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Video Representation of Dopamine-Responsive Multiple System Atrophy Cerebellar Type

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 61-year-old
Final Diagnosis: Multiple system atrophy cerebellar type
Symptoms: Ataxia • cogwheeling rigidity • polyneuropathy • weakness
Medication: Carbidopa-levodopa
Clinical Procedure: —
Specialty: Neurology

Objective: Unusual or unexpected effect of treatment

Background: Multiple system atrophy cerebellar type (MSA-C) is a subtype of MSA that presents with predominant ataxia along with lesser signs of parkinsonism and autonomic dysfunction. Previous studies have shown benefits from carbidopa/levodopa therapy for the MSA parkinsonian subtype but few studies have focused on the MSA-C subtype. We present a video case of MSA-C that demonstrated significant improvement with carbidopa/levodopa therapy.

Case Report: A right-handed 61-year-old man with a past medical history of chronic microvascular ischemia, mild lower extremity neuropathy, and lumbar and cervical stenosis status after decompression presented with progressive worsening gait changes over several months with acute deterioration before admission. The initial neurological workup demonstrated bilateral cogwheel rigidity; difficulty with movement initiation. including standing up from a seated position; slow saccadic eye movements; masked facies (hypomimia); right ankle clonus; bilateral upper and left lower limb ataxia; and hyperreflexia. A follow-up workup was negative for metabolic, infectious, and paraneoplastic causes, but magnetic resonance imaging demonstrated cerebellar atrophy along with a "hot cross bun sign" suggestive of probable MSA-C according to consensus criteria, and the patient was started on carbidopa-levodopa. He subsequently demonstrated improvement in key motor domains, including his cogwheel rigidity and gait testing, and was discharged shortly thereafter.

Conclusions: Through this case report, we highlight a significant response to L-dopa therapy beyond what is normally expected according to diagnostic criteria for MSA. MSA treatment responsiveness can vary significantly across patients, which warrants additional studies into appropriate treatment choices for patients with Parkinson's disease and MSA.

Keywords: Levodopa • Ataxia • Multiple System Atrophy

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/933995

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Background

Multiple system atrophy cerebellar type (MSA-C) is a subset of MSA that presents with predominant ataxia along with lesser signs of parkinsonism and autonomic dysfunction [1]. Per established consensus criteria developed in 2008, an MSA diagnosis is categorized as definite, probable, or possible [1,2]. The consensus criteria utilize neuropathological findings, clinical signs (autonomic instability, Parkinson traits, cerebellar syndromes), and poor levodopa response as rated per the Movement Disorder Society Unified Parkinson's Disease Rating Scale or the Unified Multiple System Atrophy Rating Scale [1-5]. MSA is further classified by subtype based on the predominance of symptoms at presentation, either parkinsonian or cerebellar (although autonomic symptom predominance is another possibility, it is not officially recognized as a subtype) [1,2]. The predominance can change with serial examinations, and the classification of the MSA subtype may consequently change as well [1,2]. Previous studies have shown benefits from carbidopa/levodopa therapy for the MSA parkinsonian subtype (MSA-P), but few studies have focused on MSA-C. Martin et al [6] conducted a retrospective review of patient clinical history through electronic medical records and found a response rate to carbidopa/levodopa of up to 50%; however, they included data before the differentiation of MSA-P vs MSA-C via the first consensus criteria. Ishida et al [7] conducted a small clinical trial with 9 patients with either MSA-P or MSA-C who were treated with levodopa. Clinical improvement was seen in 4 MSA-P patients and 1 MSA-C patient in this trial. Lin et al [3] reviewed previous studies of MSA, including MSA-C, and found that up to 40% of MSA patients were responsive to carbidopa/levodopa. The apparent benefit seen in MSA-P patients treated with carbidopa/levodopa therapy has been theorized to be due to parkinsonism symptoms being the target of carbidopa/levodopa; these symptoms are more prominent in MSA-P than in MSA-C [1,2]. With the predominance of MSA-P in North America and Europe, more studies have been conducted on MSA-P than MSA-C [3]. The MSA-C subtype is predominant in Japan, but the existing literature of MSA-C therapy with carbidopa/levodopa in that population is limited [6-8]. We present a video case of MSA-C that demonstrated significant improvement with carbidopa/levodopa therapy.

Case Report

A right-handed 61-year-old man presented to the hospital with progressive gait changes that had been slowly worsening over the past several months and had rapidly deteriorated several days preceding his hospitalization. He had been able to use a walker prior to this exacerbation but was forced to transition to a wheelchair. He also noted stiffness and pain bilaterally in his lower extremities along with an inability to perform

Video 1. Pretreatment with carbidopa-levodopa neurological examination.
Rapid Alternating Movement: • Dysdiadochokinesia is noted with coarse and irregular movement, along with double and triple claps on the palmar and dorsal hand surfaces. Stuttering of movements is also seen. **Finger Tap Test:** • The patient attempts to perform finger tapping with his index finger and thumb. • A decreased amplitude of finger tapping on the right in comparison with the left with appreciable asymmetry is noticeable in the video. **Gait and Turn en Bloc Assessment:** • As the video depicts, the patient's gait shows short steppage with a shuffling pattern and it is unstable as he uses a walker to maintain his stability. • His turn en bloc is also unsteady. In the video, the patient keeps his right foot stationary, and without lifting it, he uses the floor to his advantage to slowly shift his feet on the horizontal plane toward the right. He then uses his left foot to make small pivoting movements, taking at least 6 steps to make a full turn. • After a successful turn, he continues with his shuffling pattern of gait with unsteadiness. **Finger-Nose and Past-Pointing Tests:** • The patient is first assessed with his eyes open. With his dominant hand, he has noticeable ataxia when stretching his arm and finger as he attempts to make contact with the examiner's finger. • Upon reaching his target, the patient has dysmetria with overshoot of his finger beyond the examiner's finger on multiple occasions. • His nondominant hand displays evidence of asymmetry with less ataxia on reaching out toward the target in comparison with his dominant hand, but the dysmetria is consistent with significant overshoot and complete miss of the target, especially at 1 min 47 s. • The patient's deficits are apparent, especially when he transitions to the eye closure component of the finger-nose and past-pointing assessment, with multiple attempts at reaching the target with complete miss and overshoot. **Heel-Knee Test:** • As the patient slides his right heel up and down his left shin, he has noticeable side-to-side oscillations representative of a mild degree of cerebellar ataxia. He does not overshoot the knee and does not shoot off his left foot in an uncontrolled manner. • When transitioning to the left heel to shin he has a continuation of side-to-side oscillation but an absence of any overshoot.

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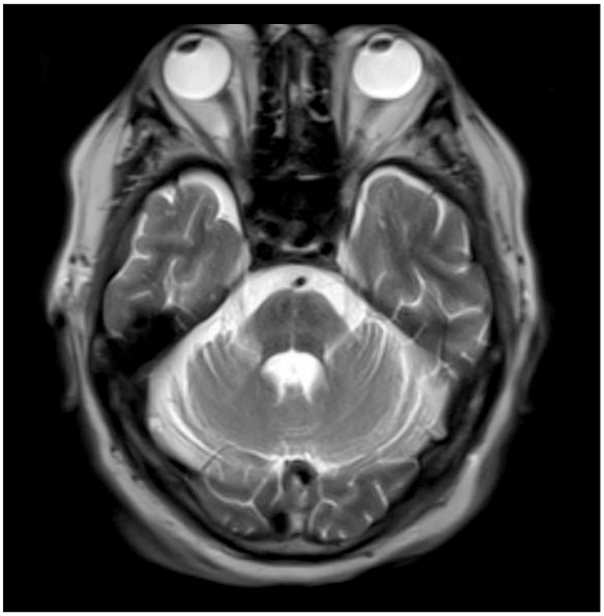

Figure 1. Patient T2 axial brain magnetic resonance imaging with and without contrast showing characteristic "hot cross bun" sign located in the pons.

actions at work. He had previously consulted outpatient neurology at other institutions for his gait instability. Prior electromyography and nerve conduction study revealed mild sensory neuropathy in his lower extremities. Additional prior brain and cervical and lumbar spinal magnetic resonance imaging (MRI) revealed no significant pathologic processes aside from chronic microvascular ischemia and past lumbar and cervical decompression surgeries in 2016 and 2019, respectively.

The patient was evaluated and admitted to the hospital for further workup. His neurologic examination was positive for bilateral cogwheeling rigidity that was more pronounced in the lower extremities, difficulty initiating movement, difficulty standing up from a seated position, slow saccadic eye movements, masked facies (hypomimia), dysarthria, bilateral upper and left lower extremity ataxia, and reflexes 3/4 in the upper extremities bilaterally and left lower extremity, as well as right ankle clonus (**Video 1**). Cervical and lumbar spine MRI was consistent with prior imaging and no neurosurgical intervention was recommended.

Brain MRI showed diminished volume of the cerebellar hemispheres, middle cerebellar peduncles, and inferior pons with the presence of a "hot cross bun sign" (**Figure 1**). Lumbar puncture was performed and was negative for any infectious or paraneoplastic process. Laboratory serum testing was done for copper, angiotensin-converting enzyme, HIV, human T-lymphotropic virus, heavy metals, vitamin B1, and tissue transglutaminase, in addition to the Venereal Disease Research Laboratory test and measurement of Lyme antibody and gliadin antibody. Serum test results were unremarkable.

Video 2. Posttreatment with carbidopa-levodopa neurological examination.
Finger-Nose and Past-Pointing Tests: • Patient undergoes repeat assessment of finger-nose and past-pointing tests after treatment with Sinemet 25-100 CR tablet for 3 days. • A continuation of dysmetria with significant overshoot with his dominant right hand is noticeable, but the ataxia component that was seen pretreatment is reduced. • In his nondominant hand (left), the patient continues to have ataxia when he attempts to reach out toward his target, with dysmetria and overshoot that are more pronounced when the patient transitions to the eye closure component of the examination. • Despite limited improvement in this assessment, the patient has marked improvement in the fluidity of his movements. **Finger Tap Test:** • After treatment with Sinemet, the patient has improved symmetry during the finger tap assessment. • There is also marked improvement in the amplitude of his finger tapping. **Rapid Alternating Movement:** • No significant improvement in the patient's dysdiadochokinesia is noted after Sinemet treatment. He continues to have coarse and irregular movements with a remarkable double clap to triple clap with the palmar and dorsal aspect of his hand. • There is improvement in the speed of his inaccuracies, with less stuttering of movement. **Heel-Knee Test:** • There is no significant improvement in his ataxia after Sinemet treatment. There are still side-to-side oscillations of his heel when he slides his foot up his shin. **Gait and Turn en Bloc Assessment:** • After Sinemet treatment, significant improvement is seen in the patient's gait. • A pronounced reduction is seen in his shuffling, with turn en bloc improving from 6 pivot steps to 2 pivot steps with his left foot.

The patient was presumptively diagnosed with probable MSA-C and started on carbidopa/levodopa-controlled release (CR) 25-100 mg (Sinemet CR), 1 tablet 3 times daily with meals. On the first day of the trial regimen, he reported significant improvement. His gait substantially improved, and he was able to stand from a seated position with minimal assistance and ambulate with a walker prior to discharge (**Video 2**). This improvement was confirmed by the neurology team along with

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Table 1. The possible differential diagnosis with inheritance patterns, characteristic symptoms, and other helpful clinical clues to guide clinical diagnosis.

Disorder	Inheritance	Clinical symptoms	Other clues
Multiple system atrophy type cerebellar (MSA-C)	Sporadic, genetic markers currently under investigation	Dysautonomia, predominately cerebellar ataxia, sometimes accompanied by sleep disorders	Atrophy of pons, putamen, middle cerebellar peduncles, hyperintense T2 signal "hot cross bun sign," poor typically poor levodopa responsiveness compared with Parkinson's disease
Multiple system atrophy type parkinsonian (MSA-P)	Sporadic, genetic markers currently under investigation	Dysautonomia, predominately parkinsonian features, sometimes accompanied by sleep disorders	Atrophy of pons, putamen, middle cerebellar peduncles, hyperintense T2 signal "hot cross bun sign," typically poor levodopa responsiveness compared with Parkinson's disease
Parkinson's disease	Sporadic, autosomal recessive, some gene mutations reported	Tremor, bradykinesia, rigidity, and postural instability, sometimes accompanied by mood and sleep disorders	Autonomic features less severe than MSA-C/P, good levodopa responsiveness
Idiopathic late-onset cerebellar ataxia	Sporadic	Late-onset pure cerebellar ataxia with greater lower extremity impairment	Lack of autonomic features, negative MRI findings, slower progression than MSA-C
Alcohol-induced cerebellar ataxia	Sporadic	Impairment of gait usually first, some patients report upper extremity coordination issues, dysarthria, and intermittent visual symptoms	Patient social history, mild abnormalities in finger to nose testing compared with other cerebellar disorders, absence of cranial nerve disorders, age of onset can be at any age, possible postural tremor, improvement in response to drinking cessation and nutritional supplementation
Autosomal dominant spinocerebellar ataxia	AD	Can vary extensively	Many trinucleotide and gene mutations identified, family history, cerebellar atrophy on brain imaging, nerve conduction deficits
Paraneoplastic cerebellar degeneration	Sporadic	Dizziness, nausea, and vomiting followed by gait impairment and cerebellar signs	Autoantibodies, history of small cell lung cancer (minority of cases), negative MRI, inflammatory changes in CSF
Progressive supranuclear palsy	Sporadic	Supranuclear gaze palsy, progressive axial motor ataxia, pseudobulbar palsy	Truncal ataxia, behavioral issues, sleep difficulties but lack of sleep behavior disturbances
Normal pressure hydrocephalus	Sporadic or secondary with some AD cases reported	Urinary incontinence, wide-based ataxia, and cognitive impairment	Normal CSF opening pressure and lack of increased ICP symptoms, responsive to CSF tap or VP shunt

AD – autosomal dominant; CSF – cerebrospinal fluid; ICP – intracranial pressure; MRI – magnetic resonance imaging; VP – ventriculoperitoneal.

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physical and occupational therapy and physical medicine rehabilitation. The patient was discharged to inpatient rehabilitation on the same carbidopa/levodopa CR regimen, with the addition of carbidopa/levodopa immediate release (IR) 25-100 mg, 0.5 tablet, 2 times daily. The follow-up outpatient visits at 1, 5, and 9 months demonstrated minimally improved bilateral upper extremity and left lower extremity ataxia, but significantly decreased rigidity and bradykinesia. The patient continued use of his walker, and he reported no significant adverse effects from his medication. Carbidopa/levodopa IR 25-100 mg was increased from 0.5 tablet 2 times daily to 1 tablet 3 times daily at the 9-month visit due to decreased efficacy.

Discussion

With this case report we highlight the clinical presentation of MSA-C in video format and illustrate the robust response that treatment with carbidopa/levodopa CR and IR can have in patients with this disorder. Our patient had been undiagnosed for 4 years prior to his presentation, thus confirming the complex diagnostic and clinical suspicion for the disease. Identifying the type of ataxia in an adult commonly poses a unique diagnostic challenge, and there is often a delay in diagnosis, as was the case for our patient. Concurrently, he had a misdiagnosis of alcohol-induced ataxia, even in the absence of consumption. The differential diagnosis considered is shown in **Table 1**.

The consensus criteria for MSA have been used to further characterize patients with suspected MSA as having either definite, probable, or possible MSA depending on the clinical presentation and associated pathological findings [1]. Additional features supporting a diagnosis of MSA were also seen in our patient, including orofacial dystonia, dysarthria, and atrophy of the middle cerebellar peduncle and pontine region along with the "hot cross bun" sign. With a presumptive diagnosis of probable MSA, a trial of carbidopa/levodopa 25-100 mg CR 1 tablet 3 times daily and carbidopa/levodopa 25-100 mg IR 0.5 tablet 2 time daily was done, and it led to improvement in his cogwheeling, dysarthria, gait, and station.

The treatment of MSA is similar to that of sporadic parkinsonism with the use of levodopa, which can control bradykinesia and rigidity in MSA patients [2]. MSA is often clinically differentiated from Parkinson's disease owing to poor and decreased responsiveness to levodopa as determined through evaluation techniques such as clinical motor examinations, the Movement Disorder Society Unified Parkinson's Disease Rating Scale, or the Unified Multiple System Atrophy Rating Scale [4,5]. However, few trials have examined the effectiveness of levodopa therapy in MSA-C patients [6-8]. While bradykinesia and rigidity improved in our patient, he experienced minimal improvement in his ataxia. Although his movements were notably smoother, he was still considered as being ataxic. Several other studies have also demonstrated levodopa responsiveness in MSA patients that exceeds what is normally expected according to diagnostic criteria [2]. Based on the results of prior studies of MSA treatment response, the treatment methods used for patients with Parkinson's disease and those with MSA have diverged without a clear consensus of the benefits/risks of each treatment [2].

Conclusions

The variability in treatment efficacy and adverse effects along with other autonomic complications seen in MSA patients warrants additional studies to determine the most effective treatment modalities for MSA-P and MSA-C patients [2]. Further randomized controlled studies are needed to assess the efficacy of carbidopa/levodopa CR and IR in the treatment of MSA-C patients.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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