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Diagnostic Clues in Multiple System Atrophy: A Case Report and Literature Review

Multisistem Atrofi Tanısında İpuçları: Bir Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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Summary

Multiple system atrophy (MSA) is an adult-onset, sporadic, progressive neurodegenerative disease. Based on the consensus criteria, patients with MSA are clinically classified into cerebellar (MSA-C) and parkinsonian (MSA-P) subtypes. In addition to major diagnostic criteria including poor response to levodopa, and presence of pyramidal or cerebellar signs (ataxia) or autonomic failure, certain clinical features or ''red flags'' may raise the clinical suspicion for MSA. In our case report we present a 67-year-old female patient admitted to our hospital due to inability to walk, with poor response to levodopa therapy, whose neurological examination revealed severe Parkinsonism, ataxia and who fulfilled all criteria for MSA, as rarely seen in clinical practice. *(Turkish Journal of Neurology 2013; 19:28-30)*

Key Words: Multiple system atrophy, autonomic failure, diagnostic criteria

Özet

Multisistem atrofi (MSA) erişkin dönemde başlayan, ilerleyici, nedeni bilinmeyen sporadik nörodejeneratif bir hastalıktır. MSA kabul görmüş tanı kriterlerine göre klinik olarak serebellar (MSA-C) ve parkinsoniyen (MSA-P) alt tiplerine ayrılmaktadır. Düşük levadopa yanıtı, piramidal, serebellar bulguların (ataksi) ya da otonomik bozukluk olması gibi majör tanı kriterlerininin yanında "red flags" olarak isimlendirilen belirgin klinik bulgular ya da uyarı işaretlerinin olması MSA tanısı için klinik şüpheyi oluşturmalıdır. Olgu sunumunda 67 yaşında yürüyememe şikayeti ile polikliniğimize müracaat eden ve levadopa tedavisine düşük yanıt gösteren ciddi parkinsonizm bulguları ile ataksi bulunan kadın hasta MSA tanı kriterlerini tam olarak karşıladığı ve klinik pratikte nadir görüldüğü için sunduk. *(Türk Nöroloji Dergisi 2013; 19:28-30)*

Anahtar Kelimeler: Multisistem atrofi, otonom bozukluk, tanı kriterleri

Introduction

Multiple system atrophy (MSA) is an adult-onset, progressive, idiopathic neurodegenerative disease. Clinical pictures previously known as striatonigral degeneration, olivopontocerebellar atrophy, and Shy-Drager syndrome are now all named as "multiple system atrophy". MSA is one of the Parkinson plus syndromes, with an annual incidence of 0.6/100,000 (1,2). Differential diagnosis from idiopathic Parkinson's disease (PD) can be difficult, due to its rare nature. Main clinical features are autonomous failure, parkinsonism, cerebellar ataxia and pyramidal symptoms. We are presenting this case that fulfils all the rare diagnostic criteria of MSA, to remind the very significant clues in the differential diagnosis of MSA, with a literature review.

Case Report

Sixty-seven year old, right-handed woman presented at our outpatient clinic with complaint of inability to walk. Her history showed that her complaints started two years ago with slowing of walking and tremor at rest in the right hand; although she was diagnosed with Parkinson's disease at that time and dopaminergvic treatment was initiated, she did not benefit from that treatment. Swelling in the feet, dizziness, ataxia were added to these complaints one year ago, and she had been experiencing urinary and fecal incontinence for the last 4-5 months. The patient could not walk without assistance for the last one month. There was nothing special in the patient's medical history and family history.

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Her neurological history showed clear bilateral bradykinesis on the left side, hypokinesis and dysphonia and cerebellar tests were impaired on the left side. Romberg sign was positive both when eyes were open and closed, masked facies was present, and glabella reflex was positive. She could walk with assistance at anteflexion posture and her gait was ataxic.

Her routine laboratory investigations did not show any pathology. As she did not respond to levodopa treatment, and considering the present clinical picture, idiopathic Parkinson's disease was excluded and Parkinson plus syndrome was suspected.

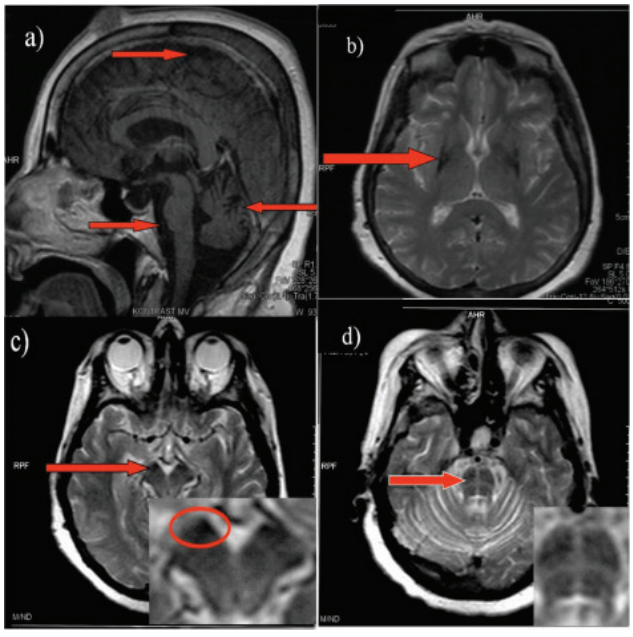

Figure 1: Cerebral MR images: a) Brain stem and cerebellar atrophy, symmetrical cerebral atrophy, b) Putaminal iron accumulation, c) Iron accumulation in the substantia nigra, d) Hot cross bun sign in the axial sections in the brain stem.

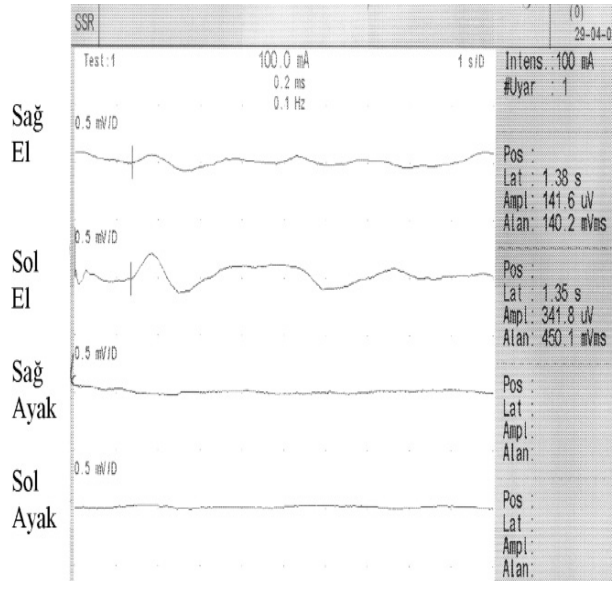

Figure 2: There was no sympathetic skin response in the lower extremities

The cerebral MRI showed brain stem and cerebellar atrophy, symmetric cerebral atrophy, as well as the corss sigh in the axial sections of the brain stem (Figure 1). Neuriphysiology tests showed median SEP to be within normal range and tibial SEP elongated on the left (right: 41 msec, left: 44.2 msec). Investigations performed to evaluate autonomous impairment showed that although sympathetic skin response in upper extremities was normal, there was no sympathetic skin response in lower extremities (Figure 2). R-R interval work-up (Figure 3) and tilt test were consistent with autonomous dysfunction. Mini mental status test results were normal. Lewy body dementia, supranuclear proximal palsy, corticobasal ganglionic degeneration were excluded based on the absence of dementia symptoms and normal mini mental test results, absence of gaze paralysis, absence of asymmetric cortical atrophy and apraxia, respectively; the patient was diagnosed with multiple system atrophy (MSA) because she fulfilled most of the diagnostic criteria. Treatment was initiated with levodopa + benzerazide 750 mg/day and amantadine 200 mg/day; however, there was no clear benefit of this treatment.

Discussion

Multiple system atrophy (MSA) is a rare neurodegenerative disease characterized with glial cytoplasmic inclusion bodies containing alpha synuclein. Clinical features can be manifested as a combination of cerebellar, autonomous and parkinsonian symptoms (Table 1). It has two subtypes: cerebellar (MSA-C) and parkinsonian (MSA-P). There are very few pathognomonic signs to differentiate MSA-P from Parkinson's disease in the early stage. In a study conducted by the European MSA Study Group (EMSA-SG) statistically significant red glags for the differential diagnosis of MSA were noted. The presence of at least 2 of six red flags (early instability, rapid progression, abnormal posture, bulbar dysfunction, respiratory dysfunction, and emotional incontinence) was reported to be 98.3% specific and 82.4% sensitive for the diagnosis of MSA (3). Early instability developing with recurring falls is frequently seen in progressive supranuclear palsy (PSP) cases (4,5,6). Among the various clinical conditions resulting in Parkinsonism, falling is seen in the very early stages in PSP patients, mid-stages in MSA patients, and late stages in Parkinson's patients (6). Although early instability is not diagnostic of MSA, it is a sign of atypical parkinsonian disorders.

Rapid progression is one of the very important warning signs for MSA patients. In a study conducted by Köllensperger et al. rapid progression was seen in 2/3 of MSA-P patients and only 2.6% of Parkinson's patients (3). Hoehn and Yahr progression rate was

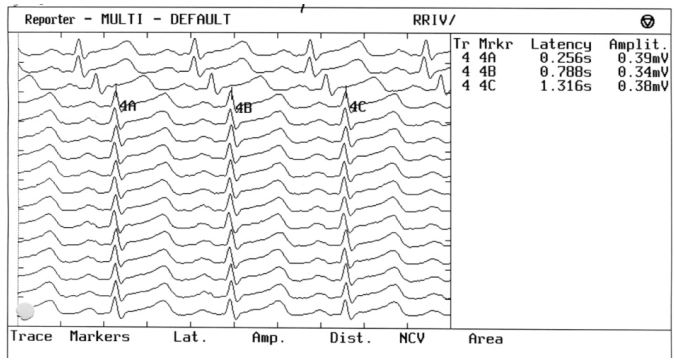

Figure 3: R-R interval work-up in hyperventilation was found to be consistent with autonomous dysfunction

found to be significantly high in atypical Parkinsonian disorders (5). Abnormal postures including Pisa syndrome, antecollis, and contractures in hands and feet are common in MSA. The pathophysiology underlying this unusual dystonic appearance was reported to be the progressive striatal degeneration in MSA (7).

Although bulbar involvement, severe dysarthria, dysphagia, and dysphonia occur in many of MSA patients, only 5% of Parkinson's patients experience these symptoms (4). Speech is also impaired in most of MSA patients (8). While speech disorder develops within 24 months in MSA patients, this period may take up to 84 months in Parkinson's patients (9). Development of dysphagia within 1 year of the onset of disease symptoms is reported to be specific (100%) for atypical parkinsonian disorders. Respiratory dysfunction such as inspiratory stridor or sighing is frequent in MSA and rare in PD. On the other hand, severe snoring and sleep apnea syndrome are not specific for MSA (3).

Table 1. Clinical diagnostic criteria

Autonomous and urinary dysfunction	Orthostatic hypotension* Urinary incontinence / incomplete voiding of the bladder, impotence
Parkinsonism	Bradikinesia* Rigidity Postural ataxia Tremor
Cerebellar dysfunction	Gait ataxia* Ataxic dysarthria Extremity ataxia
Corticospinal tract dysfunction	Hyperreflexia, extensor plantar response

*Signs that must be present

Table 2. Clinical warning signs – red flags – for MSA (3)

1- Early instability with recurring falling attacks
2- Rapid progression
3- Abnormal posture (camptocormia, antecollis)
4- Bulbar dysfunction (severe dysphonia, dysarthria, dysphagia)
5- Respiratory dysfunction (sleep apnea syndrome)
6- Emotionel incontinence (crying and laughing without reason)
7- No response to dopaminergic treatment
8- Cerebellar signs
9- Autonomic signs
10- Jerk tremor – myoclonus

Table 3. MRI findings in multiple system atrophy (10)

1) Significant atrophy in ventral medulla, pons and cerebellum
2) Clear signal decrease in the putamen compared to globus pallidus in axial T2 (putaminal iron accumulation)
3) Hot cross bun sign in pons

Although Parkinson plus syndromes are very similar clinically, they can be easily distinguished by a few distinct features which may be very important in early diagnosis of MSA. Therefore, all clinicians should be aware of the early stage symptoms listed in Table 2, investigate these symptoms in patients presenting with a parkinsonism picture and assess the development of these symptoms in the follow-up of these patients.

Magnetic resonance imaging (MRI) is an important tool not only for diagnosis but also for evaluating the clinical features of MSA and the T2-signal changes in the basal ganglia and brain stem on 1.5 tesla MRI are diagnostically significant. Hyperintense lateral putaminal ring and the hot cross bun sign are considered typical for MSA. In addition, posterior putaminal hypointensity and mid-cerebellar peduncular hyperintensity support MSA diagnosis (11).

Our patient had early instability, rapid progression, autonomic signs, abnormal posture, bulbar dysfunction, cerebellar dysfunction, and a parkinsonizm picture that did not respond to dopaminergic treatment; she fulfilled all the diagnostic criteria. In addition, cranial MRI fiundings were typical for MSA. This article aims to present this rare case to assist clinicians by reviewing literature on MSA, and summarizing important features of the condition.

References

1. Emre M, Hanağası HA, Şahin HA, Yazıcı Ş. Parkinson Hastalığı. İstanbul Üniversitesi İTF Nöroloji Anabilim Dalı Öğretim Üyeleri Nöroloji Ders Kitabı İstanbul 2009.
2. Çakmur R. Parkinson Hastalığının Epidemiyolojisi ve Klinik Özellikleri. Türkiye Klinikleri J Neurol 2003;1:160-163.
3. Köllensperger M, Geser F, Seppi K, Stampfer KM, Sawires M, Scherfler C, Boesch S, Mueller J, Koukouni V, Quinn N, Pellecchia MT, Barone P, Schimke N, Dodel R, Oertel W, Dupont E, Ostergaard K, Daniels C, Deuschl G, Gurevich T, Giladi N, Coelho M, Sampaio C, Nilsson C, Widner H, Sorbo FD, Albanese A, Cardozo A, Tolosa E, Abele M, Klockgether T, Kamm C, Gasser T, Djaldetti R, Colosimo C, Meco G, Schrag A, Poewe W, Wenning GK, European MSA Study Group. Red Flags for Multiple System Atrophy. Movement Disorders 2008;23:1093-1099.
4. Litvan I, Mangone CA, McKee A, Verny M, Parsa A, Jellinger K, D'Olhaberriague L, Chaudhuri KR, Pearce RK. Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study. J Neurol Neurosurg Psychiatry 1996;60:615-620.
5. Muller J, Wenning GK, Jellinger K, McKee A, Poewe W, Litvan I. Progression of Hoehn and Yahr stages in Parkinsonian disorders: a clinicopathologic study. Neurology 2000;55:888-891.
6. Wenning GK, Ebersbach G, Verny M, Chaudhuri KR, Jellinger K, McKee A, Poewe W, Litvan I. Progression of falls in postmortem-confirmed parkinsonian disorders. Mov Disord 1999;14:947-950.
7. Hozumi I, Piao YS, Inuzuka T, Matsuyama Z, Yamada Y, Hara A, Hirose T, Tsuchiya K, Takahashi H. Marked asymmetry of putaminal pathology in an MSA-P patient with Pisa syndrome. Mov Disord 2004;19:470-472.
8. Wenning GK, Ben Shlomo Y, Hughes A, Daniel SE, Lees A, Quinn NP. What clinical features are most useful to distinguish definite multiple system atrophy from Parkinson's disease? J Neurol Neurosurg Psychiatry 2000;68:434-440.
9. Müller J, Wenning GK, Verny M, McKee A, Chaudhuri KR, Jellinger K, Poewe W, Litvan I. Progression of dysarthria and dysphagia in postmortem-confirmed parkinsonian disorders. Arch Neurol 2001;58:259-264.
10. Horimoto Y, Aiba I, Yasuda T, Ohkawa Y, Katayama T, Yokokawa Y, Goto A, Ito Y. Longitudinal MRI study of multiple system atrophy - when do the findings appear, and what is the course? J Neurol 2002;249:847-854.
11. Schrag A, Kingsley D, Phatouros C, Mathias CJ, Lees AJ, Daniel SE, Quinn NP. Clinical usefulness of magnetic resonance imaging in multiple system atrophy. J Neurol Neurosurg Psychiatry 1998;65:65-71.