Parkinsonism and Related Disorders 65 (2019) 234–237

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Short communication

Pupillary dysfunction of multiple system atrophy: Dynamic pupillometric findings and clinical correlations

Kye Won Park[a], Nari Choi[a], Ho-Sung Ryu[b], Mi Sun Kim[a], Eun-Jae Lee[a], Sun Ju Chung[a,*]

[a] Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, 05505, South Korea
[b] Department of Neurology, Kyungpook National University School of Medicine, Daegu, 41404, South Korea

ARTICLE INFO

Keywords:
Multiple system atrophy
Dynamic pupillometry
Autonomic dysfunction

ABSTRACT

Introduction: Although autonomic dysfunction is the prominent clinical feature in multiple system atrophy (MSA), little is known about the pupillary autonomic aspect of MSA. We aimed to evaluate pupillary autonomic function in MSA patients using dynamic pupillometry, which can quantify the pupillary light reflex.
Methods: Dynamic pupillometry parameters were compared in 21 MSA patients and 21 healthy controls. Pupillometric parameters were correlated with total Unified Multiple System Atrophy Rating Scale (UMSARS) scores and autonomic symptom severity.
Results: Average constriction ($p = 0.034$) and dilation ($p = 0.003$) velocities were significantly slowed in MSA patients compared with controls. Total UMSARS correlated with the average constriction ($r = -0.527$, $p = 0.017$) and maximum constriction ($r = -0.658$, $p = 0.003$) velocities. Autonomic symptom severity correlated with average constriction ($r = -0.544$, $p = 0.013$), maximum constriction ($r = -0.607$, $p = 0.005$) and average dilation ($r = -0.499$, $p = 0.025$) velocities.
Conclusion: Dynamic pupillometry may provide useful information about pupillary autonomic dysfunction, which correlated with the clinical severity, in patients with MSA.

1. Introduction

Multiple system atrophy (MSA) is a debilitating neurodegenerative disorder with combined features of parkinsonism, cerebellar ataxia and autonomic dysfunction. Prominent autonomic dysfunction is a distinctive feature of MSA, reflecting the extensive neuronal loss and accumulation of pathologic α-synuclein proteins in the central and peripheral autonomic networks [1,2].

The pupillary light reflex (PLR) is the reflex that controls the diameter of the pupil in response to light through the modulation of the autonomic nervous system. When the light hits the retina, the sphincter iris muscle constricts and the pupillary diameter decreases. This process is under the control of the parasympathetic Edinger-Westphal (EW) nucleus and the ciliary ganglion. When the light goes away, the sympathetic nervous system activates the dilator iris muscle. PLR parameters can therefore indicate sympathetic or parasympathetic modulation [3,4]. These parameters can be digitally evaluated and quantified by dynamic pupillometry. Abnormal pupillary dynamics have been observed in patients with a wide range of central and peripheral dysautonomic syndromes, including Parkinson's disease (PD) and other neurodegenerative diseases [3,5].

Although several autonomic systems (e.g., the cardiovascular, urogenital, sudomotor, and gastrointestinal systems) are dysfunctional in patients with MSA, less is known about the pupillary aspect of MSA. Few studies to date have evaluated the PLR in patients with MSA, with most of these studies assessing the static features of MSA pupils [6,7].

The present study therefore evaluated differences in dynamic pupillometric parameters between MSA patients and age-matched controls assessing the correlations between pupillometric parameters and the overall and autonomic severity of MSA.

2. Methods

2.1. Subjects

This study included 21 probable MSA patients according to consensus criteria (12 MSA-cerebellar type and 9 MSA-parkinsonian type) [1] who visited Asan Medical Center between March 2017 to July 2018

* Corresponding author. Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, 05505, South Korea.
E-mail addresses: karabach88@gmail.com (K.W. Park), xcarpediemx86@gmail.com (N. Choi), ryuhosung138@gmail.com (H.-S. Ryu), caums@amc.seoul.kr (M.S. Kim), eunjae.lee@amc.seoul.kr (E.-J. Lee), sjchung@amc.seoul.kr (S.J. Chung).

https://doi.org/10.1016/j.parkreldis.2019.05.003
Received 2 January 2019; Received in revised form 26 April 2019; Accepted 1 May 2019

and 21 healthy controls. Patients with medical conditions associated with possible disturbance in autonomic systems (e.g., diabetes mellitus, history of stroke, and vasculitis), those with a history of ocular disease (e.g., glaucoma, severe cataract, and macular degeneration), and subjects on medications that have anti-adrenergic effects (e.g., prazosin, tamsulosin, propranolol, labetalol) or anti-cholinergic effects (e.g., amantadine, diphenhydramine, trihexyphenidyl) were excluded. The severity of MSA was evaluated using the Unified Multiple System Atrophy Rating Scale (UMSARS), with autonomic symptom severity defined as the sum of scores on questions about autonomic symptoms (Part I, items 9–12). Unless patients were unable to stand due to severe motor symptoms, changes in orthostatic blood pressure (BP) between a recumbent position and after standing for 3 min were measured. Healthy controls were age-matched (within 5 years difference from the patient's age) healthy caregivers of the patients who agreed on dynamic pupillometry. Same exclusion criteria of the patients were applied to the healthy controls.

2.2. Dynamic pupillometry

Dynamic pupillometry was performed with a FDA-approved handheld pupillometer NPi-100 (Neuroptics Inc.), which emits a 0.8 s burst of light of 1000 lux and captures pupillary changes at approximately 30 frames per second for 3.2 s [8]. A single eye of each subject was evaluated in a darkened room of illuminance less than 3 lux. After at least 3 min of dark adaptation, patients were asked to look straight, 2 m behind the examiner, with the other eye. Measured pupillometric parameters included 1) the initial resting pupil size (Max), 2) pupil size at peak constriction (Min), 3) percent change in pupil size during constriction (CON), 4) the latency between initiation of light stimulation and onset of pupillary constriction (LAT), 5) average constriction velocity (ACV), 6) maximum constriction velocity (MCV), and 7) average dilation velocity (ADV). The scheme of PLR testing and the parameters measured are depicted in Fig. 1A. Response latency and pupillary constrictions following a light stimulus are under the control of sphincter iris muscle via parasympathetic nervous system. CON and constriction velocities (ACV and MCV) are considered the most robust parameters for parasympathetic pupillary function [3]. Dilation of pupil results from the action of dilator iris muscle via sympathetic innervation. Thus, ADV is the most representative parameter for sympathetic pupillary function [3].

2.3. Statistical analysis

Continuous demographic and pupillometric parameters were compared in MSA patients and controls with Student's t-tests, and categorical parameters with chi-square test. Pearson's partial correlation analysis, with age as a covariate, was performed between pupillometric parameters and disease duration, orthostatic BP change, total UMSARS score, and the sum of UMSARS part I items 9–12. All statistical analyses were performed with IBM SPSS Statistics 21.0 software, with P values < 0.05 considered statistically significant. The study protocol was approved by the Institutional Review Board of Asan Medical Center, and all participants provided written informed consent.

3. Results

3.1. Pupillometric parameters of MSA patients and controls

Both ACV (2.65 ± 0.59 mm/s (MSA patients) vs. 2.99 ± 0.40 mm/s (controls), $p = 0.034$) and ADV (1.09 ± 0.19 mm/s (MSA patients) vs. 1.27 ± 0.16 mm/s (controls), $p = 0.003$) were significantly lower in MSA patients than in controls. Although Max, Min, and MCV were lower in the MSA than in the control group, these differences were not statistically significant (Table 1). There was no significant difference in the parameters between MSA-cerebellar type (MSA-C) and MSA-parkinsonian type (MSA-P).

3.2. Correlation between pupillometric parameters and UMSARS scores

Partial correlation analysis between pupillometric parameters and total UMSARS scores showed a significant correlation between higher total UMSARS score and the slowing of ACV ($r = -0.53$, $p = 0.017$) and MCV ($r = -0.63$, $p = 0.003$) (Fig. 1B). Other indices of pupillometric parameters, including ADV ($r = -0.42$, $p = 0.068$), did not correlate with UMSARS scores. Assessments of autonomic symptom severity showed significant negative correlations between the total score of UMSARS part I items 9–12 and ACV ($r = -0.54$, $p = 0.013$), MCV ($r = -0.61$ $p = 0.005$), and ADV ($r = -0.50$, $p = 0.025$) (Fig. 1B, Supplementary Table 1). Disease duration of MSA had correlation with ACV ($r = -0.468$, $p = 0.037$) and MCV ($r = -0.503$, $p = 0.024$), but there was no correlation between pupillometric parameters and the magnitude of orthostatic blood pressure change (Supplementary Table 2).

4. Discussion

The present study showed that the ACV and ADV of the PLR are significantly slower in MSA patients than in healthy controls, suggesting that both parasympathetic and sympathetic pupillary functions are altered in MSA patients. Furthermore, the sum of UMSARS part I items 9–12, representing the severity of autonomic symptoms, was significantly correlated with the slowing of ACV, MCV, and ADV. Total UMSARS score also showed a negative correlation with ACV and MCV. These findings suggest that the differences in PLR between the two groups may correlate with the overall and autonomic symptom severity in patients with MSA.

Although dysautonomia is a hallmark of MSA, few reports have evaluated pupillary autonomic functions in patients with MSA, with most of these studies assessing pupillary profiles [6,7]. Sympathetic pupillary dysfunction and Horner syndrome are more frequent in patients with MSA, with pupil size in response to light being reduced in MSA patients compared with healthy controls [9]. The neuropathology of MSA includes substantial involvement of the central sympathetic network, which is shared by the efferent pathway of pupillary dilation, including the hypothalamus, the intermediolateral cell column of the thoracolumbar spinal cord, and the cervical sympathetic ganglia [2]. The slower ADV in our MSA patients indicates the pathologic burden of these sympathetic structures. By contrast, it is unclear whether structures of the parasympathetic pupillary pathway, such as the EW nucleus and ciliary ganglia, are pathologically involved in MSA [2,7]. These structures, in the presence of Lewy bodies, are involved in PD [10]. However, assessment of pupillary autonomic function using pharmacologic eye-drop tests showed equal parasympathetic supersensitivity in patients with MSA and PD relative to healthy controls [7]. In addition, alterations in the parasympathetic pupillary system, as shown by slower constriction velocities, have been observed in patients with Alzheimer's disease and PD with cognitive impairment [11]. The global cholinergic deficits in these diseases resulted in slower pupillary constriction. The slow ACV in our MSA patients suggests that cholinergic parasympathetic function is also altered in pupils of patients with MSA.

We observed that the sum of scores on UMSARS part I items 9–12, indicative of autonomic symptom severity, showed significant negative correlations with both parasympathetic (ACV, MCV) and sympathetic (ADV) markers of dynamic pupillometry. ACV and MCV were also correlated with total UMSARS score. Other investigators have observed that these pupillometric indices reflect severity of global autonomic severity in various dysautonomic syndromes, including PD [3]. Our results provide further evidence that these pupillometric parameters reflect the overall and autonomic symptom severity of MSA. However, it is unclear whether the magnitude of change in PLR, a marker of progression of acute brain injury, can also serve as a marker of

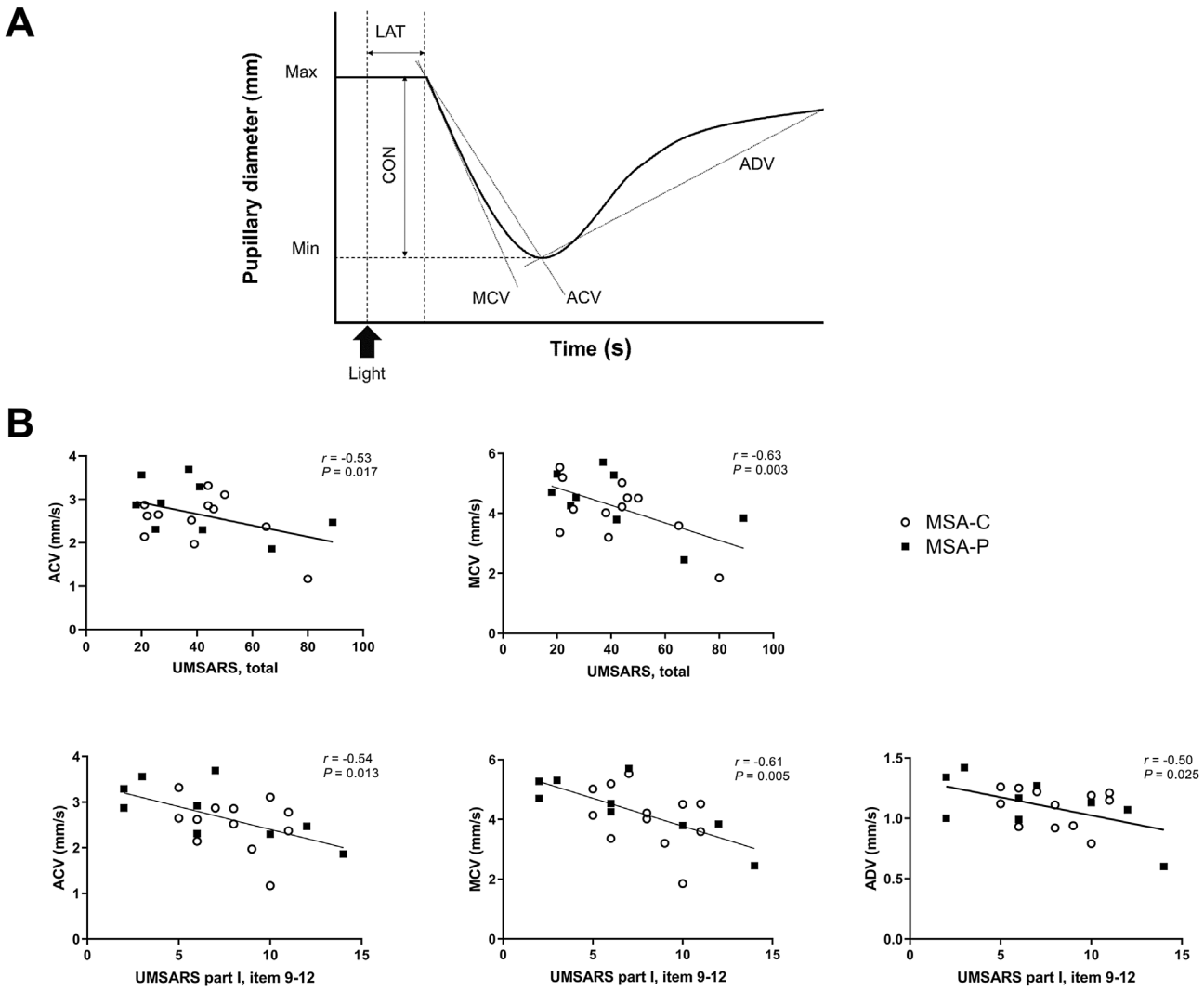

Fig. 1. Schematic diagram of the pupillary light reflex in dynamic pupillometry (A) and scatterplots of the relationships between pupillary parameters with total Unified Multiple System Atrophy Rating Scale (UMSARS, total) and the sum of UMSARS part I items 9–12 (B).

progression in neurodegenerative diseases. Research is also needed to evaluate the effect of profound retinal thinning in MSA on PLR [12].

To our knowledge, this is the first study to demonstrate the dynamics of PLR in patients with MSA. However, this study had several limitations. First, there were some technical limits regarding the environmental control of the dynamic pupillometry procedure. Although we controlled illumination intensity and dark adaptation time, the procedures were performed in different rooms, depending on whether inpatients or outpatients were being evaluated. Furthermore, PLR is affected by various environmental factors that are difficult to control, such as emotional status and previous night's sleep, resulting in substantial intra-individual variations. This limitation may be overcome by including larger numbers of subjects. Second, although majority of the MSA patients underwent pupillometry in sitting position, some patients who are not able to maintain sitting position for the dark adaptation had to be measured in supine position. As body position effects the autonomic status, it might also influence the pupillary reaction. Additionally, autonomic symptom severity was represented by scores on items in the UMSARS questionnaire rather than a more comprehensive and objective autonomic measure, such as Composite Autonomic Severity Scores (CASS).

In conclusion, pupillary constriction and dilation are slower in patients with MSA than in healthy controls, suggesting that sympathetic and parasympathetic pupillary functions are altered in MSA. The degree of slowing may reflect the severity of the disease, especially in the autonomic aspect. Further investigations on pupillary dysfunction in MSA should include a larger number of subjects, strict environmental control, and comprehensive autonomic scales.

Authors' roles

1. Research project: A. Conception and design of the study, B. Acquisition of data, C. Analysis and interpretation of data, 2. Manuscript preparation: A. Drafting the article, B. Revising it critically for important intellectual content, 3. Final approval of the manuscript.

K.W.P.: 1A, 1B, 1C, 2A, 2B, 3.
N.C.: 2B, 3.
H.S.R.: 2B, 3.
M.S.K.:2B, 3.
E.J.L.: 1C, 2B, 3.
S.J.C.: 1A, 2B, 3.
All authors approved the final version of the manuscript.

Declarations of interest

None.

Table 1
Comparison of the clinical characteristics and pupillometric parameters in MSA patients and healthy controls.

Clinical characteristics	MSA (n = 21)	Controls (n = 21)	*p*
Age at examination, years	63.0 ± 7.4	61.1 ± 6.8	0.392
Age of onset, years	60.0 ± 7.6	–	–
Female, n (%)	10 (48%)	15 (71%)	0.208
Cerebellar type, n (%)	12 (57%)	–	–
Disease duration, years	3.0 ± 1.9	–	–
UMSARS, total	41.0 ± 20.0	–	–
UMSARS, part I	20.4 ± 10.8		
UMSARS, part II	20.7 ± 9.9		
UMSARS, part I items 9–12	7.5 ± 3.2	–	–
Change in orthostatic blood pressure, mmHg	37.1 ± 20.8	–	–
Pupillometric parameters			
Max, mm	5.11 ± 1.07	5.60 ± 0.73	0.086
Min, mm	3.36 ± 0.88	3.56 ± 0.49	0.386
CON, %	34.6 ± 7.4	36.9 ± 3.7	0.360
LAT, s	0.25 ± 0.03	0.25 ± 0.04	0.857
ACV, mm/s	2.65 ± 0.59	2.99 ± 0.40	0.034
MCV, mm/s	4.24 ± 0.99	4.58 ± 0.66	0.186
ADV, mm/s	1.09 ± 0.19	1.27 ± 0.16	0.003

Data are shown as mean ± standard deviation or n (%).
UMSARS, Unified Multiple System Atrophy Rating Scale; Max, initial resting pupil size; Min, pupil size at peak constriction; CON, percentage of pupil size change during constriction; LAT, latency between light stimulation and onset of pupillary constriction; ACV, average constriction velocity; MCV, maximum constriction velocity; ADV, average dilation velocity.

Acknowledgments

This study was supported by a grant from the Korea Healthcare Technology R & D Project, Ministry of Health & Welfare, Republic of Korea (HI17C0328).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.05.003.

References

[1] S. Gilman, G.K. Wenning, P.A. Low, D.J. Brooks, C.J. Mathias, J.Q. Trojanowski, N.W. Wood, C. Colosimo, A. Durr, C.J. Fowler, H. Kaufmann, T. Klockgether, A. Lees, W. Poewe, N. Quinn, T. Revesz, D. Robertson, P. Sandroni, K. Seppi, M. Vidailhet, Second consensus statement on the diagnosis of multiple system atrophy, Neurology 71 (2008) 670–676.
[2] E.A. Coon, J.K. Cutsforth-Gregory, E.E. Benarroch, Neuropathology of autonomic dysfunction in synucleinopathies, Mov. Disord. 33 (2018) 349–358.
[3] C.A. Hall, R.P. Chilcott, Eyeing up the future of the pupillary light reflex in neurodiagnostics, Diagnostics 8 (2018).
[4] F. Bremner, Pupil evaluation as a test for autonomic disorders, Clin. Auton. Res. 19 (2009) 88–101.
[5] S. Jain, Multi-organ autonomic dysfunction in Parkinson disease, Park. Relat. Disord. 17 (2011) 77–83.
[6] F. Bremner, S. Smith, Pupil findings in a consecutive series of 150 patients with generalised autonomic neuropathy, J. Neurol. Neurosurg. Psychiatry 77 (2006) 1163–1168.
[7] F. Yamashita, M. Hirayama, T. Nakamura, M. Takamori, N. Hori, K. Uchida, T. Hama, G. Sobue, Pupillary autonomic dysfunction in multiple system atrophy and Parkinson's disease: an assessment by eye-drop tests, Clin. Auton. Res. 20 (2010) 191–197.
[8] M.H. Lee, B. Mitra, J.K. Pui, M. Fitzgerald, The use and uptake of pupillometers in the Intensive Care Unit, Aust. Crit. Care 31 (2018) 199–203.
[9] M. Kuroda, H. Fukura, N. Saruki, D. Yoshikawa, T. Morita, F. Goto, Vecuronium dose requirement and pupillary response in a patient with olivopontocerebellar atrophy (OPCA), Can. J. Anaesth. 45 (1998) 979–984.
[10] L.S. Forno, Neuropathology of Parkinson's disease, J. Neuropathol. Exp. Neurol. 55 (1996) 259–272.
[11] D.F. Fotiou, V. Stergiou, D. Tsiptsios, C. Lithari, M. Nakou, A. Karlovasitou, Cholinergic deficiency in Alzheimer's and Parkinson's disease: evaluation with pupillometry, Int. J. Psychophysiol. 73 (2009) 143–149.
[12] C.E. Mendoza-Santiesteban, I. Gabilondo, J.A. Palma, L. Norcliffe-Kaufmann, H. Kaufmann, The retina in multiple system Atrophy: systematic Review and meta-analysis, Front. Neurol. 8 (2017) 206.