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Clinical Research

The Diagnostic Challenges of Patients with Multiple System Atrophy

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ABSTRACT

Objective: Multiple system atrophy (MSA) is a neurodegenerative disease characterized by a combination of parkinsonism, cerebellar ataxia, and autonomic deficiency symptoms. The purpose of this study is to assess clinical characteristics of patients diagnosed with probable MSA and review diagnostic challenges of MSA in view of the literature.

Material and Method: Eleven patients followed-up with probable MSA diagnosis according to the second consensus statement on the diagnosis of MSA criteria were included in the study. Patient files were reviewed retrospectively and the latest clinical examination characteristics were noted.

Results: The mean age of eleven MSA patients was found to be 65.36 (±5.32). Six patients were female. The average disease time was 4 years. Ten patients were not diagnosed with MSA by the clinician when they applied with the onset of symptoms. Only one patient was diagnosed with MSA correctly. Seven out of ten patients were diagnosed with Parkinson's Disease, whereas the other three patients were diagnosed with ataxia.

Conclusion: A considerable number of patients are not correctly diagnosed with MSA during their lifetime due to difficulties in differentiating it from other diseases. It is necessary to discuss this issue in the light of existing diagnostic criteria.

Keywords: *Multiple System Atrophy, Ataxia, Parkinsonism, Differential Diagnosis.*

ÖZET

Multi Sistem Atrofili Hastalarda Tanısal Zorluklar

Amaç: Multi sistem atrofi (MSA); parkinsonizm, serebellar ataksi ve otonomik yetmezlik semptomlarından oluşan bir kombinasyon ile karakterize nörodejeneratif bir hastalıktır. Bu çalışmanın amacı; muhtemel MSA tanısı almış hastaların klinik özelliklerini değerlendirmek ve MSA'nın tanısal zorluklarını literatür eşliğinde gözden geçirmektir.

Gereç ve Yöntem: Çalışmaya MSA'nın ikinci konsensüs teşhis kriterlerine göre muhtemel MSA tanısı ile takip edilen 11 hasta dahil edildi. Hasta dosyaları retrospektif olarak incelendi ve en son klinik muayene özellikleri not edildi.

Bulgular: Onbir MSA hastasının yaş ortalaması 65.36 (±5.32) bulundu. Altı hasta kadın cinsiyetteydi. Ortalama hastalık süreleri 4 yıldı. On hasta semptomları başladığı zaman ilk başvurduğu klinisyen tarafından MSA tanısı almamıştı. Sadece bir hasta doğru tanı olarak MSA tanısı almıştı. On hastanın yedisi Parkinson Hastalığı tanısı almışken diğer üç hasta ataksi tanısı almıştı.

Sonuç: Çoğu MSA hastasının ayırıcı tanıdaki güçlüklerden dolayı yaşam boyu doğru tanı alması geç olmaktadır. Bu problemin yeniden düzenlenecek güncel teşhis kriterlerine göre tartışılması gerekmektedir.

Anahtar Sözcükler: *Multi Sistem Atrofi, Ataksi, Parkinsonizm, Ayırıcı Tanı.*

Multiple system atrophy (MSA) is a sporadic neurodegenerative disease with adult onset characterized by a combination of parkinsonism, cerebellar ataxia, pyramidal signs, and autonomic deficiency symptoms (1). MSA is one of the Parkinson plus syndromes included in the differential diagnosis of Parkinson's Disease (PD). Its incidence is 4.4/100000 (2). There are no therapeutic options which cure the disease apart from symptomatic drugs (3). The second consensus statement on the diagnosis of MSA criteria are used for the diagnosis of MSA. According to these criteria, patients are diagnosed with definite, probable, or possible MSA (4).

In clinical practice, clinicians have to rely on diagnostic criteria for MSA. But, there are no reliable biological markers. Thus, clinicians can need to see brain imaging characteristics of MSA. However, the clinical diagnostic accuracy of MSA varies between 60% and 90% even in the late stage of the disease (5, 6). Especially the early stage diagnostic accuracy of MSA is unknown (7). For this reason, there should be improvements in clinical diagnosis criteria to increase diagnostic accuracy are of great importance.

The purpose of this study is to review diagnostic challenges of MSA in view of the literature and assess clinical characteristics of patients diagnosed with probable MSA with regard to clinical subtypes of MSA-P and MSA-C.

MATERIAL AND METHOD

Patients followed-up with MSA diagnosis at the Movement Disorders Polyclinic, Neurology Depart-

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ment, Erciyes University Faculty of Medicine Hospital between June 2014 and December 2016 were included in this study. The approval of the local ethics committee was obtained and the consent of the patients was received. Eleven patients followed-up with probable MSA diagnosis according to the second consensus statement on the diagnosis of MSA criteria were included in the study (4). The patients were categorized for different types of MSA-P and MSA-C by a clinician with experience in movement disorders.

Patient files were reviewed retrospectively and the latest clinical examination characteristics were noted. Cranial magnetic resonance images (MRI) of all patients were reviewed as well. Characteristics of periputaminal hyperintensity (rim sign), putaminal hypointensity, atrophy of the brainstem and middle cerebellar peduncle, and the hot cross bun sign were determined, if present. Additionally; initial symptoms, initial diagnosis, treatment responses, the course of the disease in time, additional symptoms, previous cranial images (if available), disabling symptoms, and predominant clinical characteristics of the patients were assessed with regard to their fit with respective subtypes of MSA. Global disability status was determined for each patient according to their Unified Multiple System Atrophy Rating Scale (UMSARS) scores in order to assess clinical progression of MSA (8).

Statistics

Demographical and clinical data obtained from the participants within the scope of the study were evaluated with descriptive statistics. Mean ± SD and median 25 and 75 percentile values are presented. The results of the frequency analysis applied to certain data can be seen in *Table 1* and *2*. Statistical Package for the Social Sciences 15.0 (SPSS 15.0) was used for analysis.

RESULTS

The mean age of the patients was found 65.36. Six patients were female. The average disease time was 4 years. Ten patients were not diagnosed with MSA by the clinician when they applied with the onset of symptoms. Only one patient was diagnosed with MSA correctly. Seven out of ten patients were diagnosed with PD, whereas the other three patients were diagnosed with ataxia. *Table 1* shows the demographic data about the patients.

Table 1. *Demographic features of patients with MSA.*

n	11
Sex (F/M)	6/5
Mean age (±SD)	65.36 ±5.32 (57-75)
Age at onset (age)	61.36 ±4.96 (55-71)
Duration of MSA (years)	4.00 ±1.79 (1-6)

Clinical examination characteristics and observations of the patients were reviewed. Considering initial symptoms, five patients presented cerebellar findings, four patients presented parkinsonian findings, and two patients had cerebellar+parkinsonian findings (mixed). It was found that all patients had atrophy of the brainstem and middle cerebellar peduncle and the hot cross bun sign. Neurogenic orthostatic hypotension symptoms were observed in 10 patients. Seven patients were diagnosed with MSA-C and four patients were diagnosed with probable MSA-P after assessment according to diagnostic criteria. All MSA-P patients and four MSA-C patients had received L-dopa treatment. However, three MSA-C patients had been forced to give up the L-dopa treatment since it worsened neurogenic orthostatic hypotension symptoms. Clinical characteristics of the MSA patients can be seen in *Table 2*.

Table 2. *The clinical features of patients with MSA.*

Case	Age	Sex (F/M)	Initial symptom	Orthostatic hypotension	RBD	Hot cross sign	Global disability scale	MSA form
1	75	M	Ataxia	+	+	+	3	MSA-C
2	57	F	Ataxia	+	+	+	4	MSA-C
3	60	F	Mixt	+	+	+	5	MSA-C
4	73	F	Parkinsonism	+	-	+	2	MSA-P
5	68	F	Mixt	+	-	+	5	MSA-C
6	61	M	Parkinsonism	+	+	+	2	MSA-P
7	65	F	Ataxia	+	+	+	5	MSA-C
8	66	M	Parkinsonism	+	+	+	2	MSA-P
9	65	M	Ataxia	+	+	+	3	MSA-C
10	66	F	Parkinsonism	+	+	+	5	MSA-P
11	63	M	Ataxia	-	+	+	2	MSA-C

MSA: Multiple System Atrophy, C: Cerebellar, P: Parkinsonism, F: Female, M: Male, RBD: Rapid eye movement (REM) sleep behavior disorder.

Nine out of eleven patients had presented Rapid eye movement (REM) sleep behavior disorder (RBD) symptoms before the onset of symptoms. An assessment of the patients based on their latest examination findings showed that all patients required help with balance in everyday life activities according to the global disability scale. Four patients in particular had become wheelchair-bound due to cerebellar symptoms (stage 5). There is seen MRI image of a patient followed-up with MSA-C below (Figure 1).

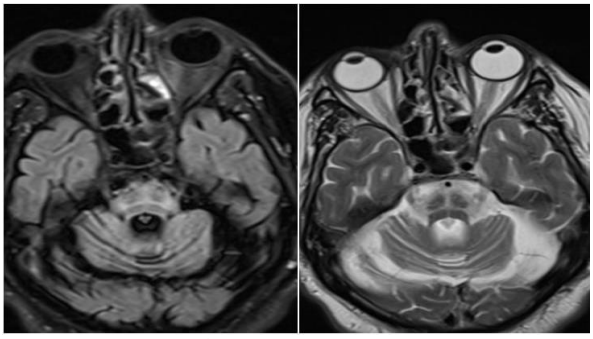

Figure 1. *The MRI scan of one patient with MSA-C. The hot cross bun sign of the pon and cerebellar atrophy is very common on course of the MSA.*

DISCUSSION

In this study, we found that MSA patients are not accurately diagnosed especially in initial years where the symptoms start to manifest themselves. Only one in eleven patients followed-up had been accurately diagnosed. This finding shows that there are diagnostic challenges throughout the clinical course of MSA, especially for patients who are followed-up in places other than centers specializing in movement disorders.

The accurate diagnosis of MSA is significant for appropriate patient management, particularly in early stages of the disease where the symptoms are not yet fully manifested. However, as far as early diagnosis goes, it is obvious that the existing clinical diagnostic criteria have certain challenges. In this context, it should be mentioned that up-to-date laboratory and clinical findings may contribute to the accuracy of the diagnosis (9).

Today, an increasing number of publications highlight the challenges in MSA diagnosis (9, 10). Existing clinical diagnostic criteria used for MSA have various limitations. First of all, these criteria mostly focus on motor findings associated with the disease. Parkinsonism and cerebellar ataxia non-responsive to L-dopa are not uncommon cases and may be observed in many disorders other than MSA (11, 12). Secondly, autonomic deficiency and genitourinary dysfunction in particular are not specific to MSA. These may be observed in other neurodegenerative diseases and even in healthy individuals between the ages of 50-60 (13, 14). Thirdly, orthostatic hypotension may be seen in many cases other than MSA. For example, it is reported in a study that 20% of PD patients present orthostatic hypotension (15). The fourth limitation is that both autonomic deficiency and motor symptoms are necessary for MSA diagnosis. However, autonomic deficiency and motor symptoms do not develop concurrently in many MSA patients. While some patients present autonomic deficiency from the onset of the disease, some do not show any symptoms even after 15 years (16). Indeed, one of our patients (Table 2, case 11) had the symptoms for four years, yet did not present orthostatic hypotension to this day.

A considerable number of patients are not correctly diagnosed with MSA during their lifetime due to difficulties in differentiating it from other diseases. (PD, pure autonomic failure, other rare movement disorders). MSA may be accompanied by Parkinsonian symptoms quite frequently. About 10% of patients diagnosed with Parkinson's Disease are reported to have MSA at autopsy. About 29-33% of patients who present isolated late-onset cerebellar ataxia and 8-10% of patients with Parkinsonism develop MSA. For this reason, it is safe to assume a higher prevalence than estimations (17).

The EMSA registry study examined 437 patients diagnosed with MSA. Sixty-eight percent of these patients were found to have symptoms that fit MSA-P and 32% were found to have symptoms that fit MSA-C. While 99% of the patients had autonomic deficiency symptoms (urinary symptoms, orthostatic hypotension, and chronic constipation), 87% had Parkinsonism, 64% had ataxia, and 43% had pyramidal symptoms. Additionally, 41% of the patients showed signs of depression (10). As explained above, MSA may be manifested with different symptoms, and the clinical table may be heterogeneous, which causes diagnostic challenges for the clinician (18).

Imaging methods are frequently used for the clinically differential diagnosis of MSA. These methods include MRI, positron emission tomography (PET), and single photon emission computed tomography (SPECT). Issues related to nerve supply to heart may demonstrate an association with MSA or PD, which may be determined using PET and SPECT scans. Also, it is not possible to exclude MSA due to normal dopamine transporter imaging. The hot cross bun sign is observed in 63% of MSA-P patients and 80% of MSA-C patients (17). This presentation may be observed in variant Creutzfeldt-Jakob disease, spinocerebellar ataxia, cerebrotendinous xanthomatosis, and vasculitis-associated parkinsonism as well (19-21). In addition, it has been shown in a considerable number of studies that lateral slit-like hyperintense putaminal rim and putaminal hypointensity are observed more frequently on conventional brain MRIs of MSA patients compared to controls and PD patients (22, 23).

It is recommended that clinicians pay attention to certain characteristics to improve the accuracy of differential MSA diagnosis (9). *Table 3* shows these characteristics recommended for clinically differential diagnosis of MSA.

Table 3. *Recent clinical and investigation findings based on clinical judgment to be considered in future.*

CLINICAL
• Combination of parkinsonism and cerebellar ataxia can occur in other diseases.
• Autonomic dysfunction (orthostatic hypotension and/or genitourinary dysfunction) is frequent in but not specific to MSA
• Detailed protocol to determine the presence of orthostatic hypotension is not provided
• Types of urinary incontinence are not considered
• Onset of autonomic dysfunction can be delayed as long as 15 years
• Familial MSA is reported rarely
• Patients with MSA may develop cognitive decline and dementia
INVESTIGATIONS
• Putaminal hypointensity on brain MRI in MSA-P
• Cardiac MIBG scan, video oculography, and TCS can help differentiate MSA from PD
• Quantitative autonomic function test can help diagnose MSA
• Mutations in the SCA genes were found in some patients presenting as MSA
• COQ2 is reported as a causative gene as well as a risk gene for familial and sporadic MSA
• MSA-P with normal DaT scan were reported

MIBG: meta-iodobenzylguanidine, SCA: Spinocerebellar ataxia, COQ2: coenzyme Q2, DaT: dopamine transporter.

The relatively low number of patients included in the study and lack of neuropathological examination of our MSA patients may be accepted as limitations of our study.

Conclusion

MSA is frequently diagnosed inaccurately by clinicians examining the patient for the first time, particularly in initial years of the disease. Therefore, clinicians should be careful and try their best to observe red flags while examining patients who may have differential symptoms associated with MSA.

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