Case 27-2004: A 79-Year-Old Woman with Disturbances in Gait, Cognition, and Autonomic Function

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PRESENTATION OF CASE

A 79-year-old woman was evaluated in a neurology clinic because of difficulty walking and cognitive changes.

The patient had been well until 18 months earlier, when she began to fall occasionally. There was no vertigo or witnessed seizure activity. Occasional memory lapses occurred, and she had difficulty performing her work as a sculptor. Six months after the first fall, her internist found that she had an abnormal tandem gait. Throughout most of her adult life, she had drunk approximately 5 oz (148 ml) of gin or vodka after dinner. The levels of vitamin B₁₂ and folate and the erythrocyte sedimentation rate were normal, and a serologic test for syphilis was negative. Her doctor advised her to stop drinking alcohol and prescribed daily thiamine.

The patient was referred to a neurologist. The score on the Mini–Mental State Examination, for which lower scores indicate greater impairment, was reduced (with 24 of 30 questions answered correctly), and there was a wide-based gait, a positive Romberg’s test, and reduced sensation of vibration and proprioception below the ankles. Magnetic resonance imaging (MRI) of the spine and the cranium without the use of contrast material showed cervical spondylisis, thoracic kyphoscoliosis, and atrophy of cerebellar structures — findings consistent with the age of the patient. There was no myelopathy. On T₂-weighted imaging, areas of increased signal intensity were detected in the periventricular, subcortical, and pontine white matter.

Electrophysiologic studies performed by a neurophysiologist revealed normal nerve-conduction velocities in the sensory and motor fibers of the ulnar and median nerves and showed no evidence of acute denervation or chronic reinnervation of muscles tested in the arms and legs. The general neurologist, the neurophysiologist, and a stroke neurologist concurred that the patient’s condition was most likely multifactorial, with causes that included her alcohol-induced peripheral neuropathy, cerebellar degeneration, and mild cervical spondylisis.

Over the course of the next six months, the falls and memory lapses became more frequent. The woman and her husband moved into an assisted-living facility, and the
patient was referred to a clinic at this hospital that specializes in Parkinson's disease and movement disorders.

The patient had worked as a sculptor — with some metals, but primarily in wood — since graduating from college. At the age of 20 years, she had undergone a partial colectomy and a bilateral oophorectomy to remove an unspecified tumor. At the age of 77 years she had undergone an emergency laparotomy for a small-bowel obstruction. She had had occasional episodes of fecal incontinence, and she had chronic obstructive pulmonary disease. She smoked 20 cigarettes daily and had done so for more than 50 years. Since her visit to her internist, she had stopped drinking alcohol. She took thiamine, multivitamins, conjugated estrogens, medroxyprogesterone, and acetaminophen. There was no history of hypertension, diabetes, stroke-like episodes, headache, trauma, infections of the central nervous system, exposure to neurotoxins, use of illicit drugs, agitated or paranoid behavior, insomnia, weight loss, swallowing difficulty, urinary incontinence, or syncope. The patient's father had had dementia (possibly Alzheimer's disease) and had died at the age of 85 years.

The patient's weight was 51 kg, and her vital signs were normal. The general physical examination revealed no abnormalities. Neurologic examination revealed an alert, oriented, attentive woman; however, her knowledge of recent events was vague, and she was not able to provide the details of her medical history or an account of her daily routines. She had fluent, circumlocutory speech without paraphasic errors. She had minor difficulty with object naming. She understood and retained in memory three out of three low-frequency words and recalled six details from a short story, but she was unable to remember what she had eaten for breakfast. She displayed social wit but little concern about her difficulties. She did not hallucinate or communicate paranoid ideas, and she had no delusions.

The patient's cranial-nerve functions were intact. The eye movements were full. There was no nystagmus, but there was variable breakdown of pursuit. Her face had a staring expression, with raised eyebrows and a reduced blinking rate, but was not weakened. The muscle strength and tone in the neck were normal. The tone was increased in both legs, and there was cogwheeling (++) in the left arm. The ability to make rapid, alternating movements was markedly reduced in the left arm and left leg, but there was no weakness, tremor, limb ataxia, or neglect. The deep-tendon reflexes were symmetrically increased in the legs, and the plantar responses were absent. She rose slowly from a chair, and both bradykinesia and truncal ataxia were evident. She walked stiffly and with a widened stance, had reduced swing of the left arm, and shuffled the left foot. Testing for sensation revealed the same results as those previously obtained.

A therapeutic trial of carbidopa (25 mg)–levodopa (100 mg), taken orally three times per day, was begun. Two months later, weakness had developed in the left arm and left leg. Her postural instability had become more pronounced and her stride more abbreviated. A repeated MRI study (performed approximately one year after the first) showed no additional changes.

Two and a half years after her illness had begun, another small-bowel obstruction occurred. After recovering from an emergency laparotomy, the patient was unable to walk, even with the use of an aid such as a walker, and began to use a wheelchair. She also needed assistance with all transfers. She subsequently moved into the nursing home at her assisted-living community. Urinary urge incontinence developed. While walking with the assistance of two people, she showed a shuffling, freezing gait; her cervical spine revealed a more forward flexed posture.

During the next six months, hypophonia, mild-to-moderate dysarthria, and difficulty swallowing pills developed. On examination, the weight was 44 kg, and she appeared cachectic. Her train of thought was slow; she had a new, sustained blink response to finger tapping on her forehead; and there were bilateral palpable reflexes. There was dyscalculia but no apraxia. A mild, action-induced tremor was visible in both arms. Laboratory test results are shown in Table 1. A modified barium-swallow examination revealed mild-to-moderate oropharyngeal dysphagia, with penetration of liquid into the laryngeal vestibule. Formal neuropsychological testing and a diagnostic electromyogram were suggested but were not performed.

Three years after the patient's initial fall, a repeated trial of carbidopa (25 mg)–levodopa (100 mg), taken orally four times per day, led to slight improvement in the need for assisted transfers but also led to episodes of confusion and disorientation. The dosage was reduced. Frequent urinary incontinence developed during the day and at night, as did chronic constipation and increased rigidity in both legs and the left arm.
Table 1. Laboratory Test Results.\(^*\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>One Year after Initial Symptoms</th>
<th>Three Years after Initial Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase (U/liter)</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase (U/liter)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/liter)</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Vitamin B(_{12}) (pg/ml)</td>
<td>462</td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen (mmol/liter)</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>207</td>
<td></td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>Chloride (mmol/liter)</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Carbon dioxide (mmol/liter)</td>
<td>24.5</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Total</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Folate (ng/ml)</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>Potassium (mmol/liter)</td>
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<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/liter)</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/liter)</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>Magnesium (mmol/liter)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Lead ((\mu g/dl))</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Protein (g/dl)</td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>4.0</td>
<td>6.9</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Globulin</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td>Thyroid-stimulating hormone ((\mu U/ml))</td>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Stool fat</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

\(^*\) To convert the value for vitamin B\(_{12}\) to picomoles per liter, multiply by 0.7378. To convert the value for calcium to millimoles per liter, multiply by 0.02586. To convert the value for creatinine to micromoles per liter, divide by 88.4. To convert the values for total, high-density lipoprotein, and low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.02586. To convert the value for glucose to millimoles per liter, multiply by 2.266. To convert the value for potassium to milliequivalents per liter, divide by 0.5. To convert the value for triglycerides to millimoles per liter, multiply by 0.01129. To convert the value for uric acid to micromoles per liter, multiply by 59.48.

Her bowel hygiene required aggressive efforts. Six months later, the patient reported recurrent dizziness with orthostasis during passive transfers. A bout of pneumonia was treated with oral levofloxacin and inhaled albuterol. Nearly five years after her first fall, the patient died in her sleep.

Permission was granted to perform an autopsy restricted to the brain.

**Differential Diagnosis**

Dr. Alan G. Cole: I began to care for this patient six months before her first fall and continued doing so until she moved into an assisted-living facility. The extent of her alcohol intake was disclosed during a visit six months after her first fall, when an unsteady gait was found. I thus focused on alcohol as the cause of her ataxia.

Acute alcohol intoxication causes an unsteady gait. Alcoholism causes ataxia by inducing a peripheral polyneuropathy, with predominantly sensory and autonomic deficits and often with a loss of deep-tendon reflexes. Alcohol consumption can also adversely affect vestibular function.\(^2\) Excessive alcohol consumption associated with thiamine deficiency causes Wernicke's encephalopathy, along with ataxia, confusion, and ophtalmoplegia; however, this triad is often not present in its entirety. Women, particularly during pregnancy, are more susceptible to this complication than men.\(^2\)

I treated this patient with oral thiamine at a dose of 100 mg per day and strongly urged her to discontinue drinking alcohol. Despite her initial reluctance, she stopped drinking entirely. Nevertheless, her condition worsened, and I referred her to a neurologist.

Dr. Michael G. Schlossmacher: I was one of several neurologists to see this patient. Three problems were identified initially: chronic alcohol and tobacco use, cognitive impairment with memory abnormalities, and a predominantly hypokinetic movement disorder. The illness had the following key features: a late age of onset, a gradually progressive course, sequential involvement of multiple sites, and a poor response to carbidopa–levodopa therapy. To establish a diagnosis, it is necessary to determine whether this disorder was acquired, sporadic, or familial and whether the phenotype could be ascribed to a single entity or to multiple disease processes.

First, the signs and symptoms should be specified. Throughout the first year after her fall, her
symptoms and physical findings suggested midline cerebellar abnormalities (causing imbalance and falls), peripheral polyneuropathy (causing reduced sensation of vibration and joint movements), and hippocampal dysfunction, frontal-lobe dysfunction, or both (causing mild memory impairment). The second phase of her illness saw the evolution of extrapyramidal changes (leading to hypokinesia, rigidity, and effortful alternating movements) and moderate pyramidal tract abnormalities (leading to left-sided weakness). The third and final stage resulted in pronounced brain-stem dysfunction (causing dysphagia and postural reflex loss) and abnormalities of the autonomic nervous system (causing urinary incontinence and severe constipation).

Numerous disorders can have one or more of these features, and more than 30 conditions may cause hypokinesia with rigidity. Many of these disorders can be ruled out on the basis of the patient’s history, the results of neurologic examination, the course of the illness, the response of the illness to treatment, the results of laboratory investigations, and radiographic imaging studies. May we review the imaging studies?

Dr. R. Gilberto Gonzalez: T2-weighted images obtained at the level of the temporal lobes showed enlargement of the ventricles and sulci, indicating diffuse shrinkage of brain parenchyma. The hippocampi were small. Images obtained at the level of the lateral ventricles and corona radiata (Fig. 1) show atrophy, with enlargement of the ventricles and sulci, and extensive areas of hyperintensity in the periventricular and subcortical white matter. These findings are common in older people but are abnormally pronounced in this patient.

Dr. Schlossmacher: The patient’s history initially prompted concern that she had a toxic or metabolic illness. The findings on MRI scanning repeatedly raised the possibility of a microvascular disease. The gradually progressive nature of the illness, however, finally led to focused attention on a neurodegenerative disorder. I shall briefly review these categories as they relate to this case.

**Metabolic Disorders**

The patient’s primary care physician suspected that her alcohol consumption may have been at the root of her truncal ataxia, memory lapses, and polyneuropathy. However, this possibility became less likely in light of the relentless progression of her neurologic problems even during oral thiamine therapy and after her cessation of alcohol consumption. Likewise, vitamin B12 deficiency (which can result in a subacute, combined-systems degeneration) as well as other conditions (hydrocephalus, a neoplastic or paraneoplastic disease process, or an insidious infectious, inflammatory, or granulomatous process) all appeared unlikely, given the results of the physical examination, cranial and spinal MRJ studies, and laboratory investigations.

A deficiency of vitamin E can result in spinocerebellar degeneration with gait unsteadiness, ataxia, and loss of both vibratory and joint-position sensations. A partial colectomy had been performed at age 20; therefore, malabsorption was considered briefly. However, there were no abnormalities in the lipid profile, no deficiency of vitamin K, and no signs of steatorrhea (Table 1), making a syndrome associated with a deficiency of vitamin E unlikely. In the absence of muscle-specific symptoms, vision problems, or hearing deficits, a mitochondrial multisystem disorder seemed equally unlikely.

**Toxic Disorders**

Memory impairment, concentration difficulties, and generalized slowing of cognition and motor activ-
ilities can be caused by neurotoxins. When these symptoms occur in combination with abnormalities in the white-matter signal on MRI scanning, the resulting conditions are referred to as toxic leukoencephalopathies. Neurotoxins that may be implicated include environmental and occupational agents, therapeutic agents, and drugs associated with abuse.

This patient had two possible types of neurotoxin exposure: occupational and recreational. She had occasionally used copper, bronze, and steel in her sculptures, but during the past 20 years she had mostly used wood. She had no systemic symptoms suggesting intoxication with lead, inorganic arsenic, or organotin. Progression of an encephalopathy usually ends when exposure to the neurotoxin ceases, but the patient's disease advanced after she stopped working. Laboratory tests showed no signs of lead poisoning. Her consumption of alcohol was a risk factor for cognitive dysfunction late in life. Nevertheless, a toxic leukoencephalopathy could not explain the plethora of neurologic signs and the progression of her illness.

MICROANGIOPATHIC CEREBROVASCULAR DISEASES

The diagnoses of vascular parkinsonism and multifocal dementia were considered in this patient. However, the absence of stepwise deterioration and the findings on two MRI scans made infarctions associated with either medium or large vessels unlikely. Instead, attention focused on microangiopathic processes. Hypertension, smoking, hyperlipidemia, advanced age, transient ischemic attacks, and heart disease can alter the perfusion of small and medium-sized cerebral arteries and accelerate cerebral degeneration and cognitive decline.

The term "leukoaraiosis" denotes microangiopathy that results in periventricular and subcortical white-matter changes on imaging studies and comprises heterogeneous diseases that can be acquired, sporadic, or familial. Untreated hypertension, which this patient did not have, is a common cause of acquired leukoaraiosis. Binswanger's disease (subcortical arteriosclerotic encephalopathy) is a rare syndrome defined clinically by the following features: cognitive deterioration, subcortical dysfunction and either a vascular risk factor (chiefly, hypertension) or a history of transient ischemic attacks or stroke, and leukoaraiosis on MRI scanning. Although parkinsonian changes may occur, the degree of progressive dysautonomia seen in this patient would be unusual in Binswanger's disease.

Other rare disorders characterized by vascular abnormalities and periventricular white-matter abnormalities can also be ruled out in this case, on the basis of the clinical and radiologic features and the late age at the onset of the illness. Among them are cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, familial Alzheimer's disease, and congophilic amytoid angiopathy due to mutations in proteins linked to Alzheimer's disease.

I suspect that the patient's radiographic changes represented microangiopathy promoted by two common cerebrovascular risk factors: smoking and advanced age. Although microangiopathy contributed to her cognitive decline, it does not explain her movement disorder. Moreover, the white-matter abnormalities did not change as her movement disorder progressed.

NEURODEGENERATIVE DISEASES

Although her team initially considered the diagnosis of idiopathic Parkinson's disease, the results of the patient's serial examinations and her marginal response to therapy with a dopamine precursor made this diagnosis unlikely. The diagnosis of "probable Parkinson's disease" can be made when two of the three cardinal signs — bradykinesia, rigidity, and tremor — are present and when one supportive feature is identified, such as a sustained response to treatment with a dopamine precursor or a postural reflex loss that evolves over time. No atypical clinical features can be present, and secondary parkinsonism must be ruled out. Parkinson's disease is now recognized to be one of a group of disorders associated with the deposition of α-synuclein in cells of the central nervous system, collectively referred to as synucleinopathies (Table 2). Symptoms of parkinsonism may accompany several of these disorders.

Atypical Parkinsonism with Early Cognitive or Psychiatric Changes

Atypical features that rule out a diagnosis of idiopathic Parkinson's disease include early memory impairment, psychiatric symptoms (hallucinations, delusions, or paranoia), and confusion that is not brought on by medication. Such signs are often seen in the parkinsonism that accompanies cortical dementias, such as Alzheimer's disease, dementia with Lewy bodies, and the Lewy-body variant of
Table 2. Synucleinopathy Diseases of the Nervous System Associated with Aggregation of α-Synuclein.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristic α-Synuclein Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary synucleinopathies</td>
<td></td>
</tr>
<tr>
<td>Sporadic (idiopathic) Parkinson’s disease</td>
<td>Neuronal Lewy bodies, Lewy neurites</td>
</tr>
<tr>
<td>Familial Parkinson’s disease (linked to mutant SNCA gene)</td>
<td>Neuronal Lewy bodies, Lewy neurites, axonal dystrophy</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Neuronal Lewy bodies, Lewy neurites</td>
</tr>
<tr>
<td>Multiple-system atrophy</td>
<td>Glial cytoplasmic inclusions</td>
</tr>
<tr>
<td>Other synucleinopathies</td>
<td></td>
</tr>
<tr>
<td>Lewy-body variant of Alzheimer’s disease</td>
<td>Neuronal Lewy bodies, dystrophic neurites</td>
</tr>
<tr>
<td>Down’s syndrome</td>
<td>Neuronal Lewy bodies, dystrophic neurites</td>
</tr>
<tr>
<td>PARK2-linked neurodegeneration with iron accumulation in the brain, type 1 (formerly known as the Hallervorden-Spatz syndrome)</td>
<td>Neuronal Lewy bodies, axonal dystrophy</td>
</tr>
</tbody>
</table>

* This information is modified from Trojanowski and Lee.  

Alzheimer’s disease. In this case, the features of cortical dementia did not develop; they would have included aphasia, agnosia, apraxia, amnesia, behavioral abnormalities, or psychiatric symptoms.

Atypical Parkinsonism with Parkinson-Plus Features
Some patients have parkinsonism with additional, atypical signs, known as Parkinson-plus disorders. A gait disturbance with falls that occur early in the course of the illness, which this patient had, often suggests progressive supranuclear palsy. Despite the staring facial expression, she did not have an impairment of voluntary gaze that affected her vertical eye movements — a feature that is commonly seen in this disorder. Prion diseases can lead to the degeneration of multiple systems and involve prominent autonomic dysfunction. The patient’s syndrome resembled aspects of one disease that is associated with prion proteins — namely, Gerstmann–Sträussler–Scheinker disease; however, the usual age of onset is before the end of the third decade of life. A Parkinson-plus syndrome with prominent autonomic dysfunction has been described in a very few families with mutations in the gene that encodes α-synuclein. However, the absence of other affected family members in this case and the late age at onset rule out such a diagnosis.

Multiple-system Atrophy
Multiple-system atrophy is a neurodegenerative disease that leads to a Parkinson-plus phenotype and prominent autonomic changes; the onset is usually in middle age or later. It is a recently recognized member of the α-synuclein-inclusion disorders, and clinically it is mistaken most commonly for Parkinson’s disease. An important clue to the diagnosis of multiple-system atrophy is the recognition of several early autonomic symptoms: fatigue, weakness, orthostatic dizziness, decreased sweating, discoloration of the hand or foot (or both) on one side, erectile dysfunction (in men), bladder dysfunction, changes in bowel motility, and sleep abnormalities (Table 3). Four clinical syndromes have been subsumed within the diagnosis of multiple-system atrophy: pure autonomic failure (the Shy–Drager syndrome), striatonigral degeneration with a predominance of parkinsonism, olivopontocerebellar degeneration with a predominance of cerebellar dysfunction, and a combination of these syndromes. Multiple-system atrophy affects both men and women and has an estimated prevalence of four to five cases per 100,000 persons. The average age at onset is in the sixth decade, which is earlier than the onset of illness in the patient under discussion. However, the mean duration of the illness is five to seven years and thus is close to the duration of her disease. The clinical diagnosis of probable multiple-system atrophy requires the fulfillment of two criteria: either autonomic failure or urinary dysfunction and either parkinsonism that responds poorly to levodopa or cerebellar dysfunction (Table 3). Corticospinal tract features are frequently present but are not required for the diagnosis.

Tests that can identify autonomic nervous-system dysfunction and direct therapeutic interventions include recording of the blood pressure and heart rate in the supine, sitting, and standing positions; tilt-table maneuvers; modified Holter monitoring; urodynamic studies; sphincter electromyography; and polysomnography. MRI scans
Table 1  Clinical Diagnosis of Multiple-System Atrophy, According to the Guidelines of the American Autonomic Society and the American Academy of Neurology.9

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible</td>
<td>One criterion plus two disease characteristics</td>
</tr>
<tr>
<td></td>
<td>from other domains</td>
</tr>
<tr>
<td>Probable, type P</td>
<td>Autonomic criterion plus criterion for poorly</td>
</tr>
<tr>
<td></td>
<td>responsive parkinsonism</td>
</tr>
<tr>
<td>Probable, type C</td>
<td>Autonomic criterion plus criterion for cerebellar</td>
</tr>
<tr>
<td></td>
<td>dysfunction</td>
</tr>
<tr>
<td>Definite</td>
<td>Pathological confirmation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feature</th>
<th>Defining Criteria</th>
<th>Disease Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic failure†</td>
<td>Orthostatic fall in blood pressure by &gt;30 mm Hg (systolic) or 15 mm Hg (diastolic)</td>
<td>Orthostatic hypotension, urinary incontinence, bladder-emptying difficulty, erectile dysfunction</td>
</tr>
<tr>
<td></td>
<td>or persistent urinary incontinence with erectile dysfunction (in men) or both</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Bradykinesia plus rigidity or postural instability or tremor</td>
<td>Progressive reduction in speed and amplitude with repetition of limb movements, rigidity, primary postural reflex loss, tremor (postural, at rest, or both), minimal or transient response to levodopa or other dopaminergic drugs</td>
</tr>
<tr>
<td>Cerebellar dysfunction</td>
<td>Gait ataxia plus limb ataxia or sustained gaze-evoked nystagmus or ataxic dysarthria</td>
<td>Wide-based stance and irregular steps, limb ataxia and ataxic speech, gaze-evoked nystagmus</td>
</tr>
<tr>
<td>Corticospinal tract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dysfunction‡</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The information is from Gilman et al.9
† Additional signs and symptoms not listed in the guidelines may include severe, chronic constipation; fecal incontinence; chronic fatigue and feeling of weakness; change in perspiration; discoloration of distal extremity (or extremities); reduced genital sensation in women; and rapid-eye-movement sleep disorder.
‡ Asymmetric pyramidal weakness, which is not listed in the guidelines, may be an additional sign.

of the brain have low sensitivity for the diagnosis of multiple-system atrophy.10 Recently, the elevation of a regional apparent diffusion coefficient on diffusion-weighted MRI scanning in the putamen has been reported in patients affected by multiple-system atrophy, with parkinsonism.25

Less than three years after its onset, this patient’s illness fulfilled the criteria for probable multiple-system atrophy, since it featured urinary incontinence and parkinsonism. Despite her early truncal ataxia, the course of her disease did not fulfill the criterion of cerebellar dysfunction. Findings of a slight corticospinal tract dysfunction in the left arm and left leg and a mild-to-moderate response to levodopa were also present.

The major argument against this diagnosis is her cognitive impairment, since the consensus guidelines for the diagnosis of multiple-system atrophy list dementia as an exclusion criterion.19 I believe that this woman’s cognitive impairment was the result of subcortical dysfunction from leukoaraiosis, chronic alcohol consumption, and the slowing of thought processes related to multiple-system atrophy, but that it was not true cortical dementia. This conclusion is supported, in the absence of formal neuropsychological testing, by her ability to interact socially until close to the end of her life.

DR. MICHAEL G. SCHLOSSMACHER’S DIAGNOSES

Multiple-system atrophy with predominant parkinsonism. Periventricular and subcortical microangiopathy (leukoaraiosis).
P A T H O L O G I C A L  D I S C U S S I O N

Dr. Matthew P. Frisch: At autopsy, the brain weighed 1110 g—slightly below normal. The cerebrum was normal on external examination. The pons was slightly shrunken (Fig. 2A). There was overall shrinkage of the cerebellar hemispheres (Fig. 2B). Examination of coronal sections revealed that the cerebral cortex and underlying white matter were unremarkable, but there was striking green discoloration of the putamen (Fig. 2C), reflecting a combination of lipofuscin and iron accumulation.24 The substantia nigra was moderately depigmented, and the basis pontis was flattened. This distribution of atrophy and abnormal pigmentation is typical of multiple-system atrophy.

On microscopical examination, there were glassy, flame-shaped eosinophilic inclusions in the cytoplasm of oligodendrocytes in the white matter of the cerebellum, the pons, and the cerebral hemispheres; the inclusions were positive for α-synuclein on immunostaining (Fig. 3A). These oligodendrogial inclusions were originally characterized by means of silver-impregnation methods and by immunostaining for ubiquitin, and they are the histopathological hallmark of multiple-system atrophy (Fig. 3B). Insoluble aggregates of α-synuclein are the core component of these inclusions.24,25 The diagnosis is now based on the identification of α-synuclein in the glial inclusions.25-29 Other changes characteristic of multiple-system atrophy were present in the cerebellum and putamen. There was a loss of Purkinje cells in the cerebellum, and there were degenerative changes in the form of swellings of the proximal portion of the axons (so-called torpedoes). Degeneration of the inferior olivary nucleus, which is typical of the olivopontocere-

Figure 2. Gross Photographs of the Brain.

When viewed from the basal surface, the sides of the pons are flattened, with no lateral bulges (Panel A). The entry zone of the trigeminal nerve is more easily seen than would be expected; normally, it is partially obscured by the lateral bulges of the pons (arrows). Examination of parasagittal sections through the cerebellar hemisphere (Panel B) reveals that there is overall shrinkage of the cerebellum (top) as compared with a control specimen (bottom): there is shrinkage of the dentate nucleus and loss of volume in the white matter of the hilum of the dentate. A coronal section through the cerebrum after fixation (Panel C) shows that the putamen has a greenish discoloration.
A bellar form of multiple-system atrophy, was not present. The putamen was severely gliotic and depleted of neurons (Fig. 3C). Combined with the loss of neurons from the substantia nigra, these changes lead to symptomatic parkinsonism as well as to relative resistance to levodopa therapy because of the severe damage to the target of the dopaminergic nigrostriatal pathway.

In addition to the diagnostic features of multiple-system atrophy, there was arteriolar sclerosis in the white matter, most prominently in the centrum semiovale, with thickening and hyalinization of the vascular walls and small amounts of hemosiderin around the vessels. These changes are typically the consequences of hypertension. In addition, plaques and tangles were present in the temporal lobe, in a distribution consistent with stage II of the pathologic changes of Alzheimer's disease, according to Braak and Braak.30 This degree of change may be seen in persons with normal cognitive function.

Unlike familial Parkinson's disease, in which missense mutations in or duplications of the α-synuclein gene cause autosomal dominant inherited disease, there are no α-synuclein mutations linked to multiple-system atrophy.31 A remaining puzzle in the pathologic features of the disease is the disparity between the distribution of the inclusions and the neuronal degeneration. Inclusions are most common in the white matter of the motor-system pathways, where there is little cellular degeneration; in gray matter, as in the putamen in this case, there is extensive neuronal degeneration but many fewer inclusions.32

**DISCUSSION OF MANAGEMENT**

Dr. Claus Hamann: Along with a nurse practitioner and a social worker, I began to care for this patient at her assisted-living community almost two years after the onset of her illness. Her many problems, including cognitive impairment, movement disorder, speech and swallowing difficulties, and autonomic dysfunction, posed challenges for the patient, her husband, and her medical team. We focused on optimizing her ability to carry out activities of daily living and safety, treating concomitant and intercurrent illnesses, managing difficult behaviors, maintaining her at home, supporting her devoted husband's caregiving, and determin-
ing and carrying out advance directives with regard to life-sustaining care. 32-34

This patient retained poignant insight into her physical condition into her final year of life. After the first of many falls, she used a personal emergency-response alarm; learned, with the help of a physical therapist, to use a walker; and attended adult day care until the transportation became too onerous. 35,36 Her injuries were limited to bruises and scalp lacerations. She managed her oral-pharyngeal dysphagia by using a chin-tuck technique for consuming liquids, by taking pills in a puree, and by performing volitional throat clearing and dry swallowing every three to four swallows to clear residue, as recommended by a speech therapist. She regained some of her weight initially with oral supplements and later with megestrol acetate. Both the technique of prompted voiding and treatment with tolterodine, a smooth-muscle relaxant with peripheral anticholinergic properties, successfully controlled her bothersome urinary frequency and incontinence. 37 Her constipation was managed with lactulose, oral docusate, senna, mineral oil, timed evacuation (with the use of rectal bisacodyl suppositories), and intermittent manual extraction.

Psychosocial support for caregivers is most effective when it is based on individualized problem-solving and behavior management, 38 and we followed this approach in the care of this patient and the support of her husband. One trial of comprehensive support and counseling for spouse-caregivers found that they increased the time that spouses were able to perform at-home care for patients with Alzheimer’s disease by almost 11 months. 39 This patient’s husband hired a personal-care attendant for help with dressing, transferring, and toileting so his wife could have daytime visits and meals with him in their apartment. The attendant also provided help with the use of a wheelchair and with supervision while the husband worked part-time at his office.

I discussed the issue of advance directives with regard to life-sustaining treatment with the patient and her husband immediately after the diagnosis of multiple-system atrophy, when it was becoming clear that her expected decline required a reaffirmation of her living will and consideration of a hospice approach to her care. 40-42 Over the years, she confirmed, in several discussions, her wish not to have her life prolonged by burdensome means. During the last two months of her life, when swallowing had become more difficult but she was still able to indicate her wishes, we confirmed her desire for only comfort care. The process of dying lasted about five days, and only two small doses of sublingual morphine concentrate were given.

ANATOMICAL DIAGNOSES

Multiple-system atrophy.
Cerebral arteriolar sclerosis.

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REFERENCES

2. Spurlin SC, Kuller JA. Hyperension gravi-
darum complicated by Wernicke’s encephalopa-
3. Lang A. Movement disorder symptoms.
ology. In: Bradley WG, Daroff RB, Fen-
ichelm GM, Marsden CD, eds. Neurology in
clinical practice. 2nd ed. Boston: Butter-
4. Vitek M. Persistent altered mentation
5. Bendayan M, Weisberg HG, Wiesbeck G,
et al. Sequential MR imaging and proton MR
spectroscopy in patients who underwent recent detoxification for chronic alcoholism:
correlation with clinical and neuropsycholo-
gical data. AJNR Am J Neuroradiol 2001;
6. Sot T, Simon RJ. Deficiency diseases of
the nervous system. In: Bradley WG, Daroff
RB, Fenichel GM, Marsden CD, eds. Neuro-
logy in clinical practice. 2nd ed. Boston: But-
terworth-Heinemann, 1996;1373-84.
7. Filley CM, Kleinachnik DeMaesters BK.
2001;345:425-32.
8. Mukhamal KJ, Kuller LH, Fitzpatrick AL,
Longstreth WT Jr, Mattinson MA, Sikovick
DS. Prospective study of alcohol consump-
tion and risk of dementia in older adults. 
9. Hijdra A. Vascular dementia. In: Brad-
ley WG, Daroff RB, Fenichel GM, Marsden
CD, ed. Neurology in clinical practice. 2nd
1602-10.
Cluster analysis and patterns of findings on
cranial magnetic resonance imaging of the
elderly: the Cardiovascular Health Study. Arch
KC, Miller DC. Binswanger’s disease pre-
senting as leuodopa-responsive parkinson-
is: clinicopathologic study of three cases. 
12. Dichgans M. Cerebral autosomal domi-
ant arteriopathy with subcortical infarcts 
and leukoencephalophathy: phenotypic and 
neuropathological spectrum. J Neurol Sci 2002;
204:77-80.
13. O’Riordan S, McMonagle P, Janssen JC,
et al. Presenilin-1 mutation (E280G), spastic 
paraparesis, and cranial MRI white-matter 
14. Lang AE, Lomena AM. Parkinson’s dis-
15. Trojanowski JQ, Lee VM. Parkinson’s 
disease and related synucleinopathies are a 
ew class of neurodegenerative disorder. 
Al. Progression of falls in postmortem-con- 
formed parkinsonian disorders. Mov Disord 

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