Medical Mimics of Neurodegenerative Diseases

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Lewis P. Rowland and Orla Hardiman

Abstract Mimic syndromes may differ from a neurodegenerative condition not only in natural history with periods of stability or even spontaneous improvement, but also because the mimic may be treatable. Careful attention to history and clinical examination are required to ensure that important clues to a mimic syndrome are not overlooked. Atypical features, failure to progress, or the development of new or atypical signs should trigger a full reevaluation and a search for a mimic syndrome.

Keywords Motor neuropathy • Reversible cognitive impairment • Conversion disorder • Autoimmune disease • Parkinsonism

Introduction

In this chapter, we consider syndromes that resemble neurodegenerative disorders but differ in some essential way. It is important to recognize these mimic syndromes, which may differ from a neurodegenerative condition not only in natural history with periods of stability or even spontaneous improvement, but also because the mimic may be treatable. Clinical examination and judicious use of ancillary studies, as described in each chapter of this book, usually exclude the mimic syndrome, as described in the pages that follow.

Mimics of Amyotrophic Lateral Sclerosis (ALS)

Benign Fasciculation

Blexrud et al. introduced this term in 1993, identifying the benign future of 121 people with fasciculation with no other abnormality on examination or in electrodiagnostic studies. Follow-up by telephone 2–32 years after this diagnosis, not one of the 121 patients had

O. Hardiman (✉)
HRB Clinician Scientist, Consultant Neurologist and Clinical Professor,
Department of Neurology, Beaumont Hospital and Trinity College, Dublin, Ireland
e-mail: orla@hardiman.net

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developed symptomatic ALS. As indicated by Eisen and Stewart in 1994, in response to that report, however, fasciculation may be the first manifestation of ALS. Blexrud et al. responded that those patients usually have "weakness or incoordination" in addition to the visible twitching and, additionally, other EMG abnormalities are usually present by that time. Others, including de Carvalho and Swash, reported similar cases in 2004. Bruyn et al. described a patient who had PLS for 27 years before lower motor neuron signs appeared.

Multifocal Motor Neuropathy with Conduction Block

Another important consideration in the differential diagnosis of ALS is multifocal motor neuropathy with conduction block (MMNCB).

ALS is only rarely reversible spontaneously and almost always progresses inexorably to death, regardless of therapy. Neither ALS nor MMNCB responds to corticosteroid therapy or plasmapheresis. In contrast, however, MMNCB improves with intravenous immunoglobulin therapy (IVIG) in doses of 400 mg/kg body weight over 5 days. Efficacy has been proven in four randomized controlled trials but there is no consensus about dosage or frequency of treatments to maintain the original improvement. Benefit may be seen within a week of the first series of treatments, and lasting for a variable number of weeks before symptoms recur. Disability may be severe, but the disease is only rarely fatal.

Demonstration of conduction block in nerve conduction studies is the sine qua non for the diagnosis. Antibodies against GM1 are found in up to 80% of cases. Clinical clues to the presence of MMNCB include onset before age 50, men affected three times more often than women, hands affected more than legs and bulbar innervated muscles spared, stuttering course and distribution of weakness suggesting mononeuropathy multiplex, more weakness than atrophy, visible fasciculations in about half the patients, and no cutaneous sensory loss. Tendon reflexes are usually absent but are active in some cases. Hoffmann and Babinski signs are rarely seen. The CSF protein content is usually normal or only slightly elevated up to 80 mg/dL (in contrast to the values near or above 100 mg/dL seen in chronic inflammatory demyelinating polyneuropathy).

Multifocal Acquired Motor Axonopathy

Conduction block is not present in all patients who have the clinical features of motor neuropathy. These patients also respond well to IVIG therapy. In other words, this disorder is a clinical look-alike for MMNCB but lacks the defining physiological characteristics in nerve conduction studies. Moreover, an axonal motor neuropathy is difficult to differentiate from a disease of the cell body itself, i.e., the progressive muscular atrophy (PMA) form of motor neuron disease, although multifocal acquired motor axonopathy (MAMA) is more likely to be subacute than PMA, which is slowly progressive.

Brachial Amyotrophic Diplegia (BAD)

The term brachial amyotrophic diplegia (BAD) has been used to describe a slowly progressive lower motor neuron disorder affecting proximal arm muscles. The wasted arms

hang limply at the sides giving the person the appearance of "a man in a barrel." Another moniker is the "flail arm syndrome." In most cases, there is no obvious cause but reports have implicated HIV or HTLV-1 infection. In one case, an axial view of the cervical spinal cord showed high signal in the anterior horns of the gray matter. Sjögren syndrome was held responsible for one patient with BAD who improved with combination therapy that included prednisone, plasmapheresis, and IVIG.

Cervical Spondylotic Myelopathy

The clinical manifestations of cervical spondylotic myelopathy can rarely mimic ALS. Observations from the Irish and Scottish Registers of ALS suggest that cervical spondylotic myelopathy is more likely to show slowly progressive wasting of the arms and hands plus spastic diplegia. However, there have been few documented reports of visible fasciculation. Also, the rate of progression is slower than in ALS, and the condition may be more symmetric than in ALS. Key clinical features identified by the Irish and Scottish Registers that raised the possibility of cervical myelopathy included the presence of upper motor signs caudal to lower motor signs, early bladder involvement, the absence of bulbar involvement and the relatively slow progression. Neuroimaging is helpful in making the diagnosis. However, some people over the age of 40 have spondylosis with cord compression and may even show high signal within the cord, but they are asymptomatic. Also, 5–10% of people with documented ALS have had cervical decompressive operations without benefit.

Misdiagnosing ALS as cervical myelopathy is more common than the converse.

HIV-Associated ALS

Brachial diplegia has been reported in HIV-positive patients. In 2006, Verma and Berger raised doubts about the possibility that HIV might cause ALS because HIV is not a neurotropic virus and because, in comparison with HIV-negative ALS patients, the reported HIV-infected patients were younger, the course of ALS was more rapid, had atypical features and, perhaps most important, the ALS improved in some of those treated with HAART for the HIV infection. On the other hand, about half of the treated HIV-infected patients succumbed to ALS. They concluded that "the causal relationship remains uncertain." Primary lateral sclerosis may also appear with HIV infections, but is rare.

Other Causes of Reversible Motor Neuron Disease

Motor neuron diseases usually progress inexorably to death. However, cases of complete resolution of sporadic motor neuron diseases with upper and lower motor neuron signs have been reported. The underlying pathology is unclear and such cases are extremely rare: no spontaneous resolutions of ALS have been noted among over 1400 population-based cases collected by the Irish ALS Register over 16 years. West Nile virus infections can cause a reversible poliomyelitis that differs from the others in having a much more acute course. Electrical injury, HTLV-1 infection, and lead intoxication can also cause reversible motor neuron syndromes.

Reversible Causes of Cognitive Decline

Delirium

This term implies an "acute impairment of cognition with a fluctuating course," including a change in the level of consciousness. Impaired cognition, the acute and transient course, and also the many evident causes of delirium including metabolic, infectious and toxic, differentiate this cerebral dysfunction from both neurodegeneration and from dementia.

However, patients with an underlying dementia are more susceptible to delirium in the context of infection, metabolic changes, or drugs (see also Chaps. 3, 4, 5, and 12).

Mild Cognitive Impairment

Alzheimer disease (AD) classically presents with both subjective and caregiver reports of memory dysfunction, which is subacute in onset but progressive. The condition tends to evolve with the pathological recruitment of other networks including the dorsolateral prefrontal cortex, causing executive dysfunction, and language networks, causing word finding problems. In clinical practice, most physicians deal regularly with patients with subjective complaints in any or all these domains, the majority of whom do not have a neurodegenerative disorder. In many cases, depression, anxiety, or psychosocial stress can play a significant role. The lack of objective concern in family and caregivers and the performance on standardized delayed word recall testing are usually enough to reassure. Nevertheless, there are some patients with mild subjective symptoms, without any negative effective on work or social performance who score poorly on testing and may have what we call "mild cognitive impairment" (MCI). This condition is believed to be in excess of what might be expected with normal aging and is a risk factor for the development of clinical dementia. The exact risk is unclear but about 80% of MCI patients progress eventually to AD (see also Chap. 3). The remaining 20% either remain stable or may even improve, two features that point toward a mimic syndrome rather than a neurodegenerative one. The mechanisms underpinning stable or improving MCI are unclear.

Drug-Induced Encephalopathy

Medications are listed as the most common cause of reversible "dementia" but some drug effects must also include obtundation in addition to cognitive decline. That would be defined as delirium rather than dementia. Common causal drugs include anticholinergics, tricyclic antidepressants, antipsychotics, bismuth (in the form of bismuth subsalicylate, available as an over-the-counter medication), bromides, antihistamines, antiepileptics, benztropine, and lithium (see Table 11.1).

The evaluation of a patient with cognitive impairment should therefore include the medication history, including a complete review of all over-the-counter medications.

Table 11.1 Common drugs that can cause cognitive impairment

Drug	Effect
Amitriptyline	Anticholinergic properties: sedation, confusion, delirium, or hallucinations
Anticholinergics	Sedation, confusion, delirium, or hallucinations
Anticonvulsants	Confusion, sedation, elevated ammonia
Valproate Levetiracetam	Confusion, hallucinations
Antihistamines	Anticholinergic properties: sedation, confusion, delirium, or hallucinations
Antipsychotics	Confusion, sedation
Antispasmodics (GI)	Anticholinergic properties: confusion, delirium, or hallucinations
Baclofen	Hallucinations, impaired memory, catatonia, mania
Barbiturates	Drowsiness, lethargy, depression, severe CNS depression
Long-acting benzodiazepines	Sedation, drowsiness, ataxia, fatigue, confusion, weakness, dizziness, vertigo, syncope, psychological changes
Bismuth subsalicylate	Encephalopathy resembling dementia, encephalopathy resembling CJD
Chlorpropamide	Hypoglycemia, which can result in altered mental state (confusion, amnesia, coma)
Digitalis	Headache, fatigue, malaise, drowsiness, and depression
H2 receptor antagonists	Confusion, hallucinations, agitation
Indomethacin	Headache, dizziness, vertigo, somnolence, depression, fatigue
Lithium	Confusion, sedation, movement disorder
Methyldopa	May exacerbate depression
Muscle relaxants	Anticholinergic properties, weakness, confusion, delirium, or hallucinations
Pentazocine	Confusion, hallucinations, dizziness, lightheadedness, euphoria, and sedation
Reserpine	Depression, sedation

Epilepsy

Nonconvulsive status epilepticus or clusters of nonconvulsive seizures may be focal onset or be part of a generalized epileptic syndrome. Occasionally, the only clinical manifestation may be altered mental status that appears more like delirium than dementia. Some patients, however, especially the elderly, may maintain such vigilance that the patient merely appears cognitively impaired. This has been called “epileptic pseudodementia” a

rare disorder that can be diagnosed only in the presence of unequivocal prolonged epileptiform discharges in the electroencephalogram (EEG) of the cognitively impaired patient. Treatment is that for other forms of nonconvulsive status but as the term epileptic pseudodementia implies a prolonged course, the prognosis for eventual recovery is poor.

Subdural Hematoma

Chronic subdural hematoma is the most frequent type of intracranial hemorrhage and may occur in the elderly following minor trauma. Patients may show a slow decline in cognitive function with confusion, impaired memory, headache, and motor deficits or aphasia. Chronic subdural hematoma should therefore be considered in the differential dementia of cognitive impairment. Diagnosis is by neuroimaging, and treatment is surgical evacuation.

Sleep Apnea

Sleep apnea can be associated with memory loss. Patients may present with symptoms suggestive on cognitive decline, and can account for up to 8% of patients attending a young onset dementia clinic. Symptoms include daytime somnolence, snoring, and morning headache. The reversible cognitive decline is thought to relate to sleep deprivation and nocturnal hypoxemia. Diagnosis is made by overnight polysomnography with oxygen saturation monitoring. Treatment is with noninvasive ventilation using a continuous positive air way pressure (CPAP) device.

Neuropsychiatric Conditions Associated with Reversible Cognitive Decline

Depression

Depressive pseudodementia has been defined as a reversible cognitive impairment of the type seen in dementia. It is associated with delusions and a history of affective illness.

There are few studies of the frequency of depressive pseudodementia, although rates as high as 18% have been reported in specialist dementia referral centers.

Patients with cognitive impairment and concomitant depression should be treated aggressively with antidepressants. However, clinically depressed patients with signs of pseudodementia are at higher risk of developing irreversible dementia in 2 or more years. This suggests that depression with reversible cognitive impairment could be a prodromal phase for dementia rather than a risk factor, and that patients with depressive pseudodementia should be followed closely.

The prevalence of depression in people with Parkinson disease varies in different reports from 20% to 80% and often starts before the motor signs appear (see also Chap. 5). This problem of diagnosis is compounded because some syndromes are common in both conditions: bradykinesia, bradyphrenia, sleep and autonomic disorders, anorexia and weight loss, apathy, and loss of libido. However, the fundamental signs of parkinsonism

(include tremor, cogwheel rigidity, loss of dexterity, deterioration of handwriting, frequent falls, or loss of postural control) are not seen in patients with depression.

Severe depression may also mimic a predominantly apathetic presentation of FTD; cognitive testing should help distinguish the two with dysexecutive features much more prominent in the dementia (see also Chap. 6).

Catatonia

This complex neuropsychiatric syndrome may be seen with either a primary psychiatric disorder or with a general medical condition. Catatonia may mimic other neurodegenerative conditions including FTD and Parkinson disease (Table 11.2). The acute onset of catatonia, with alternating agitation, stupor, and dysautonomia may respond to high-dose lorazepam or electroconvulsive therapy.

Conversion Disorder

Conversion disorder is characterized by loss or alteration of physical function that suggests a physical disorder, but that has a psychological basis. Although conversion disorders are more likely to occur in younger patients – onset is unusual after 35 years of age, symptoms can mimic neurodegenerative disease. Common psychogenic mimic symptoms include limb paralysis, diverse movement disorders, gait disturbances, blindness, and deafness. The patient's behavior seems inappropriately accepting of or indifferent to the serious physical symptoms.

The *Diagnostic and Statistical Manual of Mental Disorders* (*DSM IV*) lists six criteria that must be filled for the diagnosis of conversion disorder (Table 11.3). All neurological and medical causes must be excluded.

Late Onset Psychiatric Disease

Late-onset psychiatric disease may mimic frontotemporal dementia.

Table 11.2 Abnormal signs in catatonia

Motor	Speech and language	Behavioral	Autonomic	Laboratory
Akinesia Bradykinesia Parkinsonism Tremor Stupor Primitive Reflexes Upgoing Plantars Oculomotor signs Tics	Mutism Aphasia Palilalia	Agitation Impaired judgment Impaired insight	Hypertension Pyrexia Diaphoresis Insomnia Tachycardia	Leukocytosis Elevated creatine kinase (CPK) Abnormal EEG

Table 11.3 *DSM IV* criteria for conversion disorder

- Patient has one or more symptom affecting voluntary, motor, or sensory function that suggests a neurological or medical condition.
- Psychological factors are associated with the symptom or deficit.
- Symptom or deficit is not intentionally produced, but is maintained by secondary gain.
- Symptom or deficit cannot be fully explained by a general medical condition, by direct effects of a substance, or as a culturally sanctioned behavior or experience.
- Symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning, or warrants medical explanation.
- Symptom or deficit is not limited to pain or sexual dysfunction, and is not better accounted for by another mental disorder.

Of the three main clinical syndromes of FTD (see Chap. 6), the behavioral variant FTD (bv-FTD), is the one most likely to be confused with a mimic disorder, the others having a more characteristic language dysfunction (semantic dementia). Detailed neuropsychological testing is helpful in distinguishing organic disease from a late-onset psychiatric disorder.

Nutritional Causes of Reversible Cognitive Decline

Wernicke Encephalopathy

This is the result of thiamine deficiency, usually with other nutritional deprivations and often in the context of alcohol abuse. In addition to the cognitive disorder, the full syndrome includes ophthalmoparesis and ataxia. It is also seen with dialysis, after bariatric surgery or prolonged intravenous administration of glucose.

Pellagra

Vitamin B3 deficiency (niacin deficiency) is manifest by dementia, rash, and diarrhea. If unrecognized and untreated, it may be fatal.

Both Wernicke syndrome and pellagra differ from neurodegeneration syndromes in younger age at onset, more acute onset, more rapid progression, and reversibility with replacement therapy.

B12 Deficiency

Whether B12 deficiency causes a dementia-like disorder has been controversial, but it seems to be standard practice to test blood levels routinely and, if values are low, to administer the missing cobalamin. The neurological syndrome ("combined system disease") that accompanies pernicious anemia results from both myelopathy and sensorimotor polyneuropathy. Severity of the disorder is related to duration of symptoms before treat-

ment. Symptoms may include ataxia of gait, distal paresthesias, dementia, psychosis, or visual loss. Many individuals with B12 deficiency are asymptomatic these days but some have one or more comorbid autoimmune diseases. Tendon reflexes may be increased or decreased and upper motor neuron signs may be evident. Distal sensory loss and impaired perception of limb position may be found.

Almost all patients improve with treatment and, in about half, recovery is complete. Dementia has been reversed by treatment even when B12 levels are still in the low normal range.

Toxic Exposures

Many heavy metals, pesticides, solvents, and gasses can lead to neurological deficits that can mimic a neurodegenerative process. For example, manganese toxicity can induce a parkinsonian syndrome, lead and arsenic toxicity can induce an encephalopathy, and chronic inhalation of low-dose elemental mercury is associated with ataxia and cognitive impairment.

The most common toxic exposure is to ethanol. Alcohol abuse is associated with a wide range of neuropsychiatric syndromes including cerebellar degeneration, Wernicke-Korsakoff syndrome, and alcohol-related dementia. Although the concept of a dementia that is directly related to alcohol abuse remains controversial, in the United States, it is estimated that alcohol-related dementia accounts for up to 20% of admissions to state psychiatric facilities. The mechanism of alcohol-associated cognitive decline is poorly understood, and there are no established treatment protocols other than abstinence with psychosocial supports.

Acute exposure to carbon monoxide is one of the most common causes of poisoning requiring admission to hospital. In the United States, the incidence of suspected carbon monoxide poisoning is approximately 1/10,000 per annum. Acute intoxication can lead to encephalopathy and coma. Up to 50% of individuals with carbon monoxide poisoning subsequently develop neurologic, neurobehavioral, or cognitive sequelae. Some patients experience a progressive course, with development of a persistent akinetic-mute state. Other patients experience a delayed relapse after an initial recovery period of approximately 3 weeks. Those with the delayed relapsing course can develop a parkinsonian state with behavioral and cognitive impairment. Brain MRI reveals multiple lesions in the subcortical white matter and basal ganglia, mostly in the globus pallidus, and to a lesser extent in putamen, and caudate.

Diagnosis should be suspected if the partial pressure of blood oxygen is low, in the presence of apparently normal oxygen saturation. Treatment is with hyperbaric oxygen.

Endocrine Causes of Reversible Cognitive Decline

Thyroid Disease

Clinical hypothyroidism may cause cognitive impairment, which can be reversed if treated early. There are no long-term cognitive sequelae in treated hypothyroidism.

Hyperthyroidism can cause tremulousness, chorea, and encephalopathy. Symptoms resolve with treatment.

Hashimoto Encephalopathy

Encephalopathy in people with high levels of antibodies to thyroid antigens (thyroperoxidase and thyroid microsomal proteins) has long been considered a specific syndrome, one likely to respond to prednisone therapy, and called "Hashimoto encephalopathy." Most of the cases with this neurologic syndrome have had Hashimoto thyroiditis. Other autoimmune thyroid diseases have also been described, mainly Graves disease. The pathogenesis of this encephalopathy is still unknown and largely debated. Cerebral symptoms include stroke-like episodes, coma, seizures, subacute cognitive decline, and hallucinations. However, high serum levels of the same thyroid antibodies may be found in many asymptomatic people. Moreover, it has not been proven that the antibodies cause the symptoms (or how they might do so) and steroid therapy may fail in 50% of otherwise typical cases.

The occipital cortex may be especially vulnerable and the "posterior reversible encephalopathy syndrome" (PRES) is sometimes seen with Hashimoto encephalopathy. Some authors have advocated brain biopsy as an important diagnostic test, primarily to exclude Creutzfeldt–Jakob disease.

In 1999, Caselli et al. proposed a more formal name, but the simpler eponym, honoring Hashimoto, has not disappeared. The syndrome is subacute in onset and course, another difference from the chronic features of neurodegeneration.

Paraneoplastic Causes of Cognitive Decline

Cognitive impairment is sometimes seen in patients with malignant tumors, especially small cell lung cancer, lymphoma, thymoma, or testicular cancer (Table 11.4). The complex paraneoplastic syndromes include disordered sleep patterns, hallucinations, behavioral anomalies, orthostatic hypotension, and the Morvan syndrome (neuromyotonia, hypersalivation, hyperhidrosis, and insomnia). The clinical picture is that of limbic encephalitis with manifestations that evolve in days or weeks.

Other features that distinguish these syndromes are imaging abnormalities in the temporal lobes, noninfective CSF pleocytosis, and presence of serum antibodies to the Hu antigen, anti-Ma, and (in the Morvan syndrome) anti-voltage-gated potassium channels (VGKC), as well as other antigens.

Non-paraneoplastic Autoimmune Syndromes

Antibodies to VGKC have been found in several reversible conditions without an underlying neoplasm, but the critical antigen and target of the antibodies is the synaptic protein leucine-rich glioma-inactivated 1 (LGI1). The ensuing condition is an autoimmune synaptic encephalopathy. The clinical features of the associated limbic encephalitis may

Table 11.4 Paraneoplastic neurological syndromes

Antibody	Tumor	CNS syndrome
Hu	Small cell lung carcinoma	Encephalomyelitis, paraneoplastic cerebellar degeneration, limbic encephalitis
CV2 (CRMP 5)	Small cell lung carcinoma, thymoma	Encephalomyelitis, chorea, cerebellar degeneration limbic encephalitis
Amphiphysin	Breast, small cell lung carcinoma	Stiff person syndrome, encephalomyelitis
Ri	Breast, small cell lung carcinoma	Brainstem encephalitis, cerebellar degeneration, opsoclonus myoclonus
Yo	Breast, ovary	Paraneoplastic cerebellar degeneration
Ma2	Testicular	Limbic encephalitis, brainstem encephalitis
Voltage-gated potassium channel	Small cell lung cancer, thymoma	Limbic encephalitis, Morvan syndrome, Creutzfeldt-Jacob-like syndrome
NMDA receptor	Ovarian teratoma	Encephalitis with catatonia, dystonia, psychiatric symptoms
AMPA receptor	Small cell lung carcinoma, thymoma	Limbic encephalitis, psychosis
GABA B receptor	Small cell lung carcinoma	Limbic encephalitis
Glycine receptor	Lung carcinoma	Encephalomyelitis, stiff person syndrome

be the subacute onset of episodic memory impairment, disorientation, and agitation. Movement disorders may also occur, and some patients have hyponatremia.

Treatment with prednisone, intravenous immunoglobulins, or plasmapheresis leads to improvement of about 80% of patients with VGKC antibodies. Although these findings suggest autoimmunity, it is not clear how these or other antibodies damage the brain.

Mimics of Parkinson Disease

Tauopathies, Dementia, and Parkinsonism

Neurodegeneration may cause parkinsonian disorders that can be divided into two major categories based on postmortem histological findings. First, are the synucleinopathies, which include Parkinson disease dementia (PDD), dementia with Lewy bodies, and multiple system atrophy. Disorders in the second group are "tauopathies," including progressive supranuclear palsy and corticobasal degeneration, as well as AD and FTLD. Both categories are multisystem syndromes and both include clinical manifestations of parkinsonism in combination with dementia, oculomotor abnormalities, and other basal ganglia signs (Table 11.5). Therefore, parkinsonism can result from other mimic conditions (see also Chaps. 3, 5, 6 and 9).

Table 11.5 Classification of parkinsonian dementia syndromes

Etiology	Clinical manifestations
Degenerative	
PDD	Parkinsonism precedes dementia
DLB	Visual hallucinations, fluctuating mental state; variable parkinsonism; REM sleep disorder; neuroleptic sensitivity; falls
PSP	Impaired balance, bulbar signs, down-gaze limited
CBD	Dementia with limb apraxia, myoclonus, parkinsonism
MSA cerebellar (OPCA)	Brainstem signs; cerebellar atrophy; oculomotor disorders
MSA parkinsonism	Parkinsonism; autonomic disorders (urinary incontinence; orthostatic hypotension; cerebellar signs)
Prion disorders	Rapidly progressing dementia, ataxia, PRES
Secondary parkinsonism	
Drug-induced	Neuroleptics; metaclopramide, promethazine, valproate
Vascular	Subcortical infarcts, white matter lesions
NPH	Magnetic gait, urinary incontinence, dementia
Hereditable metabolic disorders	
Wilson disease	Abnormal copper metabolism, hepatic failure, Kayser-Fleischer rings
Hallervorden-Spatz (neurodegeneration with brain iron accumulation, NBIA)	Iron deposits in basal ganglia; familial or sporadic with parkinsonism, dystonia, dementia
Basal ganglia calcification (Fahr disease)	Familial, autosomal dominant or recessive dementia with parkinsonism

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CBD corticobasal degeneration, *CBS* corticobasal syndrome, *DLB* dementia with Lewy bodies, *PDD* Parkinson disease dementia, *MSA* multiple system atrophy, *NPH* normal pressure hydrocephalus, *OPCA* olivopontocerebellar syndrome, *PRES* posterior reversible encephalopathy syndrome, *PSP* progressive supranuclear palsy, *REM* rapid eye movement

Drug-Induced Parkinsonism

Fifty years ago, reserpine was found to cause parkinsonian symptoms and signs, an observation leading to the discovery that dopamine content in the brain is depleted in Parkinson disease. Tetrabenazine administration also depletes dopamine and can also cause parkinsonism. Later came the antipsychotic neuroleptics, which act by a different mechanism, blocking receptors for dopamine and also inducing parkinsonism. Some neuroleptic drugs were first thought to cause fewer extrapyramidal disorders and were therefore called "atypical" but that view was proven wrong with continued experience (Table 11.6).

The neuroleptic drugs include haloperidol, chlorpromazine, and metoclopramide. Other pathophysiological mechanisms seem to be involved in the parkinsonian syndromes ascribed to fluoxetine, lithium, amiodarone, or valproic acid (Table 11.4). Mild parkinsonism is sometimes tolerated for the beneficial antipsychotic effects of quetiapine, olanzapine, and risperidone.

Table 11.6 Drugs that can mimic Parkinson disease

- Neuroleptics
- Reserpine
- Tetrabenazine
- Methyldopa
- Alpha methyltyrosine
- Lithium
- Diazoxide
- Physostigmine
- Metoclopramide
- Trazodone
- Meperidine
- Cimetidine
- Cinnarizine
- Flunarizine

Table 11.7 Differentiation of parkinsonian disorders

	Idiopathic Parkinson disease	Drug-induced parkinsonism
Exposure to neuroleptics	No	Yes
Age at onset	>50	<50
Natural history	Progressive	Resolves after discontinuation of neuroleptic
Tremor	4–6 Hz, supination, pronation	Action/postural
Distribution	Asymmetric	Symmetric

Drug-induced parkinsonism can mimic Parkinson disease in all major features including rigidity, bradykinesia, tremor, and postural abnormalities. Bradykinesia is the most common symptom. The condition can be distinguished from idiopathic Parkinson disease by the history of drug exposure in the context of symptom-onset, age at onset, duration of symptoms, the nature of the tremor (pill-rolling tremor is rare in drug-induced parkinsonism), the presence of symmetry (Parkinson disease tends to be asymmetric), and response to anticholinergics (Table 11.7). Neuroleptic-induced parkinsonism usually improves when the offending drug is discontinued, but recovery may take several weeks.

Sometimes, persistent parkinsonism after withdrawal of the offending drug proves to be the onset of true Parkinson disease (see also Chap 5).

Street Drugs and Frozen Addicts

In 1984, Langston and associates described the appearance of parkinsonism in men who were using a home-brewed version of meperidine. The contaminant that proved to be causal was N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The parkinsonian

features were comparable to those seen in PD and were partially responsive to levodopa but seemed permanent. Animal models of PD have been created with MPTP and 5-hydroxytryptophan. Ephedrone (methcathinone) is another intoxicant that can cause parkinsonism in opiate addicts.

Vascular Parkinsonism

Whether cerebrovascular disease can cause parkinsonism is a question that does not go away. Critics point out that both conditions are relatively common and affect elderly people. Even by chance, the presence of either disorder is probably a risk factor for the other. Nevertheless, vascular parkinsonism and Parkinson disease differ in clinical manifestations

Vascular parkinsonism is less likely to include the pill-rolling tremor, and is more likely to affect the lower body, with postural instability, freezing, and falling, as well as hyperactive tendon reflexes with Hoffmann and Babinski signs. These patients are more likely to have had a history of stroke, are more likely to have stroke risk factors (hypertension, smoking, diabetes, hyperlipidemia, heart disease) and are much less likely to benefit from levodopa therapy (Table 11.8).

This debate involved two of neurology's leaders. In a multi-authored 1954 book on parkinsonism, the editor (Lewis J. Doshay) asked Houston Merritt to write the preface. He

Table 11.8 Clinical features of patients with vascular parkinsonism (VP) and Parkinson disease (PD)

Features	VP ($n=69$)	PD ($n+277$)	*P*
Tremor	23 (33.3)	220 (79.4)	<.00001
Gait	62 (89.9)	108 (40.0)	<.00001
Asymmetric involvement	35 (50.7)	225 (81.2)	<.00001
Upper body predominant	3 (4.3)	119 (43.0)	<.00001
Lower body predominant	41 (59.4)	27 (9.7)	<.00001
Postural instability	50 (72.5)	56 (20.2)	<.00001
Falling	32 (46.4)	29 (10.5)	<.00001
Rigidity	37 (53.6)	172 (62.1)	<.01
Response to the use of levodopa	17 (24.6)	204 (73.6)	<.00001
Dementia	31 (45.0)	28 (10.7)	<.00001
Corticospinal findings	19 (27.5)	3 (1.1)	<.00001
Incontinence	13 (18.8)	5 (1.8)	<.00001
Pseudobulbar affect	7 (10.1)	7 (2.5)	<.05

From Winnikates and Jankovic (1999). Used with permission

VP vascular parkinsonism, *PD* Parkinson disease

Values are number (percentage)

opined: "It is also possible that degeneration of the basal ganglia, as a result of arteriosclerosis, can produce the characteristic symptoms, but the pathological evidence for such a relationship is not unequivocal. In addition, there are few satisfactory criteria for the establishment of the clinical entity of arteriosclerotic parkinsonism." Merritt attributed the disorder to "unknown cause" or "so-called idiopathic parkinsonism." A few pages later, Denny-Brown wrote a section entitled "Arteriosclerotic Parkinsonism." Neither author referred to the other.

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus (NPH) is the main problem in differential diagnosis of vascular parkinsonism; bradykinesia is seen in almost half of NPH patients and frank parkinsonism has been reported in up to 11% of those patients. The clinical syndrome is the triad of dementia, ataxia, and urinary incontinence. Numerous imaging tests have been advocated to improve prediction of a good response to diverting the outflow of CSF. If CSF drainage and shunting help relieve NPH, the parkinsonism may also improve.

Binswanger Disease (Subcortical Vascular Cognitive Impairment, Leukoaraiosis)

Vladimir Hachinski, the modern authority on this syndrome, concluded that the eponym should not be used. With John Bowler, he writes that "Binswanger" has become a popular term in the era of modern imaging to describe asymptomatic changes seen in MRI or CT. However, they prefer the word "leukoaraiosis" for that asymptomatic condition. A dictionary definition of leukoaraiosis is, "Decreased vascular density, especially in deep white matter in the brain, on MRI or CT; may be caused by demyelination, gliosis, or decreased perfusion." Bowler and Hachinski describe MRI changes of "extensive deep white matter lesions sparing subcortical U-fibers and corpus callosum." That is, the disorder is defined by the MRI appearance of diffuse high signal in the white matter. It is often seen in asymptomatic people but may be seen with dementia or parkinsonism. Cognitive impairment is seen more often than the vascular parkinsonism described above. Despite admonitions from respected authorities, the eponym honoring Binswanger is still used for the combination of dementia with imaging evidence of "subcortical vascular cognitive impairment" (see also Chap. 4).

Hepatolenticular Degeneration (Wilson Disease) and Other Hereditary Movement Disorders

According to a literature review by Lorincz, parkinsonism is seen in about 17% of patients with Wilson disease, with onset of symptoms at about age 20. Liver failure is usually evident and cerebellar tremor is seen more often than parkinsonism (mean 36%) so the correct diagnosis is usually evident. Pfeiffer, however, was skeptical about any association of parkinsonism with Wilson disease. Similarly, juvenile parkinsonism may be seen with

mutations of other movement disorder genes, including Huntington disease, dentatorubropallidoluysian atrophy, Hallervorden-Spatz disease, and neuronal intranuclear inclusion disease as well as mutations of mitochondrial DNA.

Idiopathic Basal Ganglia Calcification (Fahr Syndrome)

Once again, experts disparage use of the eponym in reviewing this syndrome. Yet, once again, the eponym continues to be used. The disease is defined by the imaging abnormalities that show widespread intracranial calcification of the basal ganglia, with or without concomitant hypoparathyroidism, and clinically manifest by dementia, parkinsonism, or both. In some families, inheritance seems to be autosomal dominant. Calcific deposits are sometimes seen with other diffuse cerebral disorders.

Pantothenate Kinase–Associated Neurodegeneration (PKAN) (Hallervorden-Spatz Disease)

Most often, this is a disease of children but symptom-onset occurs after age 10 in about 25% of affected people. Inheritance is autosomal recessive and caused by mutations in *PANK2*, which leads to iron deposition in the basal ganglia. Symptoms include dystonia, dysarthria, pigmentary retinopathy, and lower body parkinsonism. Orobuccolingual dystonia may cause mutilating tongue biting. Upper motor neuron signs may be seen. MRI shows the eye-of-the-tiger sign, a central hyperintensity surrounded by hypointensity on T2 images of the globus pallidus.

Conclusion

Careful attention to history and clinical examination is required to ensure that important clues to a mimic syndrome are not overlooked. Atypical features should be assiduously assessed and pursued. Systemic signs may point to an underlying neoplasm, raising the possibility of a paraneoplastic disorder. A history of poor sleep and loud snoring may reveal a diagnosis of sleep apnea.

Routine hematological and biochemical tests should be performed in all cases, as should CSF analysis and detailed neuroimaging. Heavy metal screening may be useful in those with occupational exposures. EEG can be helpful in differentiating clinical syndromes, for example, the preservation of alpha rhythm in the FTDs and its early disintegration in AD (Chaps. 3 and 6); or the presence of epileptiform changes in a patient with epilepsy associated amnesia. Nerve conduction studies can identify evidence of conduction block in patients with multifocal motor neuropathy (Chap. 7).

The course of mimic syndromes often differs from true neurodegenerative disease, and perhaps the most important diagnostic test is careful clinical evaluation over time. Patients should be reviewed regularly.

Failure to progress or the development of new or atypical signs should trigger a full reevaluation. And during each clinician review, the clinician should pose the question, "Could this be a mimic syndrome?"

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