Original Article

International Journal of Neurology and Neurosurgery
Volume 9 Number 1, January - June 2017
DOI: http://dx.doi.org/10.21088/ijnns.0975.0223.9117.1

Variable Onset and Progression in Six Patients of Multiple System Atrophy

Hareshkumar Bharote*, Rahul Chakor, Chetan Chaudhari*****

Abstract

Background: Multiple system atrophy is a sporadic, progressive, neurodegenerative disease of undetermined etiology characterized clinically by extra pyramidal, pyramidal, cerebellar, and autonomic dysfunction in any combination. It is recognized by various names as Shy-Dragger syndrome, Striato-niagral degeneration and sporadic Olivopontocerebellar atrophy depending upon the predominant presentation. *Objective:* To study the variability in initial clinical presentation and progression of patients of multiple system atrophy. *Material and Methods:* Six patients of MSA diagnosed during December 2008 to March 2010 in a tertiary care teaching hospital were analyzed. Bedside autonomic function testing and MRI Brain was done for all these patients. *Results:* Five patients satisfied the criteria for probable MSA, one patient for possible MSA. Four patients were sub categorized as MSA-C and two as MSA-P. All patients had remarkably different modes of presentation and findings at onset. Duration between initial symptoms and combined motor and autonomic dysfunction varied in all of these patients. *Conclusion:* The clinical presentation of MSA is variable even within a particular subtype. Detailed clinical evaluation including Autonomic functions (and close follow-up) is essential for diagnosis.

Keywords: Multiple System Atrophy; Variable Presentation; Autonomic Dysfunction.

Introduction

MSA is defined as a sporadic, progressive, adult onset neurodegenerative disease characterized clinically by heterogeneous combination of extra-pyramidal, pyramidal, cerebellar and autonomic dysfunction [1]. Diagnosis is made as definite, probable and possible MSA as per the second consensus statement for diagnosis of MSA [2]. MSA-P is the Parkinsonian variant of MSA, while MSA-C is the cerebellar variant. Pure Autonomic failure is referred as Shy Dragger syndrome. MSA-P is the commonest variety of MSA in most of the reported studies [3, 4].

Author's Affiliation: *Assistant Professor, **Professor and Head, Dept. of Neurology, ***Super Speciality Medical Officer, Topiwala National Medical College & B.Y.L. Nair Charitable Hospital, Mumbai.

Reprint Request: Hareshkumar Bharote, Assistant Professor, Dept. of Neurology, Topiwala National Medical College & B.Y.L. Nair Charitable Hospital, Opposite Maratha Mandir, Mumbai Central, Mumbai 400008. Maharashtra.
E-mail: bharote@yahoo.com

Received on 13.10.2016, **Accepted on** 28.10.2016

The disease onset is defined by the time of initial manifestation of any motor (parkinsonism or cerebellar dysfunction) or autonomic feature (except for erectile dysfunction), although subclinical neuropathology is likely to start several years before overt disease [5]. Initial clinical presentation and duration for progression to combined motor and autonomic features varies between patients.

MRI Brain in MSA shows "Hot cross bun" sign which is a cruciform-shaped hyperintensity on T2-weighted axial magnetic resonance images (MRI) due to the selective loss of myelinated transverse pontocerebellar fibers and neurons in the pontine raphe and sparing of the pontine tegmentum and corticospinal tracts [6, 7].

Methods

We report a series of six patients of MSA seen at our hospital from December 2008 to March 2010. All patients were evaluated clinically and bed-side autonomic function tests were performed.MRI of brain was done for all patients. The following bedside

autonomic function tests were done 1) Supine and standing (1min and 3 min) blood pressure 2) 30:15 ratio on standing - ratio of RR interval of beat 30 and beat 15 (normal >1.04) 3)Valsalva ratio - ratio of longest RR interval in phase 4 to the shortest RR in phase 2 of valsalva maneuver (normal>1.45) 4) Diastolic BP after sustained handgrip maneuvers 5) Diastolic BP after 1 minute of immersion of hand in ice cold water.

Case Series

Case- 1

50 year old gentleman presented with eight months history of imbalance while walking. Two months later he complained of dragging of right foot and difficulty using right hand. Two months later his speech became strained and harsh. On enquiry, thrashing movements of limbs in sleep were reported by partner since past four months. He had urge incontinence, frequency of urination and erectile dysfunction since five months.

On examination his blood pressure was 126/84 when supine and 116/80 three minutes after standing. The standing 30:15 ratio was 0.98, Valsalva ratio was 1.30. Diastolic BP remained 84mmHg on handgrip maneuvers and ice cold immersion testing. There was spastic dysarthria. MMSE score was 30/30 and frontal assessment battery score was 18/18. Gaze evoked horizontal jerk nystagmus and broken pursuits were evident. There was spasticity in right upper and lower extremity. Reflexes were brisk and bilateral plantar response was extensor. There was evidence of bradykinesia (right>left).

Bilateral cerebellar signs were present. Gait was wide based with dragging of right foot and reduced right arm swing. MRI Brain was consistent with olivoponto cerebellar atrophy with hot cross bun sign on T2W axial images. This patient was categorized as probable MSA-C. Three months later he had progression of imbalance and recurrent falls.

Case- 2

46 year old right handed gentleman came with complaints of impotence, black-outs on standing, increased frequency of micturition and enacting dreams since one and half years. Five months after the onset he had ataxia. On examination his blood pressure was 140/90 when supine and106/72 three min after standing. 30:15 ratio on standing was 0.95. RR ratio on Valsalva maneuver was 1.20.Diastolic BP remained 90mmHg on handgrip maneuvers and ice cold immersion testing.

Higher mental functions, speech, cranial nerves and motor examination was unremarkable. He had significant gait ataxia and swayed on either side while walking. A diagnosis of probable MSA-C was made. MRI brain revealed pontine as well as cerebellar atrophy and a hot cross bun sign on T2W brain images. Patient was given frequent liquids with extra salt in diet and stockings.

Case-3

54 year old gentleman presented with complaints of progressive difficulty in walking, dysarthria and tremors of both hands since eight months. On enquiry he reported urinary frequency, urge incontinence and erectile dysfunction. On examination his blood pressure was 142/90 mm hg when supine and 130/80 mm hg three minutes after standing. The beat 30:15 ratio was 0.96.Valsalva ratio was 1.26. There was no diastolic rise of BP on handgrip maneuvers and ice cold immersion testing. There was executive dysfunction and perseveration with a FAB score of 14/18. MMSE was 27/30. There was bilateral cog-wheel rigidity at wrist with spasticity in lower extremeties, brisk tendon reflexes and bilateral Babinski response. Bilateral dysmetria, dysdiadokinesia and impaired tandem walking was present. MRI Brain was consistent with olivopontocerebellar atrophy. Patient was classified as probable MSA-P. Patient was started on levodopa 100mg/day and increased to 800mg/day without any significant benefit.

Case-4

50 year old lady presented with one and half year history of imbalance, difficulty in speaking and slowness of activities. On examination her blood pressure was 150/90 mm hg when supine and 142/76 mm hg three minutes after standing. The 30:15(tachycardia: bradycardia) ratio was 0.88.Valsalva ratio was 1.18. There was no diastolic rise in BP on handgrip maneuvers and ice cold immersion testing. Her MMSE score was 28/30 and FAB score was 17/18. She had scanning dysarthria and broken horizontal smooth pursuit. Bradykinesia and rigidity was present on the left side. There was no appendicular ataxia but knee-heel shin test was bilaterally impaired. Reflexes were brisk bilaterally with extensor plantar response. Gait was wide based and markedly ataxic. Her MRI Brain showed hot cross bun sign and she was categorized as possible MSA-C.

Case-5

50 year old gentleman presented with four year history of urinary frequency and incontinence. He had postural black-outs and impotence since last one year. His wife reported thrashing movements of limbs in sleep. He had slowness of activity and tremors since last six months. On examination his BP was 102/60 mm hg when supine and 72/44 mm hg three min after standing. The 30:15 ratio was 0.94. Valsalva ratio was 1.28.There was no diastolic rise in BP on handgrip maneuvers and ice cold immersion testing. MMSE was 29/30 and FAB was 18/18.Saccades and pursuit was normal. There was symmetrical bradykinesia and cogwheel rigidity at wrist. Deep tendon reflexes were all exaggerated with bilateral extensor plantar response. Diagnosis of probable MSA-P was considered in view of autonomic and REM sleep disturbance and symmetric parkinsonism. MRI however was normal. Patient was treated with frequent oral fluids and extra salt in diet and stockings along with levodopa.

Case-6

55 year old gentleman presented with urinary frequency, incontinence and black-outs since seven years. One year later he had imbalance while walking which progressed over the next six years. On examination his blood pressure was 110/80mmHg when supine and 70/50 mm hg three minutes after standing. The 30:15 ratio was 0.90. Valsalva ratio was 1.26. There was no diastolic rise in BP on handgrip maneuver and ice cold immersion. MMSE score was 25/30 and FAB score was 10/18. Cranial nerve examination was normal. There was spasticity in all four limbs and all deep reflexes were brisk. The stance was wide based and gait was broad based ataxic. A diagnosis of probable MSA-C was made. MRI Brain showed olivopontocerebellar atrophy with a hot cross bun sign.

Results

Among the six patients of MSA, five patients were males (case 1, 2, 3, 5 and 6) and one patient was female (case 4). Mean age of onset of symptoms was 51.16 years (46-55 years).Mean duration of symptoms before diagnosis was thirty months (range eight months to seven years). Five patients satisfied the clinical criteria for probable MSA (case 1, 2, 3, 5 and 6) and one for possible MSA (case 4).

Four patients were subcategorized as MSA-C (case 1, 2, 4 and 6) and two as MSA-P (case 3 and 5). The demographic, clinical and MRI features are summarized in table1 and 2.

AF – Autonomic functions, OH- Orthostatic hypotension, V- Valsalva, IE- Isometric exercises, CI- Cold immersion, TBR- Tachycardia-bradycardia ratio,

Table 1: Variable clinical features of six patients of MSA

Clinical feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
AF (OH, V, IE, CI, TBR)	OH- A V, IE, CI, TBR- Impaired	Significant OH. V, IE, CI, TBR- Impaired	OH- A V, IE, CI, TBR- Impaired	OH- A V, IE, CI, TBR- Impaired	Significant OH. V, IE, CI, TBR- Impaired	Significant OH. V, IE, CI, TBR- Impaired
Autonomic features at onset	A	P	A	A	P	P
ED	P	P	P	NA	P	P
Age of onset	50	46	54	50	50	55
EP	As right > left	A	Bilateral cogwheeling and postural tremors	As left> right	S bradykinesia and rigidity	NA
Py	As right> left	A	Lower limb spasticity and extensor plantars	S brisk DTR, extensor plantars	S brisk DTR, extensor plantars	S brisk DTR, extensor plantars
C	Predominant gait ataxia	Gait ataxia	Appendicular +gait ataxia	Lower limb dysmetria and wide based gait	None	Lower limb dysmetria and wide based gait
Cog	N	N	Mild Ex D	N		Ex D
Speech	Spastic	Normal	Spastic +ataxic	Scanning	Hypophonic	Scanning
Levodopa response	Minimal	NA	Absent	Minimal	Minimal	NA
Gait	Wide based, hemiparetic, reduced arm swing on right side.	N	Wide based gait.	Wide based with Reduced arm swing on left side	Normal stance and stride. Reduced arm swing(bilateral)	Wide based markedly ataxic.
Sex	Male	Male	Male	Female	Male	Male
RBD	p	P	p	A	P	P
MRI	Pontocerebellar atrophy	Pontocerebellar atrophy	Pontocerebellar atrophy	Pontocerebellar atrophy	Normal	Pontocerebellar atrophy

P- Present, A-Absent, NA-not applicable, EP- extra-pyramidal, C-Cerebellar signs, Py- pyramidal, Cog-Cognitive, ED-Erectile dysfunction. S- Symmetric, As-Asymmetric, DTR- Deep tendon reflexes, N-Normal, Ex D- Executive dysfunction, RBD- REM sleep behavior disorder.

Urinary incontinence was the most common autonomic symptom. On bedside testing orthostatic hypotension was present in three patients (case 2, 5 and 6). Patients (Case 1 and 3) did not have orthostatic hypotension, however they presented with urinary incontinence and erectile dysfunction. Patient 4 did not have autonomic symptoms or orthostatic hypotension.

The Parkinsonian features in MSA – P were symmetrical bradykinesia, rigidity and postural tremors. Predominant pyramidal dysfunction (spasticity, pyramidal weakness and extensor plantar) was seen in case 1 with marked asymmetry. Pyramidal dysfunction was also seen in (Case 3, 4, 5 and 6). Cerebellar signs were present in all patients except case 5. REM sleep behavior disorder was present in all but one (case 4) patient. MRI brain was suggestive of olivopontocerebellar atrophy with 'hot cross bun sign' **(Figure 1)**.

Table 2: Comparison of combinations of systems involved in six patients of MSA

Systems	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Pyramidal	+++ (asymmetric)	-	++ (symmetric)	++(symmetric)	++(symmetric)	++ (symmetric)
Extra-pyramidal	++	-	++	++	+++ (symmetric)	-
Cerebellar	++	++	++	++	-	+++
Autonomic	++	+++	++	++	+++	+++

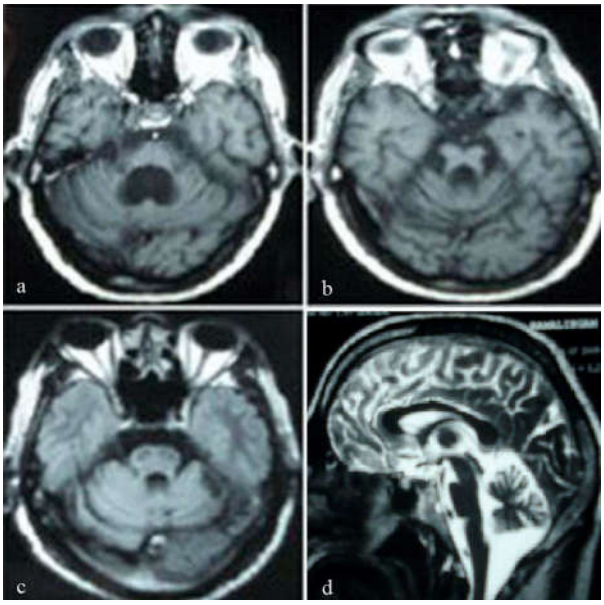

Fig. 1: a. T1 axial image of case 1- Pontocerebellar atrophy. **b.** T2 axial image of case 2 – Hot cross bun sign. **c.** Flair axial image of case 3 – Hot cross bun sign. **d.** Sagittal T2 image of case 6 – Severe pontocerebellar atrophy.

Discussion

MSA is a rare neurodegenerative disorder. In this study of six patients of MSA, we emphasize on variability of presentation. There is variation in initial presenting symptom (either autonomic or motor) among patients of a particular MSA subtype. Variability also occurs in interval from initial symptom to combined motor and autonomic dysfunction. Based on predominant initial motor manifestations patients are categorized either into MSA – C or MSA-P.

MSA-C: Four patients were categorized as MSA-C. Initial ataxia and pyramidal findings were followed three months later by autonomic involvement and extra-pyramidal symptoms in one patient. This patient could have been initially misdiagnosed as cervical myelopathy since he did not have significant ataxia at presentation. Significant autonomic dysfunction at presentation was followed by ataxia five months and one year later respectively in two patients. These patients could have been missed if a detailed bed side autonomic function was not performed. One patient had cerebellar ataxia without significant autonomic involvement until two years of follow-up. This patient could have been initially misdiagnosed as sporadic cerebellar ataxia.

MSA-P: Two patients were classified as MSA-P. One patient presented with dysarthria and postural tremors followed by autonomic and cerebellar features within one month. Second patient had significant orthostatic hypotension followed by Parkinsonism three and a half years later. These patients categorized as MSA-P had remarkably different presentation.

There is no large Indian study defining variability of initial presentation and interval between initial

presentation and development of combined motor and autonomic features in prognosis of patients of multiple system atrophy. However a large Japanese study including 230 patients of MSA concluded that the interval from initial symptom to combined motor and autonomic dysfunction can predict functional deterioration and survival in MSA [8]. In this study patients initially complaining of motor symptoms had accelerated risk of aid-requiring walking ($P < 0.01$) and confinement to a wheelchair ($P < 0.01$) compared with those initially complaining of autonomic symptoms but the time from confinement to bedridden state and survival was the same. However, another study done in 49 Japanese patients concluded that patients with early development of autonomic dysfunction (within 2.5 years of onset) had significantly higher risks of being in wheel-chair bound state, being in bedridden state, having a shorter survival and sudden death [9].

Our study is ongoing and with continued follow-up some definitive conclusions about prognosis can be drawn. The main limitation of our study is small sample size (n=6) and short follow-up. This study paves way for future prognostic studies in patients of MSA.

Conclusion

The clinical presentation of MSA is variable even within a particular subtype hence the diagnosis may be missed initially. Patients should be carefully followed up for autonomic dysfunction and progression.

Key Message

The clinical presentation of MSA is variable hence the diagnosis may be missed. Our case series highlights the importance of bedside autonomic function tests and close follow up in patients with atypical parkinsonian syndrome or isolated cerebellar ataxia for evaluating progression to multiple system atrophy.

References

1. Gilman S, Low P, Quinn N, Albanese A, Ben-Shlomo Y, Fowler C et al. Consensus statement on the diagnosis of multiple system atrophy. American Autonomic society and American Academy of neurology. Clin Auton Re, 1998; 8:359-62.
2. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ. Trojanowski JQ et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology, 2008; 71:670-76.
3. Geser F, Wenning GK, Seppi K, Stampfer-Kountchev M, Scherfler C, Sawires M et al. Progression of multiple system atrophy (MSA): a prospective natural history study by the European MSA Study Group (EMSA SG). Mov Disord, 2006; 21:179–86.
4. May S, Gilman S, Sowell BB, Thomas RG, Stern MB, Colcher A et al. Potential outcome measures and trial design issues for multiple system atrophy. Mov Disord, 2007; 22:2371–77.
5. Stefanova N, Bucke P, Duerr S, Wenning GK. Multiple system atrophy: an update. Lancet neurol, 2009; 8: 1172-78.
6. Gulati A, Virmani V, Singh P, Khandelwal N. The Hot cross bun sign. Neurol India, 2009; 57:104-5.
7. Schrag A, Kingsley D, Phatouros C, Mathias CJ, Lees AJ, Daniel SE, Quinn NP et al. Clinical usefulness of magnetic resonance imaging in multisystem atrophy. J Neurol Neurosurg Psychiatry, 1998; 65:65-71.
8. Watanabe H, Saito Y, Terao S, Ando T, Kachi T, Mukai E et al. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain 2002; 125:1070-83.
9. Tada M, Onodero O, Tada M, Ozawa T, Piao YS, Kakita A et al. Early development of autonomic dysfunction may predict poor prognosis in patients with multiple system atrophy. Arch Neurol 2007; 64:256-60.