stimulus for the monocular testing at Beth Israel Deaconess Medical Center. The healthy control subjects were tested with identical monocular and binocular stimulation protocols. Patients without AAG who were referred to us for autonomic testing underwent binocular pupillometry testing using the same protocol. Raw dynamic pupil diameter data were 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 that 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 subjects who did not have AAG.

STATISTICAL ANALYSIS

Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc). Results were compared by 1-way analysis of variance, with significance set at $P < .05$.

RESULTS

By inclusion criteria, all patients with AAG had severe diffuse autonomic dysfunction and serological evidence of ganglionic acetylcholine receptor antibody. Table 1 sum-

Table 2. Pupillometry Data in 7 Patients with Autoimmune Autonomic Ganglionopathy^a

Patient No.	Eye	Baseline Dark Adapted Pupil Diameter, mm	Maximum Constriction Velocity, mm/s ^b	Relative Constriction Amplitude, % ^c	Time to Redilation, s
Binocular					
1	Left	6.30	4.15	65.8	2.53
	Right	4.96	1.55	14.4	1.00
2	Left	5.52	4.65	37.5	1.16
	Right	4.50	4.11	36.1	0.86
3	Left	4.06	3.38	42.7	1.75
	Right	4.38	4.62	45.2	1.56
4	Left	4.93	3.26	36.8	1.03
	Right	5.11	3.31	35.6	1.10
Healthy control subjects, mean (range)		5.87 (4.03-7.22)	5.26 (3.78-7.03)	53.2 (49.0-60.6)	2.26 (2.10-2.40)
Monocular					
5	Left	5.14	1.68	18.1	1.39
6	Right	6.21	4.12	25.2	0.90
7	Right	6.16	3.29	19.3	0.82
Healthy control subjects, mean (range)		6.63 (4.94-7.78)	5.07 (3.37-6.32)	44.5 (33.3-55.3)	2.36 (1.99-2.80)

^aThe left eye of patient 1 did not reveal any abnormalities, but all others tested were abnormal.

^bCalculated from the steepest part of the downslope during the pupillary constriction.

^cRatio of change in pupillary diameter and baseline pupil diameter.

marizes the demographic and clinical data including the duration of AAG. Pupillometry data from the 7 patients with AAG are summarized in **Table 2**. Patients 1 through 4 were tested with binocular pupillometry, and patients 5 through 7 were tested using monocular pupillometry. Normal data were obtained from healthy control subjects for each technique. The baseline dark-adapted pupillary diameter was within normal range in patients with AAG. The pupillary constriction parameters, particularly relative constriction amplitude, were decreased compared with those of control subjects ($P = .03$). More importantly, the time to redilation was less than 2 seconds (with 2-second light stimulus) in all patients with AAG 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.⁷ **Figure 1** is a composite image of pupillometric waveforms from the 7 patients with AAG and healthy control subjects.

One patient with AAG (patient 2) also underwent testing of the pupil light reflex using 2-second 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 control subjects and 110 consecutive patients with other autonomic disorders. Healthy control subjects and patients with non-AAG autonomic disorders were tested with the same 2-second binocular pupillary light stimulation as the 4 patients with AAG at University of Texas Southwestern Medical Center. The mean (SD) time to redilation was 2.24 (0.10) seconds in healthy control subjects, 2.30 (0.12) seconds in patients with autonomic diseases other than AAG, and 1.02 (0.2) seconds in patients with AAG ($P < .001$, **Figure 3**). Only patients with AAG showed premature redilation of the pupil, with redilation in less than 2 seconds.

COMMENT

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

Pupillary abnormalities in antibody-positive AAG are well known, but to our knowledge 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 patients with AAG from healthy control subjects. The normal pupil size in AAG is likely a consequence of concomitant sympathetic and parasympathetic impairment. Although significant parasympathetic failure is noted in patients with AAG, similar parasympathetic dysfunction is seen in other autonomic disorders such as diabetes mellitus.⁸ Therefore, dark-adapted pupillary diameter and pupillary constriction measures (eg, maximum constriction velocity and relative constriction amplitude) are not conclusive in differentiating patients with AAG from those with other autonomic disorders.

We used 2 different pupillometry techniques (binocular and monocular) in patients with AAG. It would have been ideal to perform both techniques in all patients with AAG; however, the monocular and binocular techniques in healthy control subjects provided similar results. Our group of patients without AAG

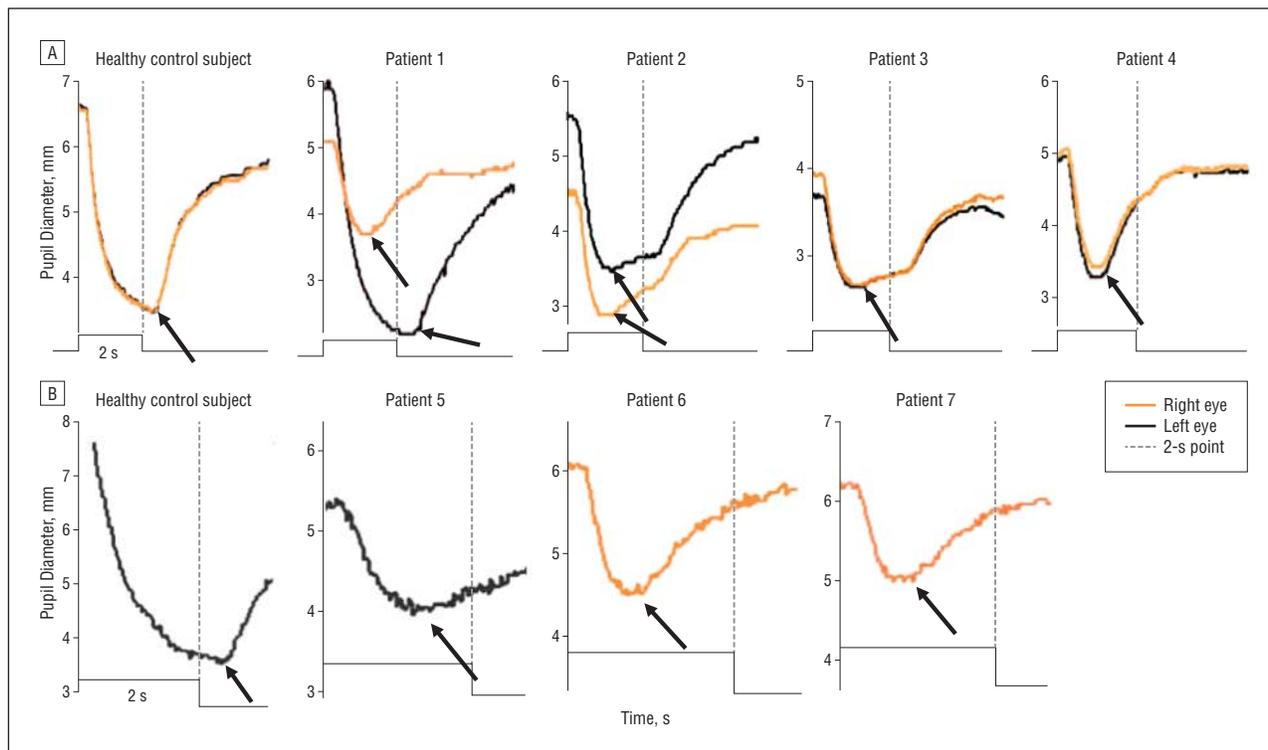


Figure 1. A composite image of binocular (A) and monocular (B) pupillometry in healthy control subjects and patients with autoimmune autonomic ganglionopathy (AAG). Arrows indicate the time of onset of redilation that follows the cessation of the light stimulus in healthy control subjects. Note that patient 1 had an unaffected left eye and the onset of redilation was after the end of the 2-second light stimulus. In all patients with AAG, there was at least 1 eye with premature pupillary redilation. All light stimuli were of 2-second duration.

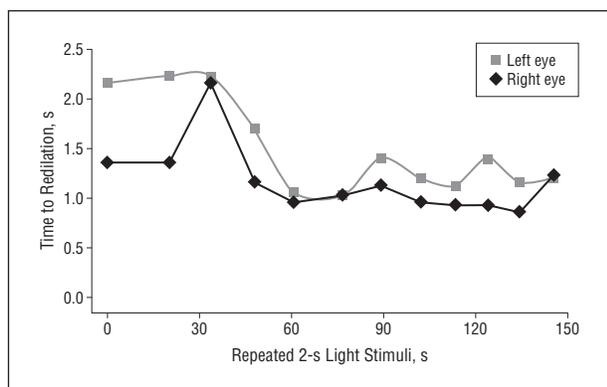


Figure 2. Time to redilation with repeated light stimulation. Each point refers to data from 1 light stimulus. Note that the time to onset of redilation gradually decreased.

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 because similar findings were not seen in any of the patients without AAG, even those who had evidence of pupil dysfunction.

This brief article 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 noninvasive and relatively

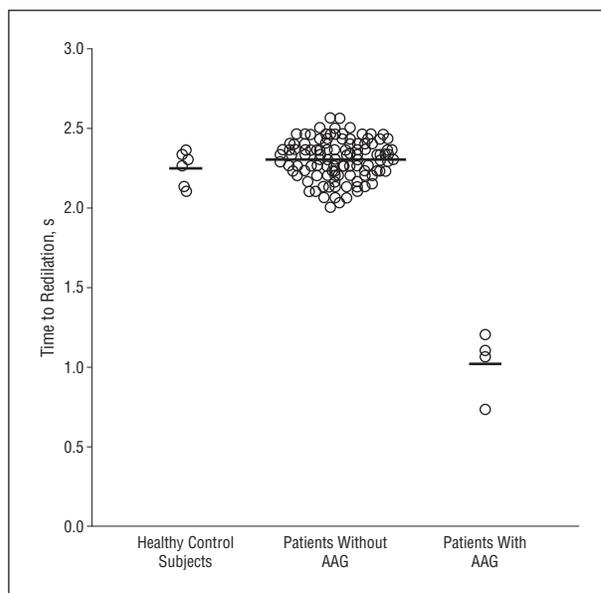


Figure 3. One-way analysis of variance testing with binocular pupillometry among the 3 groups revealed that the mean time to redilation (horizontal line) in the group with autoimmune autonomic ganglionopathy (AAG) was significantly lower than that in the other groups ($P < .001$). Only the 4 patients with AAG who underwent binocular pupillometry were included in this analysis.

easy to perform, this technique offers a new diagnostic testing method to distinguish patients with AAG from all others with autonomic dysfunction. Further studies are needed to investigate whether the severity of pupil-

lary fatigue correlates with antibody titers or disease severity or is responsive to short- or long-term immunomodulatory treatment. We plan to pursue similar studies in patients with antibody-negative AAG in the future because this could potentially help differentiate antibody-negative AAG from other chronic progressive autonomic disorders.

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REFERENCES

1. 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.
2. 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.
3. 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.
4. Bremner F. Pupil evaluation as a test for autonomic disorders. *Clin Auton Res.* 2009;19(2):88-101.
5. Mukherjee S, Vernino S. Dysfunction of the pupillary light reflex in experimental autoimmune autonomic ganglionopathy. *Auton Neurosci.* 2007;137(1-2):19-26.
6. Lowenstein O, Loewenfeld IE. Influence of retinal adaptation upon the pupillary reflex to light in normal man, part I: effect of adaptation to bright light on the pupillary threshold. *Am J Ophthalmol.* 1959;48(5, pt 2):536-550.
7. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. *Mayo Clin Proc.* 1993;68(8):748-752.
8. Ferrari GL, Marques JL, Gandhi RA, et al. Using dynamic pupillometry as a simple screening tool to detect autonomic neuropathy in patients with diabetes: a pilot study. *Biomed Eng Online.* 2010;9:26.