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Case report

Differential Diagnostic Relevance of High Resolution Magnetic Resonance in Patients with Possible Multiple System Atrophy (MSA) – A Case Report

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A B S T R A C T

Multiple system atrophy (MSA) is sporadic, progressive neurodegenerative disorder characterized clinically by autonomic dysfunction, Parkinsonism (MSA-P), and cerebellar ataxia (MSA-C) in any combination. Parkinsonism is present in the majority of patients (80%). Early in the course of the disease autonomic dysfunctions are present in approximately 40% of patients, while the domination of cerebellar symptoms is present in 20% of all patients[1,2]. According to second consensus statement on diagnosis of MSA, to make the diagnosis of possible MSA, except Parkinsonism or a cerebellar syndrome, there must be one feature involving autonomic dysfunction plus one other additional that can include findings on history, clinical examination or changes in structural or functional imaging[3]. We present a case of 60-year old male with Parkinsonism and cerebellar symptoms accompanied with signs of autonomic nervous system involvment. Level of autonomic dysfunction was not the level required for the diagnosis of probable MSA. On initially performed 1.5T MRI, the most prominent neurodegenerative feature of brain stem, cerebellum and basal ganglia was atrophy, however features like »hot-cross bun« sign, »slit-like« putaminal rim and middle cerebellar peduncle hyperintensities were detected only after MR imaging on higher resolution (3T) device[4]. Our case points to the possibility that some typical structural changes that can help in diagnostic process may not be clearly visible on 1.5 T MRI devices. In such cases we suggest using 3T MRI device, if feasible, in order to demonstrate findings that may help in establishing the diagnosis of possible MSA.

Key words: *multiple system atrophy, magnetic resonance imaging, diagnosis*

Introduction

Multiple system atrophy (MSA) is a sporadic, adult-onset and progressive neurodegenerative disease of undetermined etiology, characterized with combination of Parkinsonism (MSA-P), cerebellar ataxia (MSA-C) and autonomic dysfunction (MSA-A)[1,2]. Symptoms of MSA vary in distribution, onset and severity. Early in the course of the disease autonomic dysfunction is present in approximately 40% of patients and later it is present in almost all patients. Parkinsonism is present in the majority of all patients (80%), while the domination of cerebellar symptoms is present in 20% of all patients[1,2]. Cell loss, gliosis, and glial cytoplasmatic inclusions (GCIs) are the typical pathologic features that can be found in several brain and spinal cord structures. In MSA-P the neurodegeneration is most prominent in the nigrostriatal system, while in MSA-C it is more expressed in the olivopontocerebellar system. Autonomic system involvement is related to cell loss in the dorsal motor nucleus of the vagus nerve, the locus coeruleus, and the ventrolateral medulla, as well as parasympathetic preganglionic

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nuclei in the spinal cord[1]. The pathologic hallmark of MSA is the presence of cytoplasmatic inclusion bodies in glial cells (GCIs) of the basal ganglia, supplementary and primary motor cortices, reticular formation, and pontocerebellar system. These inclusions called Papp-Lantos inclusions contain ubiquitin, tau, and fibrillized alpha-synuclein proteins and are definitive for the diagnosis of MSA[1,5,6]. The prevalence of MSA is higher in male than female patients (approximately 1.3:1). The symptoms typically begin in the 6th decade of life, with approximately 6–9 years survival after the establishing the diagnosis. It is a relatively rare disorder, with annual incidence of 3 new cases *per* 100,000 people. Until now, there is no strong evidence supporting genetic nature of MSA[7].

In order to uniform the diagnostic process, consensus conference on the diagnosis of MSA was held in 1998. According to these criteria, there were two categories of MSA: MSA with predominant cerebellar ataxia (MSA-C) and MSA with predominant Parkinsonism (MSA-P). Three levels of certainty were established, possible, probable, and definite MSA[8]. Many following studies demonstrated high predictive accuracy but low level of sensitivity of these criteria[9,10]. Practical implementation of these criteria was sometimes very difficult and complicated. Due to additional information relevant to diagnostic criteria that occurred from following clinical and laboratory studies[11], biochemical and neuropathologic findings[12], and neuroimaging studies[13,14], new (second) consensus conference was held in order to create new guidelines, with higher accuracy and much more practical use in diagnostic process of MSA[3]. According to the second consensus criteria, the diagnosis of MSA should be divided into three groups;

1. Definite MSA requires the neuropathologic findings of widespread CNS α-synuclein–positive GCIs and neurodegenerative changes in nigrostriatal or olivopontocerebellar structure[15],
2. Probable MSA – criteria listed in Table 1,
3. Possible MSA – criteria listed in Tables 2 and 3.

The definition of the disease onset include first sign of any motor problem, whether parkinsonian or cerebellar, or autonomic features, that are listed in Table 2. The male erectile dysfunction (ED) is excluded[3].

TABLE 1
CRITERIA FOR PROBABLE MULTIPLE SYSTEM ATROPHY

A sporadic, progressive, adult (>30 years) onset disease characterized by
• Autonomic failure involving urinary incontinence (inability to control the release of urine from bladder with erectile dysfunction in male) decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic and
• Poorly levodopa-responsive parkinsonism (bradikynesia with rigidity, tremor or postural instability) or
• A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)

TABLE 2
CRITERIA FOR POSSIBLE MULTIPLE SYSTEM ATROPHY

A sporadic, progressive, adult (>30 years) onset disease characterized by
• Parkinsonism (bradikynesia with rigidity, tremor or postural instability) or
• A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) and
• At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in male, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA) and
• At least one of the additional features listed in Table 3.

MSA – multiple system atrophy

TABLE 3
ADDITIONAL FEATURES OF POSSIBLE MULTIPLE SYSTEM ATROPHY

Possible MSA-P or MSA-C
• Babinski sign with hyperreflexia
• Stridor
Possible MSA-P
• Rapidly progressive parkinsonism
• Poor response to levodopa
• Postural instability within 3 years of motor onset
• Gait ataxia, cerebellar dysarthria, limb ataxia or cerebellar oculomotor dysfunction
• Dysphagia within 5 years of motor onset
• Atrophy on MR of putamen, middle cerebellar peduncles, pons or cerebellum
• Hypometabolism on FDG-PET in putamen, brainstem or cerebellum
Possible MSA-C
• Parkinsonism (bradykinesia and rigidity)
• Atrophy on MR of putamen, middle cerebellar peduncles, pons
• Hypometabolism on FDG-PET in putamen
• Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

MR – magnetic resonance, MSA-P – multiple system atrophy with predominant Parkinsonism, MSA-C – multiple system atrophy with predominant cerebellar ataxia, FDG (^{18}F) – fluorodeoxyglucose, FDG-PET – positron emission tomography with fluorodeoxyglucose, PET – positron emission tomography, SPECT – single photon emission computerized tomography

Autonomic dysfunction

At the onset of the disease, autonomic failure is present in about 40% of patients, with impotence as the most frequent initial symptom in males[16], while in females it was the urinary incontinence. Fecal incontinence and constipation affects about 30% of patients. Criteria for autonomic failure are listed in Table 1. Orthostatic hypotension is present in about 60% of patients. The clinical diagnosis of probable MSA requires a reduction of sys-

tolic blood pressure by at least 30 mm Hg, or reduction of diastolic blood pressure by at least 15 mm Hg after 3 minutes of standing; (previously, the patient had to spend 3-minute in the recumbent position). Usually, during this orthostatic blood pressure decrease, compensatory increase of the heart rate is to low for the level of blood pressure decline. Other disorders which may cause orthostatic hypotension, like diabetic autonomic neuropathy and drug induced hypotension should be excluded.

Parkinsonism

Parkinsonism, with different level of akinesia and rigidity is present in most patients with MSA. The tremor is usually asymmetric, postural and related to action. The response to chronic levodopa therapy is usually poor, although initially 30% of patients may show some, but usually waning response[17]. Escalating doses of levodopa with a peripheral decarboxylase inhibitor over 3 months up to at least 1 g/d should be used to test the response. A positive response is characterized with clinically significant motor improvement like an improvement of 30% or more on part III of the UPDRS or on part II of the Unified Multiple System Atrophy Rating Scale[18].

Cerebellar syndrome

Gait ataxia is the most common cerebellar symptom and is often accompanied by cerebellar dysarthria (ataxia of speech) and oculomotor dysfunction of cerebellar origin.

Other symptoms that occur frequently in MSA include dysphagia, sleep disorders, obstructive sleep apnea, memory impairment, vivid dreams and confusion. According to Second criteria, new powerful tools in establishing the diagnosis are some structural and functional imaging methods: positron emission tomography with fluorodeoxyglucose (FDG-PET), singe photon emission computerized tomography (SPECT) and magnetic resonance imaging (MRI).

In both MSA-P and MSA-C, typical MRI atrophic changes are visible in putamen, pons and middle cerebellar peduncle (MCP)[19]. The recent (second) criteria operate standard with 1.5-Tesla MRI and T2 weighted images, that demonstrate changes in the basal ganglia (posterior putaminal hypointensity and hyperintense lateral putaminal rim) and brainstem (hot cross bun sign and MCP hyperintensities)[3].

FDG-PET demonstration of hypometabolism in striatum and brainstem can also help in diagnosis of MSA[20].

Case Report

We present a case of 60-year old male with onset of symptoms six months prior to his first neurological exam. Initially, he complained about clumsiness and stiffness, gait unsteadiness, speech disturbance and change in handwriting. He also reported erectile dysfunction and feeling of dizziness after standing up from the sitting position. Later, he started to use artificial tears due to dry eyes. There was no family history of similar illness. On the neurologic exam he had hypomimia, with a reduced blink rate. The speech was disarthric. There was cogwheel rigidity of right > left upper extremity, tone of the right extremities was increased. Intention tremor, dyssynergia and dysmetria, and dysdiadokinesia were noted. There was reduction in speed and amplitude during repetitive actions of right extremities. The muscle stretch reflexes were brisk and plantar response was flexor. The gait was broad-based, with variable stride length and swaying. After 3 minutes of standing we measured a blood pressure falling by 20 mmHg systolic and 15 mm Hg diastolic. Time and frequency domain 24 hours heart rate variability as well as tilt table test showed no clinically relevant autonomic disorder. Schirmer test showed decreased basal secretion of tears. All laboratory tests were normal including complete blood count, sedimentation rate, blood glucose, urea and creatinine levels, liver functions, blood and urine cooper and ceruloplasmin level, serum lipids and electrolytes and analysis of urine. The mini-mental score was 27/30. The response to levodopa therapy was poor.

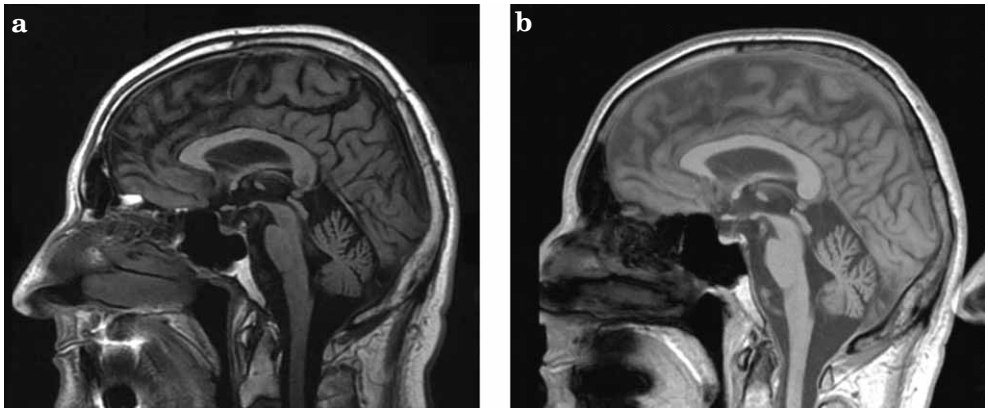

Fig. 1. a) Mild to moderate brainstem and cerebellar atrophy in a patient with a clinical diagnosis of MSA with predominant Parkinsonism and cerebellar symptoms on T1 weighted sagittal sections on 1.5 T MR device (GE Signa 1.5 T Excite Scanner, General Electric Company, Milwaukee, WI, USA); b) Similar level of atrophy visible on T1 weighted sagittal sections on 3T MR device (Magnetom 3T Trio Tim Vision, Siemens, Erlangen, Germany).

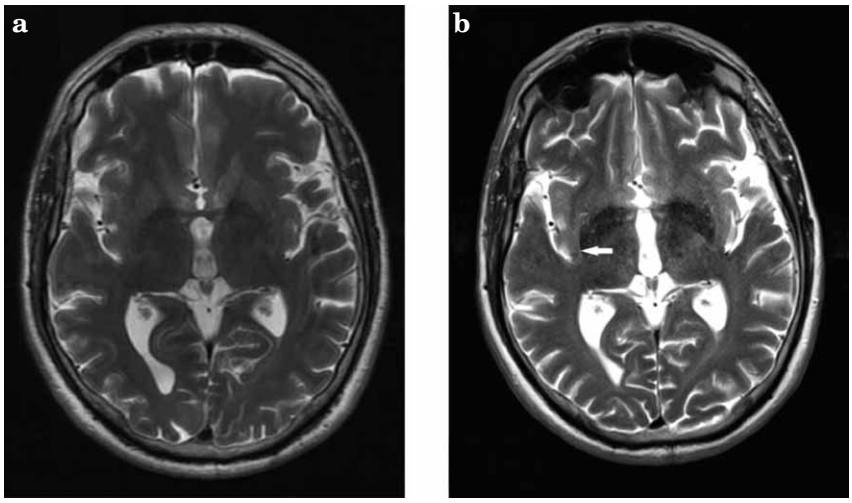

Fig. 2. a) axial T2 weighted section in patient on 1.5 T MR device shows normal posterolateral putaminal margin (GE Signa 1.5 T Excite Scanner, General Electric Company, Milwaukee, WI, USA); b) Mild slitlike hyperintensity of the posterolateral putaminal rim (arrow) in same patient with diagnosis of possible MSA (Axial section, T2 weighting / Magnetom 3T Trio Tim Vision, Siemens, Erlangen, Germany).

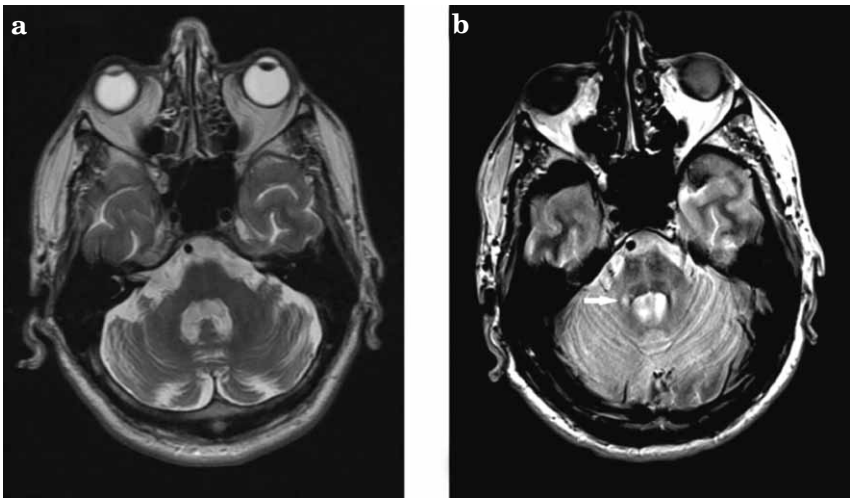

Fig. 3. a) Normal pons in patient on 1.5 T MR device (Axial section, T2 weighting / GE Signa 1.5 T Excite Scanner, General Electric Company, Milwaukee, WI, USA) b) Cruciform degeneration of pontine fibers »Hot-cross bun« sign and predominant right middle cerebellar peduncle hyperintensity (arrow) in same patient detected only on 3T MR device (Axial section, T2 weighting / Magnetom 3T Trio Tim Vision, Siemens, Erlangen, Germany).

On initially performed 1.5T MRI, the most prominent neurodegenerative feature of brain stem, cerebellum and basal ganglia was atrophy (Figure 1a, b). Typical features like slit-like hyperintense putaminal rim (Figure 2a, b), »hot-cross bun sign« and MCP hyperintensities (Figure 3a and b) were detected in T2 weighted images and FLAIR sequences only on higher resolution (3T) MRI device.

Patient was suggested to wear elastic compressive stocking, to make postural changes and head-up tilt of the bed at night. Liberal salt intake was recommended. He was referred to speech-language therapist who started speech therapy. Intense physical therapy was also started.

Discussion and Conclusion

Six months from the onset of the first symptoms our patient has had both cerebellar and parkinsonian symptoms accompanied with signs of autonomic dysfunction. However, orthostatic blood pressure decline did not meet the level required for diagnosis of probable MSA so the diagnosis of possible MSA was made. According to second consensus statement on diagnosis of MSA, for making a diagnosis of possible MSA in addition to Parkinsonism or cerebellar syndrome, there must be one feature involving autonomic dysfunction plus one other additional feature that can include findings on history, clinical examination

or changes in structural or functional imaging (Table 3)[3]. MRI changes (Table 3) that can help diagnose possible MSA-P and MSA-C include putaminal, pontine and middle cerebellar peduncle atrophy. T2-signal changes including posterior putaminal hypointensity, hyperintense lateral putaminal rim, »hot cross bun« sign and hyperintense MCP are also helpful[3]. All those MRI changes should be visible on imaging using 1.5 T MR device according to second consensus statement on diagnosis of MSA[3]. In previous studies on MRI of MSA patients 1.5 T MR devices were used for demonstration of those structural changes[4,13,19] but our case showed that some of those changes may not be visible on 1.5 T MRI device. Although our patient already had both cerebellar and parkinsonian symptoms together with signs of involvement of autonomic system so the criteria for diagnosis of possible MSA according to second consensus statement were fulfilled, the 1.5 T MRI imaging did not demonstrate some of typical findings for possible MSA[3]. »Hot cross bun« sign, MCP hyperintensities and hyperintense slit like putaminal rim were demonstrated only after using 3T MRI device. The most of other additional features required for making the diagnosis that are listed in Table 3, are much more difficult to use. Confirmation of rapidly progressive Parkinsonism, poor response to levodopa, development of swallowing problems (dysphagia) or postural instability, require significant period of time (from 3 months to 5 years), while other functional studies like SPECT or FDG-PET may be preformed only in well equipped hospital centers. Additionally, using MRI instead of PET or SPECT avoids radioactive exposure of patients. Despite the fact that our patient already had fulfilled criteria for diagnosis of possible MSA, imaging on conventional 1.5 T MRI device did not demonstrate some of structural changes as additional diagnostic features that can help in establishing the diagnosis of possible MSA. Our case points to the assumption that if typical structural changes that can help in diagnostic process of possible MSA are not clearly visible on routinely used 1.5 T MRI devices[19], exams should be repeated on 3T MRI device if feasible, in order to demonstrate findings that are required for establishing the diagnosis of possible MSA.

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VAŽNOST UPORABE MAGNETNE REZONANCIJE VISOKE REZOLUCIJE U DIJAGNOSTICI MOGUĆE MULTIPLE SISTEMNE ATROFIJE – PRIKAZ SLUČAJA

S A Ž E T A K

Multipla sistemna atrofija (MSA) je sporadična, progresivna neurodegenerativna bolest klinički karakterizirana znakovima autonomne disfunkcije, parkinsonizma (MSA-P) i cerebelarnim simptomima (MSA-C) u bilo kojoj kombinaciji. Parkinsonizam je prisutan u većine bolesnika (80%). U početku bolesti autonomna disfunkcija je izražena kod otprilike 40% bolesnika dok je kod 20% bolesnika dominantna cerebelarna simtomatologija[1,2]. Prema kriterijima za dijagnozu MSA koje su postavili eksperti na drugoj konferenciji o dijagnostici MSA za dijagnozu moguće MSA uz postojanje parkinsonizma ili cerebelarnih simptoma moraju postojati i znaci autonomne disfunkcije i jedna od dodatnih karakteristika koje uključuju anamnezu, klinički nalaz ili strukturne ili funkcionalne promjene verificirane slikovnim metodama[3]. Prikazujemo šezdesetgodišnjeg bolesnika sa parkinsonizmom, cerebelarnim simptomima i znacima zahvaćanja autonomnog živčanog sustava čiji stupanj prema zadanim kriterijima nije dovoljan za dijagnozu vjerojatne MSA. Rezultati laboratorijske obrade su bili unutar granica normale. Na inicijalno učinjenoj magnetnoj rezonanciji (MR) mozga vidljiva je atrofija moždanog debla, malog mozga i bazalnih ganglija. Promjene tipične za MSA kao »hot-cross bun« znak, hiperdenzni posterolateralni rub putamena i hiperdenzni srednji cerebelarni pedunkuli su bili detektirani korištenjem MR aparata jačine 3 T[4]. Naš slučaj ukazuje na mogućnost da se neke strukturalne promjene mozga koje mogu pomoći u dijagnozi moguće MSA ne moraju uvijek jasno prikazati korištenjem MR mozga jačine 1.5 T te stoga preporučamo, ukoliko je izvedivo, korištenje aparata jače rezolucije u svrhu prikaza karakteristika koje mogu pomoći u postavljanju dijagnoze moguće MSA.