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A 46-year-old woman with rigidity and frequent falls

A 46-YEAR-OLD WOMAN presents to the movement disorders clinic for a reevaluation after three neurologists said she probably had Parkinson disease.

Her symptoms started 3 years ago with stiffness in both hands and the gradual onset of an intermittent resting tremor in her right (dominant) hand. Soon after, she started to fall forwards frequently without losing consciousness.

She was treated with amantadine and combined levodopa and carbidopa, which partially improved her symptoms. Although the dosage was gradually increased, she began noticing a tremor in her left hand and her balance worsened. One year after her symptoms began, she began to use a wheelchair because of frequent imbalance and fear of falling.

She now has malaise, generalized muscle aches, a tingling sensation in all her extremities, urinary incontinence, stiffness in both hands, and functional impairment in all activities of daily living.

She has no history of infection, toxin exposure, or use of medications that can cause a parkinsonian syndrome and no family history suggesting a hereditary degenerative disease.

Physical examination and workup

The patient's affect is depressed, and she has difficulty with attention. Neuropsychiatric testing reveals normal intelligence on the Wechsler Memory Scale with a deficit in attention. She also performs poorly on tasks requiring sustained visual attention such as the Stroop test, in which the subject is asked to name the color of words displayed in a list, each word being the name of a different color than its font color.

Cranial nerve examination is normal, except for diminished facial expression.

Extraocular eye movements are normal. When tapped on the forehead, she blinks repeatedly (Myerson sign, a sign of Parkinson disease).

Sensory examination: normal.

Motor examination. The patient has mildly rigid upper extremities (right more than left) and moderate bradykinesia. She reports a resting tremor, but it is not noticeable on examination. Her strength is normal.

Deep tendon reflexes are brisk throughout. When the soles of her feet are stroked, no plantar response can be elicited.

She can touch the examiner's finger and her nose back and forth without difficulty, but the heel-to-shin test (with the patient on her back, she slides her heel up and down along her opposite shin) shows mild ataxia. On the retropulsion or pull test (of her ability to recover from a sudden, backward pull on the shoulders), she shows moderate postural instability.

She can stand without assistance, but her gait is markedly bradykinetic. She cannot walk a straight line heel-to-toe with eyes open.

Magnetic resonance imaging (MRI) of the brain from 1 year ago was normal. Laboratory test results are normal.

Her symptoms began 3 years ago and have progressed rapidly

■ DIAGNOSING A MOVEMENT DISORDER

1 Which of the following is the most likely diagnosis?

- Idiopathic Parkinson disease
- Multiple system atrophy with parkinsonian features
- Multiple system atrophy with cerebellar features
- Progressive supranuclear palsy
- Corticobasal degeneration

Movement disorders are broadly categorized into two groups:

Hyperkinetic syndromes include dystonia (involuntary, sustained muscle contractions causing abnormal postures or twisting), tremor, myoclonus (sudden, brief, jerky involuntary movements of the limbs, face, or trunk), athetosis (slow, writhing movements, usually of the hands), chorea (involuntary, irregular, or purposeless movement of an extremity), and ballismus (jerking, flinging of the limbs).

Hypokinetic syndromes include idiopathic Parkinson disease and other forms of parkinsonism.

- Idiopathic Parkinson disease accounts for about 80% of patients who present with the classic triad of parkinsonism (resting tremor, rigidity, and bradykinesia or akinesia).¹ The remaining 20% are eventually diagnosed with one of the following:
- Parkinson-plus syndromes (multiple system atrophy, with either predominantly parkinsonian or cerebellar symptoms, progressive supranuclear palsy, or corticobasal degeneration)
- Other hereditary degenerative parkinsonian syndromes
- Secondary parkinsonian syndromes.²

Our patient's motor examination shows features of a hyperkinetic syndrome. Her history, medications, and MRI of the brain do not reveal any cause of secondary parkinsonism, and no one in her family has parkinsonian symptoms. This leaves idiopathic Parkinson disease and the Parkinson-plus syndromes.

Idiopathic Parkinson disease

Idiopathic Parkinson disease, initially described in 1817, is characterized by resting tremor, rigidity, and bradykinesia or akinesia. The annual incidence increases with age: from 114 per 100,000 in people age 50 and older, to 304 per 100,000 in those age 80 and older.³ The pathologic hallmarks are degenerated dopaminergic neurons in the pars compacta of the substantia nigra and eosinophilic cytoplasmic inclusions, known as Lewy bodies. More than 90% of patients have a good-to-excellent response to levodopa.

The classic triad of symptoms has drawbacks for diagnosing Parkinson disease. Bradykinesia and rigidity are nonspecific and

can be seen in all forms of parkinsonism. The following combination is more useful^{4,5}:

- Asymmetry of symptoms and signs (especially at the onset)
- Slow progression of bradykinesia/rigidity
- Resting tremor
- Excellent response to dopaminergic medication during the first 3 to 5 years.

On the other hand, the following features make the diagnosis of idiopathic Parkinson disease unlikely⁶:

- Upper motor neuron findings (hyperreflexia, spasticity, and decreased strength)
- Ataxia
- Marked autonomic dysfunction in the first 3 to 5 years
- Supranuclear gaze palsy (a derangement in the neural mechanisms that enable the eyes to move together—other than restricted upward gaze)
- Early onset of prominent postural instability, motor fluctuations, freezing phenomena, and hallucinations unrelated to medications
- Dementia starting before parkinsonian symptoms appear
- Use of agents that block dopamine receptors or deplete presynaptic dopamine within 6 months of onset of parkinsonism
- Poor response to levodopa therapy (1,500 mg/day in 3–4 divided doses).

Our patient probably does not have idiopathic Parkinson disease because she had early onset of postural instability, ataxia, poor response to levodopa, and urinary incontinence.

Multiple system atrophy

Multiple system atrophy is a neurodegenerative parkinsonian syndrome that includes the conditions formerly known as striatonigral degeneration, Shy-Drager syndrome, and olivopontocerebellar atrophy. Multiple system atrophy is characterized by:

- Early onset of autonomic and urinary dysfunction
- Parkinsonism (mostly with poor response to levodopa)
- Cerebellar dysfunction
- Corticospinal tract dysfunction (extensor plantar responses with hyperreflexia).

Symptoms of either parkinsonism or cerebellar ataxia may dominate the clinical pic-

It is crucial to detect potentially reversible causes of parkinsonism

**TABLE 1****Idiopathic Parkinson disease vs Parkinson-plus syndromes**

FEATURE	IDIOPATHIC PARKINSON DISEASE	PROGRESSIVE SUPRANUCLEAR PALSY	CORTICOBASAL DEGENERATION	MULTIPLE SYSTEM ATROPHY
Parkinsonian symptoms	Asymmetric onset	Symmetric	Mostly asymmetric	Symmetric
Early gait impairment	Rare	Early in course	Common in those with leg onset	Occasional
Early impairment of postural reflexes, falls	Rare	Common	Rare, develops commonly later	Occasional
Resting tremor	Common	Uncommon	Rare	Occasional
Response to levodopa	Good	Poor or absent	Poor	Variable
Levodopa-induced dyskinesia	Common	Rare	Rare	Variable
Wearing-off phenomena	Common	Unusual	Unusual	Unusual
Dementia at presentation	Rare	Uncommon, often develops later	Rare, develops later	Rare
Autonomic failure at presentation	Uncommon	Rare	Rare	Occasionally
Cerebellar signs	Rare	Rare	Rare	Uncommon at presentation, develop later

ture. Multiple system atrophy commonly involves difficulty articulating speech, trouble swallowing, frequent falling, and attention deficits. Within a year of disease onset, symptomatic postural hypotension develops in 75% of patients and urinary incontinence in 56%.⁷ In a prospective series, all of the 67 men studied experienced impotence as an early symptom.⁸

Exclusion criteria for diagnosing multiple system atrophy include dementia, vertical gaze palsy, focal cortical dysfunction, and hallucinations unrelated to excess dopaminergic medication.⁹

MRI may show putamen atrophy and a hyperintense putaminal rim. This provides helpful information but is not sufficient to make the diagnosis.¹⁰

Our patient's rapid progression of parkinsonian symptoms with partial response to levodopa suggest Parkinson-plus syndromes. Urinary incontinence and gait ataxia early in the course of the disease make multiple system atrophy the most likely diagnosis. Further, her neurologic examination reveals many features of the parkinsonian-dominating type of multiple system atrophy, ie, postural instability,

autonomic disturbance, symmetric bradykinesia, hypertonia, and ataxia.

Progressive supranuclear palsy

Progressive supranuclear palsy (also known as Steele-Richardson-Olszewski syndrome) is clinically characterized by supranuclear gaze palsy involving downward gaze, neck dystonia, parkinsonism, pseudobulbar palsy, and early gait imbalance with frequent spontaneous falls backward.¹¹ Within a year after disease onset, 68% of patients experience recurrent falls.

Corticobasal degeneration

Corticobasal degeneration typically presents with unilateral parkinsonism, which may partially respond to dopaminergic medications. Patients characteristically have apraxia of the affected limb and cortical sensory loss. Half of patients develop involuntary and often unconscious movements of the affected limb, a condition known as alien limb phenomenon.¹²

Prognosis is poor

Multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration are rapidly progressive, and most patients survive

less than 10 years after symptoms appear.^{8,13,14} Therefore, all other possible conditions should be systematically excluded. In addition, the patient should be examined every 6 months, and imaging studies may need to be repeated after 1 year to manage symptoms and follow the disease progress.

■ DIAGNOSING PARKINSONIAN SYNDROMES

Diagnosing parkinsonian syndromes can be challenging. In one study, the diagnosis of idiopathic Parkinson disease could not be substantiated by autopsy in nearly 24% of cases.¹⁵

Parkinsonian syndromes are differentiated on the basis of a thorough history and clinical examination (TABLE 1). It is crucial to determine if the patient has a potentially treatable condition such as drug-induced parkinsonism or normal-pressure hydrocephalus.

Most degenerative parkinsonian syndromes, both hereditary and nonhereditary, are chronic and gradually progressive. An exception is Wilson disease, an autosomal-recessive disorder of copper metabolism usually seen in young patients. It can be controlled with chelating agents and has an excellent prognosis if detected early.

Laboratory testing

Routine laboratory testing is not indicated but can be useful to help diagnose certain causes of parkinsonism if they are suspected on the basis of clinical factors.

Liver function tests can demonstrate whether extrapyramidal symptoms are associated with hepatic encephalopathy.

Thyroid function tests should be obtained if hypothyroidism is suspected, which can be mistaken for Parkinson disease.

Calcium and phosphorus levels should be obtained if basal ganglia calcification is detected by computed tomography (CT) or MRI.

A 24-hour urine collection for copper and serum ceruloplasmin and an **ophthalmologic slit-lamp examination** should be performed in young parkinsonian patients to rule out Wilson disease.

Imaging studies

CT can reveal normal-pressure hydrocephalus and noncommunicating hydro-

cephalus, which are potentially treatable causes of parkinsonism.

MRI is the most sensitive test to detect vascular causes of parkinsonism, such as Binswanger dementia and multi-infarct dementia. MRI is also highly specific but not very sensitive for detecting advanced Parkinson-plus syndromes. MRI is not recommended routinely for diagnosing idiopathic Parkinson disease, as its positive and negative predictive values are unknown.¹⁶

Single-photon emission CT and positron emission tomography are used mainly in research but can help in complicated cases.

■ TREATING PARKINSONISM

2 Which drugs are used to treat parkinsonism?

- Levodopa
- Combined levodopa and carbidopa
- COMT inhibitors
- Dopamine agonists
- Combined carbidopa, levodopa, and entacapone (Stalevo)
- Amantadine
- Selegiline (Eldepryl)
- Anticholinergic agents

All of the above are used to treat parkinsonism.

Levodopa was first tried in patients with Parkinson disease in 1961.¹⁷ Since then, the mortality rate in idiopathic Parkinson disease has dropped dramatically and the quality of life of patients with idiopathic Parkinson disease and parkinsonism has improved.

Levodopa is still the mainstay of treatment, although long-term side effects such as motor fluctuations and dyskinesia are inevitable.¹⁸

Dyskinesia develops in half of patients with multiple systemic atrophy treated with levodopa, and unlike in patients with Parkinson disease, side effects may develop even if motor function does not improve.^{16,19} The dyskinesia of patients with multiple system atrophy often involves the face and tends to be more dystonic than choreic, as is typical of patients with Parkinson disease.

Combined levodopa and carbidopa was introduced in 1975.¹⁷ Levodopa is decarboxylated to dopamine peripherally, and only 1%

MRI is not routinely used to diagnose idiopathic Parkinson disease



crosses the blood-brain barrier to reach the striatal neurons. Carbidopa inhibits this peripheral decarboxylation, increasing the amount of unmetabolized levodopa that can cross the blood-brain barrier.²⁰

Therapy can start with half a tablet of combined levodopa 25 mg/carbidopa 100 mg twice a day. The dose can be gradually increased by half a tablet every 5 days to 1 tablet three times a day. To increase the dosage further, follow-up visits are needed to evaluate symptoms and side effects.

Carbidopa is usually prescribed in a fixed combination with levodopa. However, if peripheral decarboxylation is inadequately inhibited, patients may develop nausea and vomiting. Additional doses of carbidopa in 25-mg tablets may help in such cases.

Combined levodopa and carbidopa is also available in continuous-release and sustained-release formulations, which may help control motor complications, but may not ultimately prevent them from developing.

COMT inhibitors. Entacapone (Comtan), a catechol-O-methyl transferase (COMT) inhibitor, extends dopaminergic stimulation by maximizing the availability of levodopa to the brain throughout the waking day. It is indicated in patients with “wearing off” symptoms, characterized by a return of parkinsonian symptoms before the next scheduled dose of levodopa. COMT inhibitors may also be prescribed to reduce the risk of levodopa’s long-term side effects.

The other available COMT inhibitor, tolcapone (Tasmar), is restricted by the US Food and Drug Administration (FDA) because of reported deaths from liver toxicity.

Dopamine agonists provide only variable benefits in multiple systemic atrophy.

Bromocriptine is approved as an adjunct to levodopa therapy in idiopathic Parkinson disease and allows the maintenance dosage of levodopa to be reduced. Goetz et al²¹ reported that bromocriptine helped five patients with multiple system atrophy who had previously responded to levodopa.

The newer dopamine agonists, pramipexole (Mirapex) and ropinirole (Requip), are also approved for early monotherapy in idiopathic Parkinson disease, but no large clinical trials have assessed their efficacy in patients

with multiple system atrophy.

Apomorphine (Apokyn), the most potent dopamine agonist, is given parenterally. It was recently approved by the FDA to treat motor fluctuations or “off periods.”²² Apomorphine also improves motor scores by more than 10% in some patients with multiple system atrophy.²³

Combined carbidopa, levodopa, and entacapone was recently introduced. The more-sustained levodopa serum levels permit dosing three to four times a day.

Amantadine was developed as an antiviral medication but is also used to ameliorate levodopa-induced dyskinesia. Amantadine stimulates dopamine release in the central nervous system and may block its reuptake into presynaptic neurons. It also works via anticholinergic activity and antagonism to the N-methyl-D-aspartate receptor.

One study found that amantadine improves initiating and completing movements in patients with multiple system atrophy,²⁴ but a short-term, open-label study failed to confirm this.

Amantadine is contraindicated for patients with congestive heart failure or dementia, and it often causes cognitive disturbances and livedo reticularis.

Selegiline is used as an adjunct to prolong the symptomatic benefit of levodopa in Parkinson disease, but its role in multiple system atrophy is not clear.

Anticholinergic agents are used to treat urinary incontinence in multiple system atrophy.

Treatment recommendations

Although many antiparkinsonian medications are available, most provide only minor or no long-term benefit except to patients with idiopathic Parkinson disease. Despite efforts to establish guidelines, treatment of parkinsonism must be individualized to a patient’s age and disability.

In the early stage, parkinsonian symptoms can be satisfactorily controlled by monotherapy with levodopa-containing formulations. For early multiple system atrophy, selegiline, amantadine, anticholinergics, and dopamine agonists partially help. Which agent is best to use initially depends on a number of factors:

- The diagnosis (eg, idiopathic Parkinson disease vs multiple system atrophy)

Multiple system atrophy has an extremely poor prognosis

TABLE 2

Symptomatic treatment of autonomic failure

Orthostatic hypotension

Nonpharmacologic

- Increase fluid intake
- Increase salt intake
- Smaller, more frequent meals
- Elastic body garment (Ted hose)
- Tilt up head of bed

Pharmacologic

- Midodrine
- Fludrocortisone
- L-threo-3,4-dihydroxyphenylserine
- Ephedrine
- Octreotide
- Erythropoietin
- Indomethacin

Urinary incontinence

Nonpharmacologic

- Intermittent catheterization (neurogenic bladder)

Pharmacologic

- Anticholinergic agents (oxybutynin)

- Comorbidities (eg, cognitive deficits vs depression)
- Predominant symptom (eg, tremor vs gait dysfunction)
- Severity of disabling symptoms relative to a patient's needs (eg, tremor-predominant idiopathic Parkinson disease in a young dentist vs minimal dexterity problems in a retired patient).

There are also no established guidelines for managing the cerebellar ataxia and pyramidal dysfunction in patients with multiple system atrophy. Despite the marked involvement of the striatum, one third of patients with multiple systemic atrophy respond well to levodopa at some stage of the disease, but improvement is rarely sustained for many years.

Patients with suspected multiple system atrophy should undergo a therapeutic trial with antiparkinsonian medications, using a titration regimen similar to that used to treat idiopathic Parkinson disease.

For our patient, the dose of combined carbidopa and levodopa is increased and entacapone is added. Her orthostatic hypotension, gait disturbance, and imbalance should also be managed with appropriate interventions.

Managing autonomic symptoms of multiple system atrophy

TABLE 2 summarizes how autonomic symptoms should be managed.

Orthostatic hypotension can be challenging to treat. Patients with low standing blood pressure but no symptoms may not need medical treatment. Unfortunately, levodopa may exacerbate orthostatic hypotension.

Patients should be advised to sit back down as soon as symptoms occur, usually when rising from a chair. They should avoid drinking alcohol, overeating, straining while urinating or defecating, extreme heat, and medications (including over-the-counter agents) that cause vasodilation.

Pressure stockings and elevating the head of the bed 6 inches may help. Water and sodium intake can be increased if it is not medically contraindicated. Mild orthostasis can be treated with prostaglandin inhibitors like indomethacin.

If simple measures are ineffective, fludrocortisone or midodrine are favored by most experts.²⁵ Midodrine, an alpha-agonist, can be started at 2.5 mg three times a day and increased stepwise. Adverse effects are usually mild, although urinary retention and scalp pruritus occur rarely.

Another promising drug is L-threo-3,4-dihydroxyphenylserine, an epinephrine precursor used in Japan for many years.

Urinary symptoms in multiple system atrophy result from both central and peripheral nervous system abnormalities: combined detrusor hyperreflexia and urethral sphincter weakness, followed by failed detrusor contraction. One study found poor results for both men and women who underwent surgery on the bladder neck or prostate.²²

Peripheral-acting anticholinergic agents, such as oxybutynin, improve incontinence but may eventually cause urinary retention.

Erectile dysfunction has been treated with sildenafil in patients with Parkinson disease and multiple system atrophy.^{26,27} It may exacerbate orthostatic hypotension.

Constipation can be relieved by increasing intraluminal fluid with a macrogol-water solution.

Respiratory problems. Inspiratory stridor may occur in 30% of patients with multiple



system atrophy. It can be improved with continuous positive airway pressure. Vocal cord abductor paralysis is a life-threatening complication and may require tracheostomy. Patients are at risk of nocturnal sudden death.²⁸

More research needed

Further studies are needed to evaluate new drugs and the role of neurosurgical interventions for multiple system atrophy.

Terazosin has been reported to improve parkinsonian symptoms in animal models of multiple system atrophy.²⁹

Although patients with Parkinson disease may benefit from deep brain stimulation, no strong evidence supports neurosurgical intervention for patients with multiple system atrophy. Novel approaches include neurotransplantation and trophic factor delivery.



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