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Review Article

Clinical-Phenotypic Spectrum and Course Characteristics of Multiple System Atrophy: a Retrospective Case Series Analysis

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ABSTRACT

Multiple system atrophy (MSA) remains one of the most challenging neurodegenerative disorders to diagnose, clinically characterized by various combinations of levodopa-resistant parkinsonism, cerebellar, autonomic, and pyramidal dysfunction. Early diagnosis of this disease is challenging, with post-mortem studies showing that the accuracy of diagnosis is only 62-79%. Late diagnosis is common, with an average of 3-4 years from the onset of the first symptoms to diagnosis. Given that the average survival is about 7-9 years, early diagnosis is crucial for the patient's quality of life and effective treatment.

This article provides a comprehensive analysis of three distinct clinical cases (MSA-P, MSA-C, and Mixed phenotype), highlighting the critical role of the 2022 Movement Disorder Society (MDS) diagnostic criteria in refining clinical accuracy, offers a practical framework for clinicians to improve early detection and symptomatic management of MSA, ultimately aiming to enhance patient quality of life in the absence of a curative therapy.

Keywords: Multiple System Atrophy; Autonomic Failure; Orthostatic Hypotension; UMSARS; 2022 MDS Criteria; A-Synuclein; Neurodegeneration

Introduction

Multiple system atrophy (MSA) is a severe neurodegenerative disorder characterized by prominent and rapidly progressive autonomic failure (orthostatic hypotension, urogenital dysfunction) in combination with movement disorders, specifically akinetic-rigid syndrome and cerebellar ataxia. Early diagnosis of MSA remains challenging; post-mortem studies indicate that clinical diagnostic accuracy ranges from only 62% to 79% [1]. Delayed diagnosis is common, with an average interval of 3 to 4 years between the onset of the first symptoms and the formal diagnosis [2]. Given that the median survival rate for these patients is approximately 7–9 years [3, 4], timely identification of the disease is crucial for maintaining quality of life and determining optimal management strategies. The disease typically develops in the fifth or sixth decade of life, and never manifests before the age of 30 [5]. MSA accounts for only 10–12% of all cases of parkinsonian syndromes, with an estimated prevalence of 3–5 cases per 100,000 population—approximately 20 times less frequent than Parkinson's disease [6, 7]. MSA is considered the most aggressive synucleinopathy: the disease progresses rapidly, leading to severe disability within 5–6 years, while the average life expectancy does not exceed 10 years from the onset of symptoms [21, 22].

Historically, MSA was first described in 1969 as Shy-Drager syndrome. The term "multiple system atrophy" was subsequently proposed by Graham and Oppenheimer in 1969 to unify such nosological entities as olivopontocerebellar atrophy, striatonigral degeneration, and Shy-Drager syndrome [8].

Epidemiology

Recent meta-analyses suggest that the prevalence of Multiple System Atrophy (MSA) may be higher than previously estimated (the historically cited 4.4 per 100,000), primarily due to improved diagnostic sensitivity at the early ("possible") stages. In individuals over the age of 50, prevalence rates reach between 7.8 and 10.2 per 100,000. The implementation of the 2022 Movement Disorder Society (MDS) diagnostic criteria has facilitated detection approximately 1.5 years earlier than previous protocols. While this has extended the recorded "duration of life with the diagnosis," it has not translated into an increase in actual overall survival [23].

Pathomorphology

MSA is characterized by a combination of degenerative changes in the basal ganglia, cerebellum, and brainstem. The hallmark morphological feature is the presence of glial cytoplasmic inclusions (GCIs) composed of aggregated α-synuclein. In contrast to Parkinson's disease and dementia with Lewy bodies, which are dominated by neuronal inclusions, glial inclusions are pathognomonic for MSA. As a synucleinopathy, the key diagnostic feature of MSA is the presence of α-synuclein-positive oligodendroglial inclusions, also known as Papp-Lantos bodies [8]. Clinically, two main phenotypes are distinguished: the parkinsonian variant (MSA-P), characterized by predominant parkinsonism, and the cerebellar variant (MSA-C), associated with olivocerebellar atrophy [7, 9].

Pathophysiology

The disease is characterized by the pathological accumulation of α-synuclein within oligodendrocytes, leading to their dysfunction, apoptosis, and subsequent secondary neuronal degeneration. In the early stages of the disease, the phosphoprotein p25-alpha (TPPP/p25), which normally regulates myelination, translocates from the myelin sheath to the oligodendroglial cytoplasm, where it promotes α-synuclein aggregation. This process triggers a neuroinflammatory cascade involving microglial activation, the release of pro-inflammatory cytokines, mitochondrial impairment, and oxidative stress. Furthermore, toxic α-synuclein species exhibit the capacity to propagate to functionally interconnected brain regions, resulting in the development of multisystem neurodegeneration [10].

Genetics

Increasing evidence underscores the significant role of genetic factors in the predisposition to MSA. Mutations in the COQ2 gene, associated with impaired coenzyme Q10 (Co-Q10) biosynthesis, have been identified in Japanese families with familial MSA [11, 12]. Furthermore, associations with polymorphisms in the SNCA (α-synuclein) [13], the V393A variant in the COQ2 gene [14], MAPT (microtubule-associated protein tau), LRRK2, C9orf72 [15], and the GBA (glucocerebrosidase) gene [16] reinforce the multifactorial nature of the disease. The spectrum of genetic risk factors varies across different ethnic groups, indicating regional specificities in disease susceptibility.

Recent Genome - Wide Association Studies (GWAS) have identified potential risk variants in the EDN1 (endothelin 1), FBXO47 (F-box protein 47), and ELOVL7 (fatty acid elongase 7) genes, which are linked to impaired vascular regulation and lipid metabolism in MSA [15]. These findings suggest that the pathogenesis of the disease involves not only neurodegenerative processes but also complex metabolic mechanisms.

In summary, MSA is currently viewed as the result of a complex interplay between α-synuclein aggregation, neuroinflammation, mitochondrial dysfunction, and genetic factors. This integrated perspective opens new avenues for the identification of

biomarkers and the development of disease-modifying therapies [17].

Clinical features

MSA can manifest with a broad spectrum of clinical and pathological features, including atypical variants with diverse ages of onset, prodromal forms, and coexistence with Lewy body pathology or prominent hippocampal alterations. Stridor, associated with vocal cord abductor paralysis, is considered one of the pathognomonic symptoms and frequently leads to asphyxiation. Myoclonus is observed less commonly [7, 10]. In recent years, cases of MSA presenting with cognitive impairment, dementia, and even rare familial forms have been increasingly described. These clinical phenotypes complicate early diagnosis and differentiation from other proteinopathies. The primary manifestations of autonomic dysfunction include orthostatic hypotension and urological disturbances, such as urinary retention (74%) and urge incontinence (63%); notably, bladder symptoms may serve as early and frequent indicators of the disease [18, 19, 20].

According to the Movement Disorder Society (MDS) criteria (2022), four levels of diagnostic certainty for MSA are defined (see Table 1): neuropathologically established MSA, clinically established MSA, clinically probable MSA, and clinically possible prodromal MSA [23]. A diagnosis of neuropathologically established MSA requires autopsy findings of widespread and abundant α-synuclein-positive glial cytoplasmic inclusions (GCIs) within the central nervous system (CNS), associated with neurodegenerative changes in the strionigral or olivopontocerebellar structures [23]. The 'possible prodromal MSA' category remains under investigation; future research into diagnostic biomarkers is expected to expand the criteria for this diagnosis.

Magnetic resonance imaging (MRI) findings play a crucial role in the diagnosis of multiple system atrophy and are incorporated into the updated MDS-2022 criteria, which classify MRI markers as mandatory components for diagnostic confirmation. In the cerebellar subtype (MSA-C), typical features include atrophy of the cerebellum and pons, as well as thinning and T2-weighted hyperintensity of the middle cerebellar peduncles. A characteristic 'hot cross bun sign' is observed in the pons, resulting from the degeneration of transverse pontocerebellar fibers. In the parkinsonian subtype (MSA-P), typical findings include putaminal atrophy and T2-weighted hypointensity in the posterolateral putamen, occasionally accompanied by the formation of a 'putaminal rim' sign (marginal hypointensity). Additional features include atrophy of the midbrain and medulla oblongata, as well as dilatation of the fourth ventricle. In some patients, a combination of MSA-P and MSA-C features is observed, reflecting a mixed phenotype [24].

Table 1. International Parkinson and Movement Disorder Society (MDS) Criteria for Multiple System Atrophy (MSA), October 2024: Four levels of diagnostic certainty incorporating clinical features, MRI markers. MSA, multiple system atrophy; PVR, post-voiding residual volume; NA, not applicable.

	Core clinical features	Supportive clinical features*	MRI†
Clinically established MSA	At least ONE of: Autonomic dysfunction • Unexplained urinary voiding difficulties with **PVR >100ml** • Unexplained urinary urge incontinence • Neurogenic OH (>= 20/10mmHg drop) after **3 minutes** standing/head up tilt test + At least ONE of: Poorly L-dopa responsive parkinsonism OR Cerebellar syndrome **(at least 2 of)** • gait ataxia • limb ataxia, • cerebellar dysarthria, or • oculomotor features	>=2	Required
Clinically probable MSA	At least TWO of: Autonomic dysfunction (at least 1 of) • Unexplained urinary voiding difficulties with presence of post void residual • Unexplained urinary urge incontinence • Neurogenic OH (>= 20/10mmHg drop) after **10 minutes** standing/head up tilt test OR Parkinsonism OR Cerebellar syndrome **(at least 1 of)** • gait ataxia • limb ataxia, • cerebellar dysarthria, or • oculomotor features	>=1	Not required

Possible prodromal MSA (Research)	At least ONE of:
	Non-motor criteria (at least 1 of)
	• RBD (on polysomnography)
	• Neurogenic OH (>= 20/10 mmHg drop) after **10 minutes** standing/head up tilt test
	• Urogenital failure
	  • ED in males <60yo AND
	  • Unexplained voiding difficulties with PVR>100ml OR unexplained urinary urge incontinence
	+
	At least ONE of:
	Subtle Parkinsonism
	OR
	Subtle cerebellar signs
		NA	NA

Essential features			
Sporadic, progressive, adult onset (>30y)			

Neuropsychological aspects of MSA

According to current literature, up to 70% of patients with MSA exhibit various forms and degrees of behavioral changes. Affective disorders - including anxiety, depression, and apathy - are common and associated with reduced life satisfaction and impaired functional status. The severity of these symptoms varies across MSA phenotypes and may be more pronounced in the parkinsonian variant (MSA-P) [29, 30].

Cognitive impairment in MSA often follows a frontal-subcortical pattern (affecting executive functions, attention, and psychomotor speed) and may remain "occult" despite normal scores on the Mini-Mental State Examination (MMSE). For their detection, more sensitive tools, such as the Montreal Cognitive Assessment (MoCA) and comprehensive neuropsychological testing, are preferred [31]. Mild anxiety has been reported in 46.8% of MSA patients, while moderate-to-severe forms affect 24.9%.

Sleep disturbances, particularly rapid eye movement (REM) sleep behavior disorder (RBD), are among the most frequent non-motor manifestations in the early stages and are associated with more rapid disease progression and deterioration of activities of daily living [32].

Apathy and depression in MSA are linked to cortical atrophy in the frontotemporal regions, atrophy of subcortical structures, and involvement of pathways connecting the prefrontal cortex with the limbic system [30]. Gray matter atrophy in the fronto-cingulate cortex and white matter atrophy in frontostriatal regions disrupt the cortico-striato-thalamo-limbic circuits, leading to anxiety and other affective symptoms.

Diagnostic biomarkers for MSA

Several investigated biomarkers, including α-synuclein, neurofilament light chain (NfL), and total tau protein, have demonstrated potential value; however, they are not utilized in routine clinical practice due to their limited availability. A recent study has shown that phosphorylated α-synuclein (p-syn) in erythrocytes is a potential diagnostic biomarker for MSA [25]. Skin biopsy for α-synuclein detection [26] and skin α-synuclein seeding aggregation assays [27] have also shown potential as diagnostic biomarkers for MSA.

To detect pathological α-synuclein in the cerebrospinal fluid (CSF) with high sensitivity and specificity, seeding aggregation assays have been developed, including Protein Misfolding Cyclic Amplification (PMCA) and Real-Time Quaking-Induced Conversion (RT-QuIC) [28]. The diversity of clinical and pathological presentations of MSA significantly complicates an accurate and reliable diagnosis. Therefore, there is a critical need to establish more sensitive and specific measurement methods to facilitate the differentiation of MSA from mimicking disorders and to prevent diagnostic errors.

UMSARS

To assess the severity and progression of multiple system atrophy (MSA), the Unified Multiple System Atrophy Rating Scale (UMSARS) was developed approximately twenty years ago. It comprises four parts: functional disability (UMSARS-I), motor examination (UMSARS-II), orthostatic hypotension (UMSARS-III), and global disability (UMSARS-IV) [33, 34]. Despite its widespread clinical application, the scale's sensitivity and specificity for the early diagnosis of MSA remain limited.

According to prospective cohort studies, the combined sensitivity of UMSARS-I and II for detecting disease progression within the first two years ranges from 73% to 82%, while the specificity for differentiating MSA from Parkinson's disease and other atypical parkinsonian syndromes does not exceed 65–70% [34]. Specific items within the scale (speech, swallowing, gait, and posture) demonstrate higher sensitivity - up to 85% - positioning them as key indicators of early deterioration [35].

To improve diagnostic accuracy, a modified version, the mUMSARS-23, was proposed, which has shown a sensitivity of up to 88% and a specificity of approximately 72% in multicenter studies [36].

In conclusion, while the UMSARS remains an essential tool for monitoring MSA dynamics, its diagnostic value is significantly enhanced when combined with MRI markers and diagnostic biomarkers, such as α-synuclein.

Therapeutic strategies and future perspectives

To date, no disease-modifying therapy for MSA is available. In approximately 30% of cases, a transient and modest response to levodopa is observed. However, while dopaminergic agents may exacerbate orthostatic hypotension and intensify dystonic symptoms, their complete withdrawal is often discouraged [18]. Dystonic phenomena, such as anterocollis, torticollis, focal dystonia, and orofacial dyskinesia, are frequently aggravated by levodopa therapy.

Current research is focused on developing disease-modifying therapies. Particular attention is being paid to antisense oligonucleotides (ASOs); in Parkinson's disease models, α-synuclein-specific ASOs have demonstrated the ability to reversibly modulate pathological processes [37]. Currently, a Phase I clinical trial (NCT04165486) is underway to evaluate the safety and tolerability of ION464, an intrathecally administered ASO targeting α-synuclein in patients with MSA [38, 39].

Furthermore, recent studies have highlighted significant activation of the NLRP3 inflammasome in MSA and its correlation with neurodegeneration. This discovery suggests potential for targeted therapies aimed at suppressing the excessive inflammatory response [40]. Despite numerous clinical trials exploring various approaches, the efficacy of any single strategy in MSA has yet to be convincingly established (see Table 2).

Table 2. Ongoing and recent clinical trials for disease-modifying therapies in Multiple System Atrophy (MSA). ASO, antisense oligonucleotide; GLP-1, glucagon-like peptide-1; MSA-P, MSA-parkinsonian type; MSA-C, MSA-cerebellar type.

Agent / Intervention	Target / Mechanism	Phase	ClinicalTrial.gov ID	Status / Notes
ION464 (BIIB101)	α-synuclein (ASO)	I	NCT04165486	Evaluating safety of intrathecal ASO *was discontinued in early 2025
Lu AF82422	α-synuclein (Monoclonal antibody)	II	NCT05102214	AMULET study; targeting extracellular α-syn
Pridopidine	Sigma-1 receptor agonist	II	NCT04412733	Neuroprotective potential in MSA-P and MSA-C
Exenatide	GLP-1 receptor agonist	II	NCT04431713	Investigating metabolic and neuroprotective effects
Ambroxol	Glucocerebrosidase (GCase) activity	II	NCT04821817	Improving lysosomal function
ABBV-0805	α-synuclein (Monoclonal antibody)	I	NCT04658186	Focused on aggregated α-synuclein *MSA patients were officially enrolled

Materials and Methods

Patient evaluation and treatment were conducted at the Central Clinical Hospital in Almaty, Kazakhstan. The diagnostic workup included clinical neurological examination, laboratory testing, and instrumental investigations, such as brain MRI, carotid duplex ultrasound (CDU), and bladder ultrasound. Clinical severity and progression were assessed using the UMSARS.

The therapeutic program comprised pharmacological management of parkinsonian symptoms and autonomic dysfunction, as well as non-pharmacological interventions, including physical therapy and massage. Clinical dynamics were monitored throughout a two-week hospitalization period. Written informed consent was obtained from all patients for the publication of their clinical data.

Case report 1 (MSA-P).

Patient M., a 44-year-old male, was admitted for inpatient treatment in October 2024. Upon admission, the patient presented with the following complaints: generalized stiffness and bradykinesia, impaired gait and balance, pronounced fatigue, anxiety, dizziness, episodes of orthostatic weakness, urinary incontinence, and nocturnal awakenings.

Medical history: The initial symptoms, characterized by episodes of dizziness and significant fatigue, emerged approximately two years ago. Over the following months, the patient noted a gradual decline in exercise tolerance. Approximately seven months prior to admission, motor impairments developed, including muscle rigidity, bradykinesia, micrographia (changes in handwriting), and difficulty performing activities of daily living (ADL).

Gait disturbances progressed steadily, the patient reported frequent stumbling and a persistent sense of instability. Concurrent autonomic dysfunction manifested as nocturia, followed by urinary incontinence. During the last few months, the clinical course showed rapid deterioration: the patient became dependent on caregiver assistance for ambulation, dizziness intensified, and hypersalivation was noted. A trial of levodopa therapy proved ineffective, facilitating the exclusion of Parkinson's disease.

Neurological examination revealed: bradykinesia and hypokinesia, marked plastic rigidity

predominantly affecting the lower extremities, and moderate resting tremor in the upper limbs. The face was symmetric with prominent amimia; the tongue was midline. Muscle tone was increased according to the plastic type ('cogwheel' phenomenon). Pathological pyramidal signs were present, including bilateral Babinski signs and ankle clonus. Coordination testing was performed with difficulty, showing slowness and dysmetria, more pronounced on the right side.

Significant orthostatic hypotension was documented: Supine blood pressure: 120/75 mmHg (right), 125/80 mmHg (left). Standing blood pressure (after 3 minutes): 98/62 mmHg (right), 104/68 mmHg (left), accompanied by mild dizziness. Heart rate: 83 bpm (supine) increasing to 96 bpm (standing at 3 minutes). Respiratory rate: 17 breaths per minute. All maneuvers were performed with the assistance of medical staff. The patient reported difficulties with eating due to stiffness, decreased appetite, and persistent constipation. All laboratory findings were within normal limits.

Upon admission, the UMSARS scores were as follows: UMSARS Part I (historical): 20 points; UMSARS Part II (motor examination): 45 points; UMSARS Part III (Autonomic assessment): 22 mmHg decrease in systolic blood pressure and 13 mmHg decrease in diastolic blood pressure after 3 minutes in the orthostatic position, accompanied by dizziness. UMSARS Part IV (Global disability scale): 5 points.

Diagnostic workup: Carotid and vertebral artery duplex ultrasonography (October 2024): Evidence of carotid atherosclerosis and signs of cerebral venous dyscirculatory changes. Bladder ultrasound with Post-void residual (PVR) volume (October 2024): No significant structural abnormalities were identified. The PVR volume was measured at 135 mL.

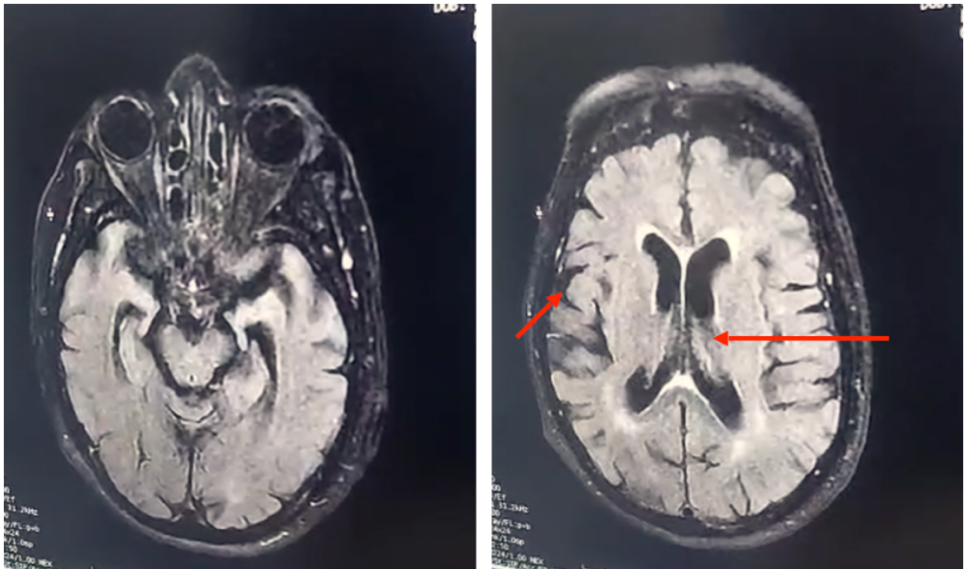

Figure 1. MRI study of the brain, performed in the axial plane in T1-weighted imaging (T1WI) mode. The presented MRI tomograms of the brain show moderate signs of cerebral atrophy. This is evidenced by a slight widening of the cortical sulci and convexal subarachnoid spaces, as well as a moderate, symmetrical enlargement of the lateral ventricles. Atrophy of the putamen: a decrease in the volume of the putamen is observed.

Neuropsychiatric and cognitive aspects: In addition to motor and autonomic manifestations, the patient exhibited irritability, anxiety, and episodes of aggression.

Clinical diagnosis: Clinically probable Multiple System Atrophy (parkinsonian phenotype: MSA-P), characterized by rapid progression within the first year of disease onset.

Management: From the first day of hospitalization, levodopa/carbidopa (250 mg/25 mg) was reintroduced at a dosage of 1/2 tablet four times daily, supplemented with B-complex vitamins. To manage constipation, probiotics and antispasmodics were prescribed. For urinary incontinence, an M-cholinoceptor antagonist (solifenacin, 5 mg) was initiated; urinary catheterization was not performed. Orthostatic hypotension was managed with a conservative starting dose of the alpha-adrenomimetic agent midodrine (2.5 mg once daily, administered in the morning). This cautious dosing strategy was selected to minimize the risk of nocturnal supine hypertension, a common complication in patients with autonomic failure. Further titration was planned based on the patient's clinical tolerance and blood pressure response. Physical therapy was also commenced, including supervised therapeutic exercise (kinesitherapy) and massage of the limbs and back.

Clinical progress (Day 10): By the 10th day of hospitalization, a reduction in rigidity and hypersalivation was observed, along with improved appetite. The patient achieved the ability to sit without

support; however, standing and ambulation still required significant assistance. No dizziness was reported. The gait remained unsteady with a shortened step length (shuffling gait).

Orthostatic challenge results: Supine blood pressure: 123/80 mmHg (right arm), 125/80 mmHg (left arm). Standing blood pressure (at 3 minutes): 107/70 mmHg (right arm), 110/70 mmHg (left arm). Heart rate: 78 bpm (supine), 86 bpm (standing at 3 minutes). The patient remained asymptomatic during the orthostatic test despite the pressure drop.

Follow-up UMSARS assessment: UMSARS-1 (Activities of daily living): 18 points. UMSARS-2 (motor examination): 41 points. UMSARS-3 (autonomic assessment): A decrease in systolic blood pressure of 16 mmHg and diastolic blood pressure of 10 mmHg after 3 minutes of standing (asymptomatic). UMSARS-4 (Global disability scale): Grade 5.

Case report 2 (MSA-C).

Patient K., a 56-year-old female, was admitted for inpatient treatment in July 2024. Upon admission, the patient reported gait instability, frequent falls, difficulty maintaining a standing position, postural instability during turns, dizziness, and dysarthria. Additionally, she noted involuntary muscle twitching in the limbs, sleep disturbances, low mood, and apathy. According to the patient's history, previous treatment with sertraline resulted in mood stabilization and a reduction in the frequency of aggressive outbursts.

Medical history: The patient is a former teacher. The onset of the disease occurred approximately three years ago, characterized by the gradual development of postural instability and gait disturbances. Over the past year, she has experienced rapid symptomatic progression, including worsening balance, pronounced dysarthria, and occasional dysphagia (choking on liquids). In recent months, symptoms of autonomic dysfunction have emerged, including orthostatic hypotension, diaphoresis (excessive sweating), and urinary urgency.

Clinical status upon admission: Ambulation was impossible without assistance, and the weight-bearing function of the limbs was significantly impaired. Autonomic assessment: Supine blood pressure: 130/80 mmHg. Standing blood pressure: 100/65 mmHg (demonstrating significant orthostatic hypotension). Cognitive screening: MMSE: 28/30 points (indicating preserved cognitive function).

Neurological examination: Speech was characterized by bradyphrenia, slurring, and dysarthria. Marked ataxia was observed during finger-to-nose and heel-to-shin testing, accompanied by intention tremor. Muscle tone was decreased (hypotonia); dysmetria and dysrhythmia were present. No pathological pyramidal signs were elicited. Dysphagia was noted, with reported episodes of liquid aspiration. Neuropsychiatric features: The patient exhibited emotional lability (tearfulness), anxiety, irritability, and episodes of fear.

Baseline assessment (on admission): UMSARS-1 (Activities of daily living): 18 points. UMSARS-2 (motor examination): 42 points. UMSARS-3 (Autonomic assessment): Orthostatic challenge at 3 minutes revealed a systolic blood pressure drop of 30 mmHg and a diastolic blood pressure drop of 15 mmHg, associated with symptomatic dizziness. UMSARS-4 (Global disability scale): Grade 4.

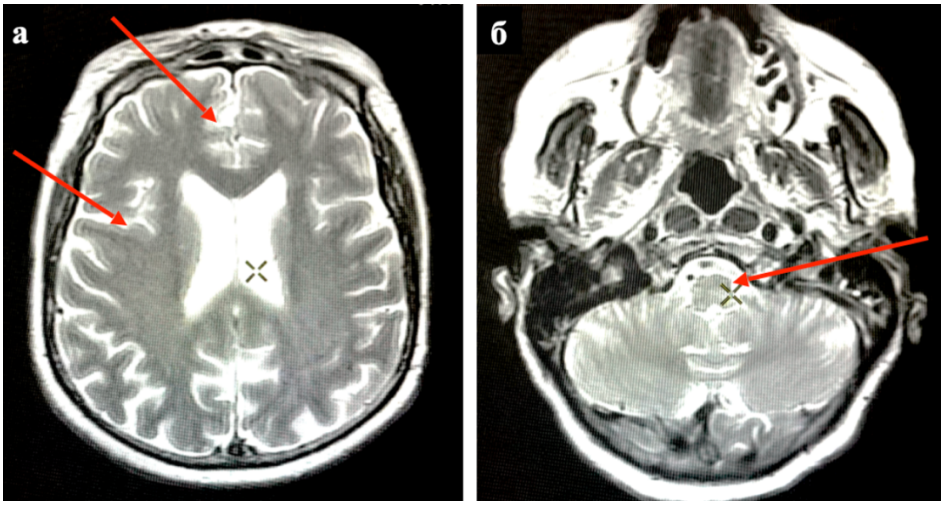

Figure 2. Brain MRI scan in the axial plane using T2-weighted imaging (T2WI). The presented brain MR tomograms show marked atrophy of a number of structures: a) Atrophy of the cerebral cortex, widening of the subarachnoid spaces; b) Atrophy of the pons: there is marked pontine atrophy, which leads to the formation of the characteristic "hot cross bun sign" - a hyperechogenic (bright) signal in the shape of a cross against the background of atrophied fibers. This sign is due to the degeneration of transverse pontine fibers and tracts, which is a pathognomonic sign.

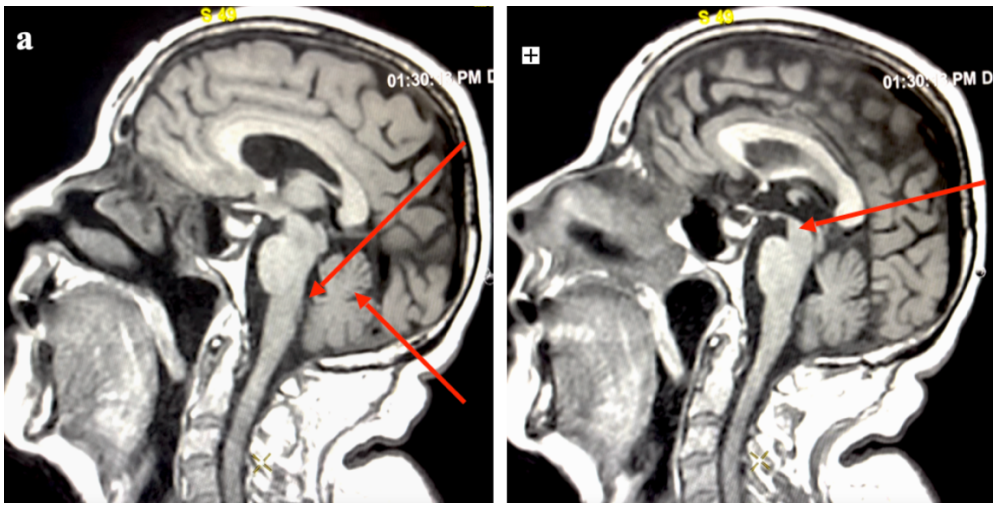

Figure 3. MRI scan of the brain performed in the sagittal plane in T1-weighted images (T1WI) mode. The presented brain MRIs show atrophy of several structures: a) Cerebellar atrophy: significant atrophy of the cerebellum is visualized, especially its hemispheres and vermis; atrophy of the middle cerebellar peduncles: thinning and atrophy of the middle cerebellar peduncles, which connect the cerebellum to the pons, is noted; b) Moderate atrophy of the midbrain.

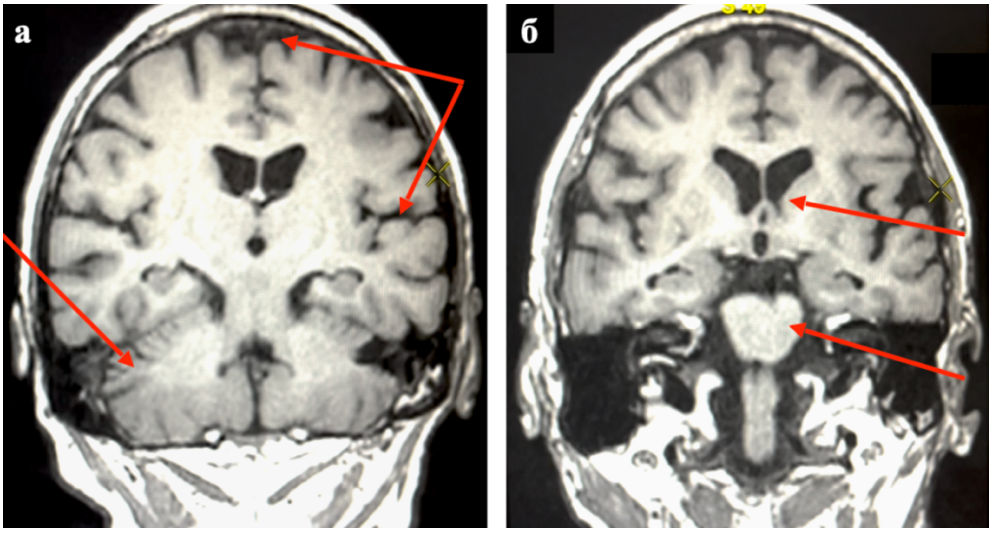

Figure 4. MRI study of the brain, performed in the frontal projection in T1-weighted imaging (T1WI) mode. The presented MRI tomograms of the brain show atrophy of several structures: a) Atrophy of the cerebral cortex, expansion of subarachnoid spaces, and moderate atrophy of the cerebellum; b) Atrophy of the putamen: a decrease in the volume of the putamen is observed, and Atrophy of the pons: a decrease in the volume of the pons is observed.

Diagnostic workup: Carotid and vertebral artery doppler ultrasound (07/2024): Evidence of atherosclerosis; reduced blood flow velocity in the vertebral arteries. Bladder Ultrasound (07/2024): Post-void residual volume (PVR) of 80 mL.

Clinical diagnosis: Clinically probable Multiple System Atrophy, cerebellar phenotype (MSA-C). The clinical presentation is dominated by cerebellar syndrome, including dysarthria and ataxia, in association with orthostatic hypotension and urogenital dysfunction.

Management: From the first day of hospitalization, pharmacological therapy was initiated with levodopa/carbidopa(250 mg/25 mg) at a dosage of 1/2 tablet three times daily, supplemented with B-complex vitamins. To address urinary incontinence, an M-cholinoceptor antagonist (solifenacin, 5 mg) was prescribed; urinary catheterization was not indicated. For sleep disturbances, melatonin (3 mg) was administered at bedtime. Orthostatic dysfunction was managed with a conservative dose of the alpha-adrenomimetic midodrine (2.5 mg once daily). Non-pharmacological interventions included supervised physical therapy (kinesitherapy) and massage of the limbs and back.

Clinical progress (Day 10): By the 10th day, partial improvement in sleep quality, reduction in anxiety, and stabilization of appetite were observed. While rigidity and bradykinesia persisted, the patient was able to ambulate within the ward with assistance.

Autonomic assessment: Supine blood pressure: 128/80 mmHg (right arm), 125/80 mmHg (left arm). Standing blood pressure (at 3 minutes): 115/75 mmHg (right arm), 110/70 mmHg (left arm). Heart rate: 80 bpm (supine), 86 bpm (standing at 3 minutes). The patient remained asymptomatic, reporting no dizziness during the orthostatic test.

Follow-up UMSARS assessment: UMSARS-1 (Activities of daily living): 16 points. UMSARS-2 (motor examination): 38 points. UMSARS-3 (Autonomic assessment): A decrease in systolic blood pressure of 12 mmHg and diastolic blood pressure of 10 mmHg after 3 minutes of standing (asymptomatic). UMSARS-4 (Global disability scale): Grade 4.

Case report 3 (MSA - mixed phenotype).

Patient J., 61-year-old male. Admitted in November 2024. Chief complaints on admission: Severe rigidity and bradykinesia, gait instability, frequent falls, anxiety, urinary urgency, nocturnal enuresis, diaphoresis (excessive sweating), sleep disturbances, hoarseness, and episodes of laryngeal stridor.

Medical history: The disease manifested approximately three years ago with the gradual onset of bradykinesia and muscular rigidity. Subsequently, cerebellar symptoms (gait ataxia, postural instability) and lower urinary tract symptoms emerged. Over the past year, the patient reported significant progression of symptoms, including the development of respiratory disorders (stridor) and nocturnal apnea. Previous levodopa therapy was administered with no clinical improvement noted. Clinical status on admission: The patient was unable to ambulate and was wheelchair-dependent.

Orthostatic hypotension was confirmed: Supine blood pressure was 125/80 mmHg; standing blood pressure after 3 minutes was 97/60 mmHg. Heart rate was 96 bpm (supine) and 118 bpm (standing at 3 minutes). The patient reported dizziness during the orthostatic challenge (all maneuvers were performed with medical assistance). Urinary incontinence and episodes of enuresis were present.

Neuropsychiatric and cognitive status: The patient appeared emotionally exhausted, reporting feelings of hopelessness, low mood (depressive symptoms), and apathy. The MMSE score was 28/30. Interaction with family members resulted in transient mood improvement, though no sustained clinical effect was observed.

Neurological examination: The patient presented with pronounced akinetic-rigid syndrome, characterized by the 'cogwheel' phenomenon, amimia, and monotonous speech. Significant dysarthria was noted. Limb incoordination and intention tremor were present, with greater severity observed in the upper extremities. Pathological reflexes were elicited, including bilateral Babinski signs.

At the time of admission, the UMSARS scores were as follows: UMSARS-1 (Activities of daily living): 24 points. UMSARS-2 (motor examination): 48 points. UMSARS-3 (Autonomic assessment): Orthostatic challenge at 3 minutes revealed a systolic blood pressure drop of 28 mmHg and a diastolic blood pressure drop of 20 mmHg, accompanied by symptomatic dizziness. UMSARS-4 (Global disability scale): Grade 5.

Diagnostic workup: Chest CT (November 2024): Signs of chronic bronchitis. Bladder Ultrasound (November 2024): Post-void residual volume (PVR) of 160 mL.

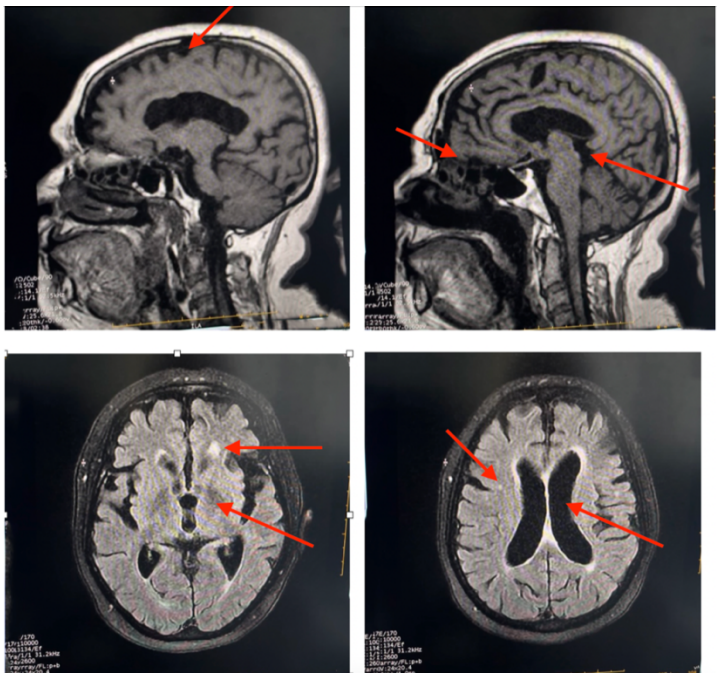

Figure 5. Brain MRI study performed in T1-weighted imaging (sagittal views, top row) and FLAIR (axial views, bottom row) sequences. The presented MR images (top row) reveal signs of atrophy: widening of the subarachnoid spaces (spaces between the brain and skull) and brain ventricles is observed, which may indicate signs of brain atrophy, specifically cortical and/or subcortical atrophy. MR images (bottom row) show multiple foci of increased MR signal in the white matter of both hemispheres, predominantly periventricularly and subcortically. Moderate signs of brain substance atrophy. Atrophy of the putamen: a decrease in the volume of the putamen is observed.

Management: From the first day of hospitalization, levodopa/carbidopa (250 mg/25 mg) was initiated at a dose of 1/2 tablet three times daily. However, the therapy was discontinued after 10 days due to a lack of clinical response. To manage tachycardia and control the heart rate, bisoprolol (2.5 mg) was prescribed. For urinary incontinence, an M-cholinoceptor antagonist (solifenacin, 5 mg) was administered; urinary catheterization was not performed. Orthostatic dysfunction was addressed with a conservative dose of the alpha-adrenomimetic agent midodrine (2.5 mg once daily). Physiotherapy was also initiated, including supervised therapeutic exercise (kinesitherapy) and massage of the limbs and back.

Due to the concurrent management of tachycardia with bisoprolol and orthostatic hypotension with midodrine, blood pressure and heart rate were monitored daily in both supine and standing positions. This dual approach allowed for effective heart rate stabilization without aggravating the orthostatic drop. The dosage of bisoprolol (2.5 mg) was carefully selected to avoid blunting the compensatory pressor response required during orthostatic transitions.

Clinical diagnosis: Clinically probable Multiple System Atrophy (MSA mixed phenotype). The clinical presentation is characterized by a combination of parkinsonian and cerebellar syndromes, alongside severe autonomic dysfunction and respiratory disturbances (stridor).

Clinical progress (Day 10): By the 10th day of hospitalization, the patient reported a reduction in the severity of orthostatic dizziness and improved urinary control (fewer episodes of incontinence). However, significant impairments in standing and ambulation persisted, with the patient requiring the assistance of two people for mobility. The frequency of stridor and nocturnal apnea episodes decreased during the hospital stay.

Autonomic assessment: Supine blood pressure: 120/80 mmHg (right arm), 122/80 mmHg (left arm). Standing blood pressure (at 3 minutes): 110/75 mmHg (right arm), 110/70 mmHg (left arm). Heart Rate: 82 bpm (supine), 86 bpm (standing at 3 minutes). The patient remained asymptomatic during the orthostatic test.

Follow-up UMSARS assessment: UMSARS-1 (Activities of daily living): 22 points. UMSARS-2 (motor examination): 44 points. UMSARS-3 (Autonomic assessment): A decrease in systolic blood pressure of 12 mmHg and diastolic blood pressure of 10 mmHg after 3 minutes of standing (asymptomatic). UMSARS-4 (Global disability scale): Grade 4.

Results and Discussion

The clinical cases reported in this study meet the criteria for 'clinically probable MSA' as defined by the MDS-2022 diagnostic framework. These observations highlight the characteristic complexities inherent in the diagnosis and clinical management of MSA. In all three cases, alternative diagnoses (e.g., Parkinson's disease, primary urological disorders) were initially considered during the early stages, leading to a delayed confirmation of MSA. Early signs of autonomic failure - including orthostatic hypotension, urinary incontinence, and diaphoresis - were common across all patients but were frequently overlooked or misinterpreted as secondary complications. According to the literature, early and severe autonomic dysfunction (dysautonomia) serves as a predictor for a more aggressive disease course [40]. Furthermore, the UMSARS scores objectively reflect the severity of the patients' condition and the extent of their motor and autonomic impairments.

The patients demonstrated a suboptimal response to the levodopa challenge, characterized by the persistence of bradykinesia, hypokinesia, and moderate rigidity. While curative interventions remain unavailable, a multidisciplinary strategy—integrating titrated dopaminergic therapy, low-dose alpha-adrenomimetics for orthostatic hypotension, and intensive physical rehabilitation—may facilitate transient enhancements in functional mobility and quality of life. Notably, the clinical stabilization achieved in Case 3 through a midodrine-bisoprolol regimen underscores the efficacy of targeted symptomatic management in mitigating the burden of the disease despite its irreversible progression.

Neuroimaging data not only support the clinical diagnosis but also facilitate phenotypic classification, which carries significant prognostic and differential diagnostic value. Several pathognomonic radiological markers were verified in these patients: the "hot cross bun" sign, as well as pronounced atrophy of the cerebellum, putamen, and middle cerebellar peduncles. These findings are consistent with the neuroimaging requirements for "clinically probable MSA" according to the MDS-2022 criteria. The absence of specific markers in Case 1 initially (showing only microangiopathy) underscores the necessity of repeated MRI monitoring when MSA is suspected.

Table 3. Comparative clinical and diagnostic profiles of three Multiple System Atrophy (MSA) cases. OH – Orthostatic Hypotension, UMSARS – Unified Multiple System Atrophy Rating Scale, MRI – Magnetic Resonance Imaging.

Feature	Case 1 (MSA-P)	Case 2 (MSA-C)	Case 3 (MSA-Mixed)
Age / Sex	44, Male	56, Female	61, Male
Initial symptoms	Rigidity, tremor	Gait instability, ataxia	Bradykinesia, rigidity
Core manifestations	Parkinsonism, levodopa resistance	Cerebellar ataxia, dysarthria, dysphagia	Combined parkinsonism and cerebellar ataxia
Autonomic dysfunction	OH, urinary incontinence	OH, urogenital dysfunction	OH, nocturnal incontinence, diaphoresis
Additional Features	Distal tremor (feet/hands), back pain	Frequent falls, food aspiration	Stridor, nocturnal apnea
Neuroimaging (MRI)	Microangiopathy, encephalopathy	Cerebellar atrophy, "hot cross bun" sign (pontine streaks)	Brainstem, cerebellar, and basal ganglia atrophy
Total UMSARS Score	~90	~85	~95
Disease Progression	Rapid (1 year to severe disability)	Rapid (2 years to severe ataxia)	Aggressive (3 years to severe disability and respiratory failure)
Clinical Subtype	MSA-P	MSA-C	MSA-Mixed
Response to Therapy	Poor response to levodopa	No response to symptomatic treatment	Partial autonomic stabilization with midodrine

Recent longitudinal studies provide precise quantification of annual clinical deterioration. The mean rate of disease progression, as measured by the Unified Multiple System Atrophy Rating Scale (UMSARS) Parts I and II, ranges from 10.9 to 12.0 points per annum. Furthermore, there is a noted increase in

early-onset cases (debut before age 50), which now account for 5–7% of all instances. These cases are frequently characterized by a more protracted disease course but exhibit more severe autonomic failure [41].

Geographic phenotypic variability between MSA-P and MSA-C remains distinct: in Asian populations (notably Japan and South Korea), the cerebellar phenotype (MSA-C) continues to predominate, accounting for approximately 65–70% of cases. Conversely, the parkinsonian phenotype (MSA-P) is more prevalent in Europe and North America, representing 60–65% of the patient population. However, in admixed populations, such as those in Central Asia, an increasing incidence of "mixed" clinical forms is observed during the early stages of the disease [42].

As of 2025, epidemiological assessments of MSA have become inextricably linked to plasma neurofilament light chain (NfL) concentrations. A plasma NfL threshold exceeding 33.7–35.0 pg/mL serves as an independent predictor of high mortality within a 24-month period (HR 2.4). Patients with NfL levels below this cutoff exhibit a median survival duration that is 2.1 years longer than those with elevated baseline concentrations [43].

Patients with MSA also suffer from a range of non-motor symptoms, including cognitive impairment, depression, anxiety, sleep disturbances, and inspiratory stridor. In the presented clinical cases, no significant cognitive deficits were recorded (MMSE score of 28/30). However, distinct disturbances in the emotional and volitional spheres were observed, manifesting as heightened anxiety, irritability, and episodic outbursts of aggression. These symptoms were transient in nature and did not necessitate specific pharmacological or psychotherapeutic interventions.

For clinical practice, the following recommendations are proposed for the management of MSA patients: Supplement routine cognitive screening with more sensitive instruments, such as the MoCA. Utilize validated scales for the assessment of anxiety, depression, and apathy. Conduct targeted screening for sleep disorders and nocturnal stridor. The results of these assessments should be integrated into the planning of neurorehabilitation programs, family psychoeducation, and personalized symptomatic therapy.

Diagnostics were performed using standard modalities, including brain MRI and the UMSARS. However, certain innovative diagnostic approaches were not utilized, such as DaT-SPECT, PET imaging with α-synuclein ligands, skin biopsy for the detection of pathological α-synuclein deposits, and diffusion tensor imaging (DTI) with tractography. These methods have recently demonstrated high sensitivity in the differential diagnosis between MSA and Parkinson's disease.

Given the orphan nature of MSA, the practical feasibility and cost-effectiveness of implementing advanced diagnostic modalities - such as high-sensitivity plasma Neurofilament Light chain (NfL) or other diagnostic approaches - warrant distinct evaluation within the Central Asian healthcare context. Although the establishment of a centralized laboratory model necessitates substantial initial capital expenditure, this investment must be weighed against long-term regional healthcare expenditures. The clinical utility of such diagnostics lies in the optimization of high-cost resource allocation for palliative care and neurorehabilitation. By facilitating early and accurate differential diagnosis, these tools potentially mitigate the economic burden associated with protracted 'diagnostic odysseys' and the administration of ineffective therapeutic interventions.

Therapeutic management relied primarily on symptomatic correction, including levodopa and agents targeting orthostatic hypotension and urinary dysfunction. Notably, the adverse effects of commonly prescribed medications - such as orthostatic crises secondary to levodopa, cognitive impairment associated with anticholinergic agents, and supine hypertension during midodrine therapy - are of significant clinical interest. These complications substantially impact the patients' quality of life and necessitate a highly personalized approach to treatment.

The analysis of these three clinical cases underscores the necessity for early recognition of combined motor and autonomic symptoms, which should prompt clinicians to maintain a high index of suspicion for MSA. Timely differential diagnosis is critical to avoid the inappropriate prescription of high-dose levodopa and ensures the implementation of a more accurate and evidence-based management strategy.

Conclusion

Evaluation for MSA is recommended for all adult patients presenting with the following clinical features: parkinsonism or ataxia; autonomic dysfunction; atypical tremor with a myoclonic component; mixed dysphonia characterized by hypophonia, cerebellar dysarthria, and spasticity; and REM sleep behavior disorder (RBD). New diagnostic criteria for MSA and α-synuclein-based biomarkers,

aimed at enhancing diagnostic precision, are currently under development.

In the management of MSA, it is critical to recognize that the adverse effects of levodopa in these patients are generally more pronounced, complex, and less predictable than in those with idiopathic Parkinson's disease. Consequently, from a clinical perspective, symptomatic management combined with intensive physiotherapy and kinesiotherapy remains the most effective strategy for improving patient outcomes. As our understanding of the molecular mechanisms underlying MSA evolves and biomarker identification techniques advance, real prospects are emerging for the development of comprehensive, personalized therapeutic approaches - including disease-modifying therapies capable of slowing or halting disease progression.

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