PARKINSONIAN SYNDROMES
Dr.M. YASSER METWALLY

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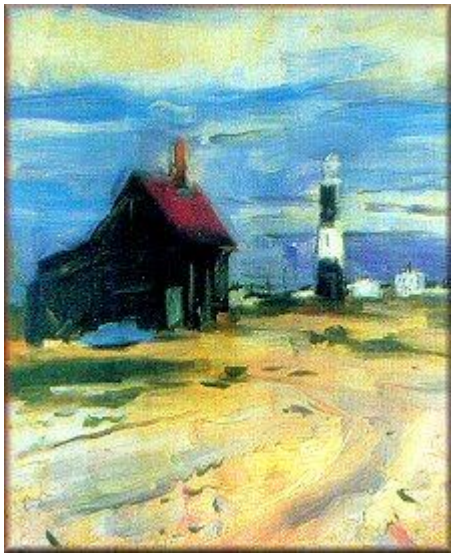

DIFFERENTIAL DIAGNOSIS IN A PATIENT WITH PARKINSONIAN MANIFESTATIONS

Parkinsonism appears clinically in a variety of neurologic disorders (Table 1). Differentiating these syndromes from idiopathic Parkinson's disease (PD) is usually not difficult after a thorough history and examination. In the course of many of these disorders, parkinsonism may be a prominent feature and this makes the diagnosis more challenging. In this chapter, the authors examine a variety of diverse syndromes that can resemble PD in their clinical pictures.

Table 1. CLASSIFICATION OF PARKINSONISM

I. Idiopathic parkinsonism or Lewy body Parkinson's disease (PD)

11. Secondary (symptomatic) parkinsonism

1. **Drug-induced**
2. **Toxin-induced (manganese, methanol, carbon monoxide, MPTP)**
3. **Metabolic disorders (Wilson's disease)**
4. **Vascular parkinsonism**
5. **Postencephalitic/infectious**

6. **Post-traumatic (Pugilistic encephalopathy)**

7. **Others, brain tumours, hypoparathyroidism**

III. Neurodegenerative disease

1. **Progressive supranuclear palsy**

2. **Multiple-system atrophy**

   - **Striatonigral degeneration**
   - **Shy-Drager syndrome**
   - **Olivopontocerebellar atrophy**

3. **Cortico-basal ganglionic degeneration**

4. **Dementia with Lewy bodies**

5. **ALS-parkinsonism-dementia complex of Guam**

6. **Alzheimer's disease with extrapyramidal signs**

7. **Rigid variant of Huntington's disease**

8. **Hallervorden-Spatz disease**

9. **Neuroacanthocytosis**

10. **Fahr disease**

IV Other disorders with parkinsonian features

1. **Normal pressure hydrocephalus**

2. **Psychogenic parkinsonism**

PARKINSONIAN SYNDROMES

- **Drug-induced Parkinsonism**

Drug-induced parkinsonism (DIP) is the most common cause of symptomatic parkinsonism. 7 Any agent that inhibits dopamine metabolism can cause parkinsonian symptoms. The best recognized offending agents are neuroleptics (NL), because of their ability to block postsynaptic D2 receptors. 95 The reported prevalence of DIP in patients receiving long term NL therapy is 10%-15%, which might be an underestimated value. 94 No correlation between cumulative NL-dose intake and the development of DIP has been established; however, the high-potency NL (haloperidol, fluphenazine) are more likely to cause Symptoms. 121 Antiemetics, metoclopramide and prochlorperazine, have a phenothiazine chemical structure, and are frequently overlooked as the

cause of DIP. 44 The clinical features of DIP may be indistinguishable from PD, but for the symmetry of the Symptoms. 85 Usually, symptoms start shortly after the initiation of NL therapy, and 90% of cases are apparent within three months. 85 Elderly women are more prone to the development of DIP. 44 Compared to tardive dyskinesia, symptoms of DIP are reversible with discontinuation of the offending agent. 83 Symptoms usually resolve within a few weeks, however, some cases can last longer, even up to a year. Rare cases of persistent parkinsonism despite withdrawal of NL have been reported. 73 Such cases should raise the suspicion of underlying PD that was clinically unmasked by NL exposure. 15 The presence of mild DIP is not necessarily an indication for NL withdrawal. Functionally disabling DIP should be managed by withdrawal of the offending agent. Atypical NL (clozapine, quetiapine) 145 work through predominantly non-dopaminergic pathways, and as such have much lower propensity to cause DIP. 69, 96,135 These agents provide an alternative option for patients requiring chronic antipsychotic therapy, as well as PD patients with drug-induced psychosis.

Dopamine metabolism can also be blocked at the presynaptic membrane, resulting in DIP. Reserpine (an older antihypertensive agent) and tetrabenazine (an agent used for treatment of hyperkinetic disorders, not available in the United States) deplete brain dopamine by interfering with presynaptic vesicular storage. 100 Neither of these agents has wide clinical use. Aside from the dopamine-depleting/blocking agents, there is a long list of other drugs, reported to be associated with DIP. 86 Calcium channel blockers, used in Europe (cinnarizine, flunarizine), have been implicated in DIP, because of their presumed pre /postsynaptic antidopaminergic effect. 87 The mechanism of DIP in other cases is unclear, but familiarity with the list of offending agents (Table 2) is helpful in making the diagnosis.

Table 2. DRUGS ASSOCIATED WITH PARKINSONISM

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1. Neuroleptics and related agents

2. Presynaptic dopamine-depleting agents (reserpine, tetrabenazine)

3. Miscellaneous*

- **Alpha-methyldopa**
- **Ca-channel Mockers (cinnarizine, flunarizine)**
- **Amiodarone Amphotericine B**
- **Lithium**
- **Pyridostigmine**
- **Fluoxetine**
- **Phelelzine**
- **Procaine**
- **Meperidine**

- **Wilson's Disease**

Parkinsonism as a presenting neurologic manifestation of Wilson's disease (WD) is rare. Familiarity with this condition and a high level of suspicion, especially in young patients with extrapyramidal symptoms, is imperative because of the availability of effective therapy for this disease if diagnosed early. WD is a rare, autosomal recessive condition with a prevalence of 30 cases per million people. 124 The gene is located on chromosome 13. 114 The genetic defect is responsible for excessive deposition of copper in the liver and other organs. 119 The exact molecular defect responsible for these events is unclear, though it has been suggested that the gene codes for the copper transporting ATPase is responsible for keeping copper in the correctly oxidized state. 119 The defect leads to impaired incorporation of copper into ceruloplasmin, the major copper-transporting protein, and reduced biliary copper excretion. 8 Copper excess first accumulates in the liver, and as the liver copper storage capacity is exceeded, the heavy metal is spilled into the other organs, including the brain, causing the neurologic manifestations of the disease. 90

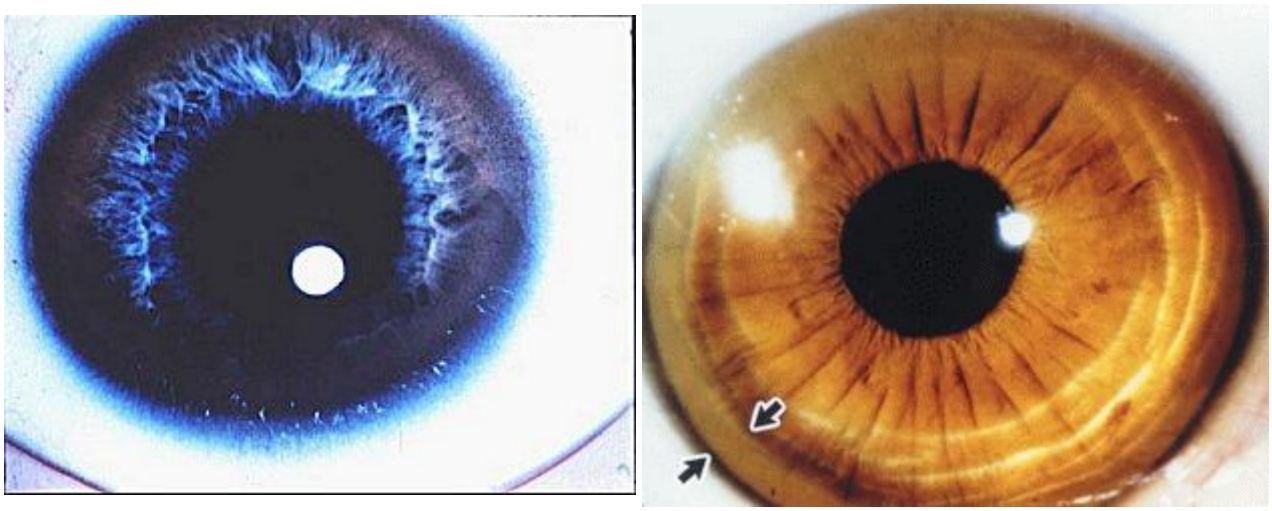

Figure 1. Kayser-Fleischer rings

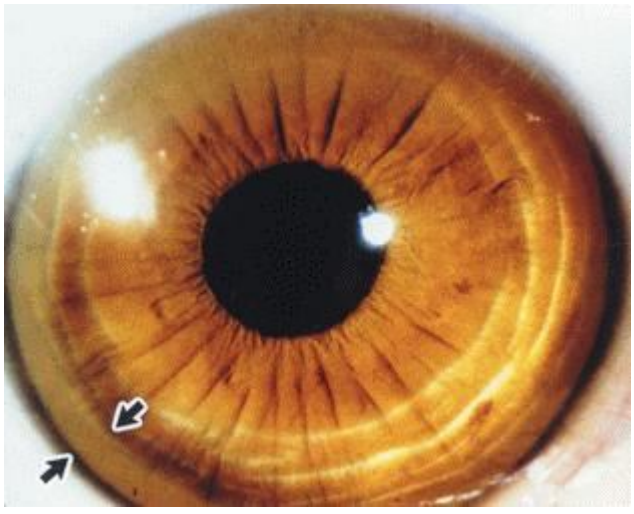

Figure 2. A case of Wilson disease showing degeneration of the caudate nucleus and parts of the corpus striatum. The lesions are symmetrically and bilaterally distributed, presumably representing chronic gliotic and edematous changes. Mild degree of central atrophy is present.

Hepatic dysfunction is the most common presentation in WD. 151 The spectrum can vary from asymptomatic hepato-splenomegaly to fulminant acute hepatitis. 37 Ultimately, patients develop progressive cirrhosis with a postnecrotic picture. 151 The average age of onset of liver dysfunction is 11.4 years, with an average of an eight-year latency to the onset of neurologic manifestations if

the disease is left untreated. 152

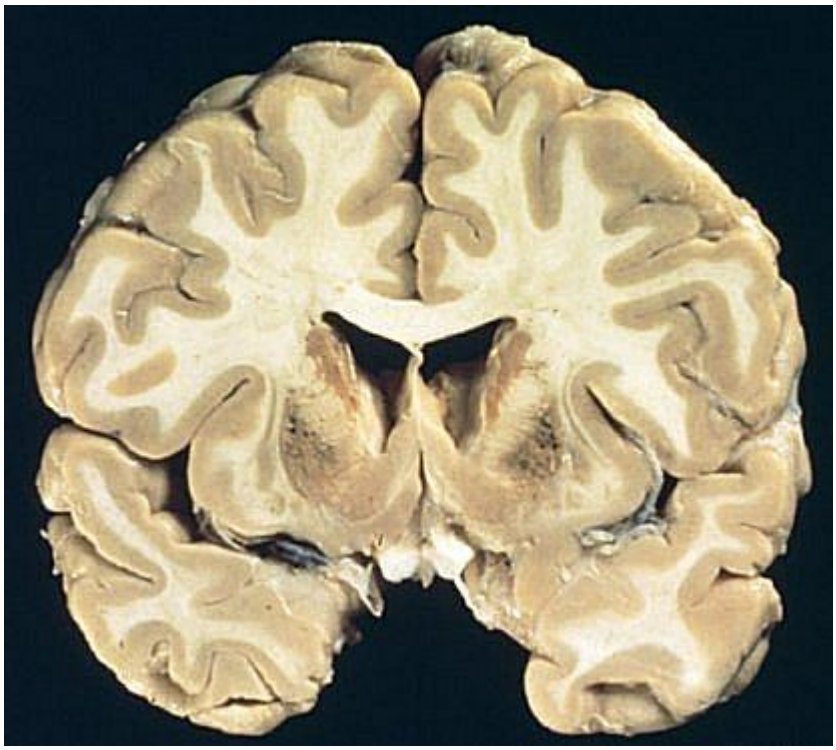

Figure 3. A case of Wilson disease showing degeneration of the caudate nucleus and parts of the putamen. The lesions are symmetrically and bilaterally distributed, presumably representing chronic gliotic and edematous changes. Notice central atrophy.

Neurologic manifestations of WD are highly variable. They are traditionally divided into two forms: classic, characterized by predominantly extrapyramidal dysfunction, mainly dystonia; and pseudosclerotic (West-phal), characterized by predominantly cerebellar dysfunction in the form of intention tremor and dysarthria. 21 **Such classification is arbitrary, as there is a significant overlap of the symptoms. Tremor is the most common neurologic manifestation of WD, present in 50% of individuals.** 42 **The pattern of tremor is highly variable: it can be resting, postural or kinetic; proximal or distal; fine or coarse. A proximal tremor component, if present, is responsible for the characteristic "wing-beating" appearance. Dysarthria is common, eventually affecting the majority of patients; it can be either extrapyramidal (hypokinetic), or cerebellar (scanning) in character. Additional signs of cerebellar dysfunction include gait ataxia and intention tremor. Focal dystonia (facial, pharyngeal, or cervical) can be another neurologic manifestation of WD. An isolated parkinsonian syndrome is unusual, but bradykinetic-rigid features along with other signs of basal ganglia dysfunction can be seen.** 150 **Upper or lower motor neuron dysfunction, as well as sensory deficits are exceedingly rare in WD.** 150

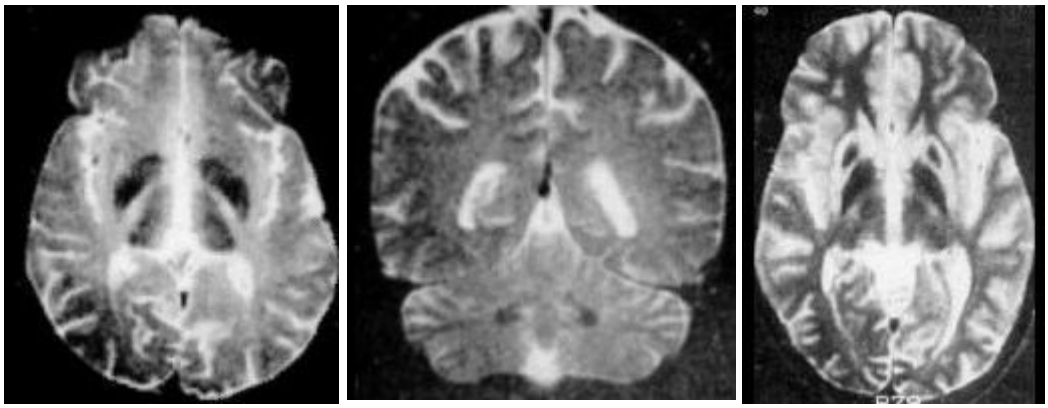

Figure 4. MRI T2 images of wilson disease cases showing hypointensity involving the thalamus and corpus stratum (left image), the dentate nucleus (middle image) and the caudate nucleus

(right image)

Psychiatric symptoms are common in WD, and are the presenting manifestation of the disease in 20% of patients. 92 Signs can vary from behavioral changes to frank psychosis. 93 Dementia is uncommon; however, a certain degree of cognitive deficit can occur. 91

The diagnosis of WD can be readily made as long as the condition is suspected. 117 WD should be considered in the differential diagnosis of any young patient with unexplained neurologic dysfunction involving the basal ganglia and cerebellum. The diagnosis is based on laboratory confirmation of impaired copper metabolism that includes 24-hour urine copper excretion, serum ceruloplasmin, and serum copper in order of sensitivity. 49 Slit-lamp ophthalmologic examination for the presence of copper deposition in the cornea, known as Kayser-Fleischer rings (KFR) is an additional diagnostic tool. 125 It is believed that KFRs are invariably present in all subjects with neurologic manifestations of the disease; however, similar pigmentation can occur with other types of hepatic dysfunction. 109 The confirmatory test for WD is the determination of hepatic copper content through liver biopsy; it is elevated even in clinically asymptomatic WD gene carriers. 8

Curative therapy aimed at correcting the genetic defect is not available. The best treatment results are achieved by early identification of affected subjects and screening of family members for asymptomatic carriers. 117 Treatment is aimed at restoring normal copper balance. This can be achieved either by reducing copper absorption or increasing copper excretion. Brewer 9 provides an in depth discussion of the treatment options. Table 3 provides a brief summary of the available modalities. Therapy has to be continued lifelong. Subjects with liver failure are candidates for liver transplantation. 71

In Wilson disease, the following are observed in the basal ganglia in a bilateral, fairly symmetrical fashion

In the MRI T2 images a mixture of T2 hypointensities and hyperintensities are observed mainly in the basal ganglia and less commonly in the dentate nucleus

- T 2 hyperintense zones are primarily due to cavitations, astrogliosis and spongy degeneration
- T2 hypointense zones, are primarily due to excessive iron deposition in the same areas of copper deposition. This occurs due to low to low-normal levels of plasma iron-binding globulin. Ceruloplasmin directly affects the transfer of iron from tissue cells to plasma transferrin.

Table 3. WILSON'S DISEASE-TREATMENT OPTIONS

Agent	Dose	Side Effects	Comments
Agents that Decrease Copper Absorption			
Zinc	50 mg TID	Gastric irritation	Usually not sufficient for monotherapy in symptomatic individuals, but can be used as primary Tx in asymptomatic subjects
Tetrathiomolybdate (TM)	20-60 mg 3-6 times/day	Potential bone marrow suppression	Usually used for induction Tx for 8 weeks, then switched to zinc

Copper Chelation Therapy			
Penicillamine	**750 mg / 2 grams/day**	**Acute sensitivity reaction (rash, worsening of fever), Nephrotic syndrome. Lupus like symptoms.**	**Can cause transitory worsening of neurological signs at the initiation of Tx.**
British antilewisite (BAL)	**Parenteral administration**	**Multiple**	**This agent is practically abandoned**

WD is a rare, potentially life threatening but treatable condition, if identified early. "Suspicion of the disease" is the single most predictive factor for early diagnosis and successful treatment. 117

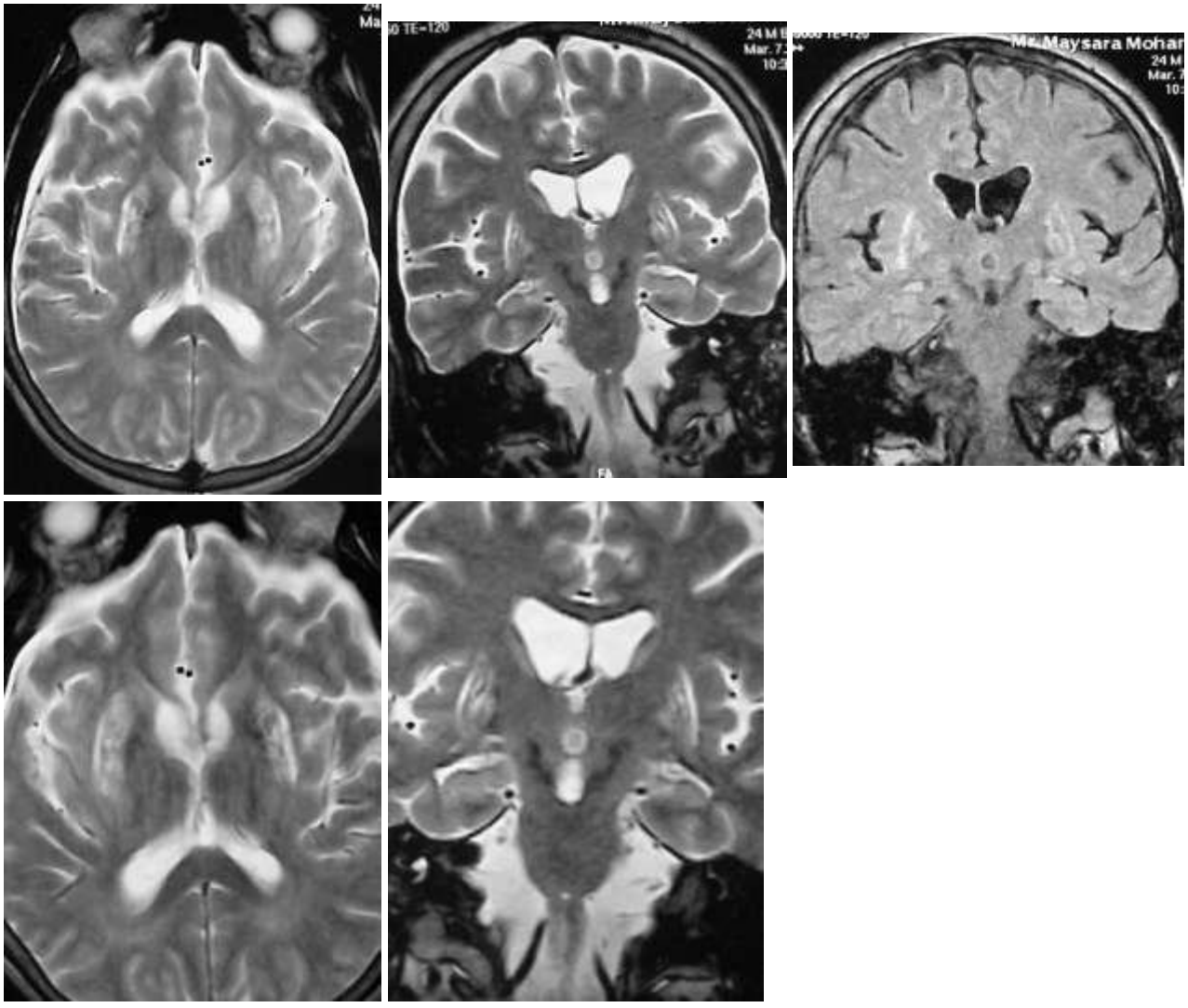

Figure 5. Wilson's disease has a relatively characteristic appearance, particularly on high field strength MR imaging studies. Signal hyperintensity on T2-weighted images exists in the putamen symmetrically and bilaterally, presumably representing chronic gliotic and edematous changes. Within the putaminal high signal intensity, irregular areas of low signal intensity are also frequently observed on the T2-weighted images. These areas of low signal intensity are somewhat characteristic of Wilson's disease and most likely represent increased iron accumulation, occurring secondary to the increased copper distribution in the putamen.

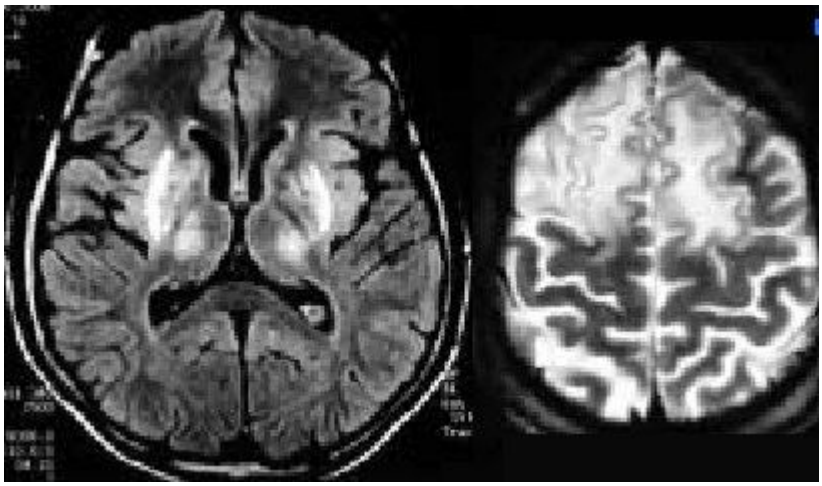

Figure 6. **MRI T2 images showing the classical picture of wilson disease. Bilateral, symmetrical hyperintensity in the thalamus and basal ganglia and the bilateral frontal regions**

SUMMARY

Wilson disease is an autosomal recessive disorder; the gene is located on the long arm of chromosome 13 at the esterase D locus. The world-wide prevalence of the disease is about 30/ million, with a gene frequency of 1:180. Although most patients show markedly diminished serum ceruloplasmin concentrations, the localization of the gene for ceruloplasmin to chromosome 3 indicates that failure to form the copper protein is not the primary defect. Studies with radioisotopes indicate that the dynamic turnover of copper is disturbed. After intravenous administration of ^{64} Cu to a normal person, there is a rapid rise of serum copper content followed by an equally rapid fall and, commencing at about 6 hours postinfusion, a secondary slow rise as ceruloplasmin enters the serum. In Wilson disease, the initial rise is more extensive, the secondary rise is not observed, and no radioactivity enters the globulin fraction where ceruloplasmin is normally found. This phenomenon is also noted in patients who have nearly normal ceruloplasmin concentration and in children who lack the protein, which is an indication that the rate of copper transfer from the albumin into the globulin fraction is reduced.

In addition to these abnormalities, plasma levels of nonceruloplasmin copper are increased, and the biliary excretion of copper is reduced-. Equally unexplained are the low to low-normal levels of plasma iron-binding globulin. These abnormalities also, occur in asymptomatic carriers and suggest that Wilson disease may also involve a disorder of iron metabolism; ceruloplasmin directly affects the transfer of iron from tissue cells to plasma transferrin.

Another metabolic feature is a persistent aminoaciduria. This is most marked during the later stages, but may be noted in some asymptomatic patients. The presence of other tubular defects (e.g., impaired phosphate resorption in patients without aminoaciduria) suggests that a toxic action of the metal on renal tubules causes the aminoaciduria. The most plausible explanation of the copper accumulation and other features of Wilson disease is that there is a defect of an energy-mediated secretary mechanism for the metal in hepatocytes, possibly in hepatic lysosomes, and that a similar defect prevents copper from entering the ceruloplasmin compartment.

The abnormalities in copper metabolism result in a deposition of the metal in several tissues. Anatomically, the liver shows focal necrosis that leads to a coarsely nodular, postnecrotic cirrhosis; the nodules vary in size and are separated by bands of fibrous tissue of different width. Some hepatic cells are enlarged and contain fat droplets, intranuclear glycogen, and clumped pigment granules; other cells are necrotic and there are regenerative changes in the surrounding parenchyma.

Electron microscopic studies have shown that copper is sequestered by lysosomes that become more than normally sensitive to rupture and therefore lack normal alkaline phosphatase activity. Copper probably initiates and catalyzes oxidation of the lysosomal membrane lipids, resulting in lipofuscin accumulation. Within the kidneys the tubular epithelial cells may degenerate and the cytoplasm may contain copper deposits.

In brain, the basal ganglia show the most striking alterations. They have a brick-red pigmentation; spongy degeneration of the putamen frequently leads to the formation of small cavities. Microscopic studies reveal a loss of neurons, axonal degeneration, and large numbers of protoplasmic astrocytes, including giant forms known as Alzheimer cells. The cortex of the frontal lobe may also show spongy degeneration and astrocytosis. Copper is deposited in the pericapillary area and within astrocytes, where it is located in the subcellular soluble fraction and bound not only to cerebrocuprein but also to other cerebral proteins. Copper is uniformly absent from neurons and ground substance.

Lesser degenerative changes are seen in the brain stem, the dentate nucleus, the substantia nigra, and the convolutional white matter. Copper is also found throughout the cornea, particularly the substantia propria. In the periphery of the cornea the metal appears in granular clumps close to the endothelial surface of the descemet membrane. The deposits in this area are responsible for the appearance of the Kayser-Fleischer ring. The color of this ring varies from yellow to green to brown. Copper is deposited in two or more layers, with particle size and distance between layers influencing the ultimate appearance of the ring.

In Wilson disease, an abnormal striatum depicted on MR images correlated with pseudoparkinsonian signs, an abnormal dentatothalamic tract correlated with cerebellar signs, and an abnormal pontocerebellar tract correlated with pseudoparkinsonian signs.

On the other hand the presence of portosystemic shunt was strongly associated with abnormality of the globus pallidus.

Table 4. Differences between brain neuroimaging findings in wilson disease and non -Wilsonian chronic liver disease

Parameter	Wilson disease	Non Wilsonian chronic liver disease
Anatomical site of cranial involvement	Putamen and caudate nuclei	Globus pallidus, pituitary gland
MRI signal changes	T1: No significant changes T2: A mixture of hyper and hypointensities	T1: Precontrast T1 hyperintensity T2: No significant changes
Aetiology of MRI signal changes	Spongy degeneration, cavitations, astrogliosis, and iron deposition	Manganese accumulation
Association with clinical symptoms and signs	Symptomatic and correlates with pseudoparkinsonian signs	Asymptomatic

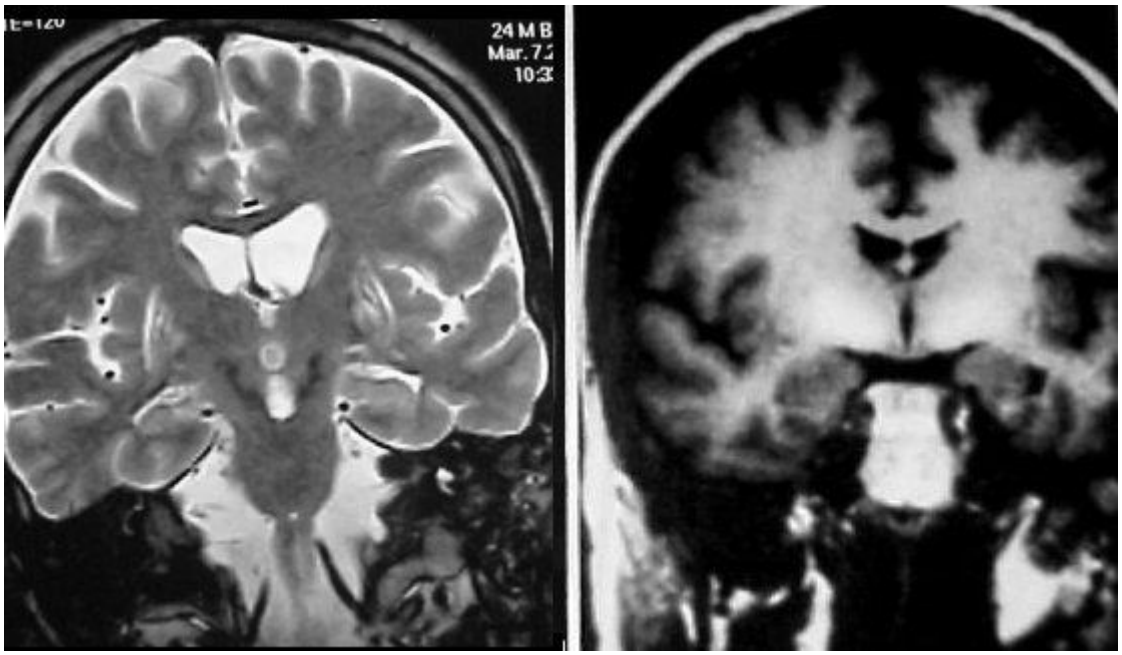

Figure 7. A, MRI T2 image of a patient with wilson disease, B, Precontrast MRI T1 image of a patient with hepatic encephalopathy due to causes other than Wilson disease. Notice the T2 mixture of hyper and hypointensities (in the putamen and head of caudate nuclei) in Wilson disease (A) which is always symptomatic and correlates with pseudoparkinsonian signs, while in hepatic encephalopathy there is asymptomatic precontrast hyperintensity in the globus pallidus.

- **Infectious and Postinfectious Parkinsonism**

The prototype of parkinsonism, caused by an infectious process, is von Economo's encephalitis (EE), also known as encephalitis lethargica. 117 This syndrome now, fortunately, of only historical interest, was the major cause of parkinsonism at the beginning of the twentieth century. It was associated with a viral epidemic in 1917. 11 It is estimated that by 1924, about one million people worldwide were affected by the disease. 101 Subsequently, the epidemic slowed, but cases continued to be reported until 1936. 143 The disease started as a nonspecific viral infection associated with fever and minimal respiratory signs. 148 Acute neurologic manifestations of the disease were highly variable but localized predominantly to the midbrain; most patients exhibited pathologic somnolence, which lasted for days or weeks. Another characteristic feature was ophthalmoplegia.

Some patients developed hyperkinetic signs: chorea, dystonia or myoclonus. 147 Parkinsonism during the acute phase of the illness was rare. The disease carried mortality rates of 30%-40% in the acute phase. 143 Patients who survived were left with variable degrees of neurologic disability. The unique feature of EE was the transformation of the acute illness into a chronic one. 99 Even subjects who had fully recovered from the initial insult had recurrence of the disease. There was no correlation between the severity of the initial insult and the final outcome. 99 The most common manifestation of the delayed sequelae of the infection was a parkinsonian syndrome, postencephalitic parkinsonism (PEP). 148 The latency from acute illness to onset of PEP varied: the minority developed it immediately, half of the patients by five years, and 80% by ten years. 26 Practically no new cases were reported by the 1950s. Clinically PEP differed from PD. Aside from parkinsonian signs, patients had various hyperkinetic movements including chorea, tics, and myoclonus. 79,155 Tremor was much less common than in PD. Ocular signs, including blepharospasm, apraxia of eye opening, and ocular motility abnormalities, including oculogyric crises occurred in up to 90% of survivors. 137 Cognitive dysfunction was notoriously absent. 155 Despite the rapid progression of the symptoms in the initial phase, there was stabilization of the

disease, with little if any progression for decades, except for rare exceptions. 13,26

The etiology of EE/PEP remains unknown. 112 **Though the influenza virus has been implicated, causality is unlikely** 23,28,110 **Multiple subsequent influenza epidemics were not associated with similar neurological manifestations. The disease was not contagious, and viruses or viral antibodies have never been recovered from PEP patients.** 28 **Autopsy data on subjects with PEP is remarkably consistent, notable for pronounced neuronal loss and gliosis in the substantia nigra and, to a lesser degree, the locus ceruleus." The degree of cell loss exceeds that of PD.** 46 **Lewy bodies are absent, but neurofibrillary tangles (NFT) are present.** 52 **It is difficult to evaluate the response of PEP to levodopa therapy because of the very small number of treated patients. Symptoms responded to levodopa less predictably than in PD, and treatment was associated with more side effects.** 12,25

The cause of EE will probably remain a mystery. It is remarkable that a disease of a presumed viral etiology that reached the extent of pandemic has never recurred. 14 **Even if the mystery of EE remains unsolved, the disease played a crucial role in the study of the pathophysiology of PD. EE experience, specifically the pathology data, helped to focus on the substantia nigra as the area of major insult in PD.** 40 **Most researchers agree that PEP and PD are two unrelated entities, though the possibility of a remote viral process being a risk factor for the development of PD is still debated.** 14,78,18,89,138

- **Other Infectious Causes of Parkinsonism**

Theoretically, any global encephalitic process, affecting the basal ganglia region, can clinically manifest with acute parkinsonian symptoms. Parkinsonism has been reported in the setting of a number of acute infectious processes, including HIV 1 infection, stage III of SSPE, various viral encephalitidies, and syphilis. 106, 118,132,139 **Such clinical reports are exceedingly rare. A more definitive relationship has been established between direct basal ganglia invasion by fungi or parasites and the development of parkinsonian symptoms.** 2,146 **Adler et al** 2 **reported a patient with bilateral straital abscesses who developed subacute asymmetric parkinsonism. Biopsy revealed the presence of hyphae, consistent with either aspergillus or mucor. Symptoms improved after systemic antifungal therapy Verma et al** 146 **reported a case of reversible parkinsonism caused by a cysticercus cyst located in the midbrain.**

- **Vascular Parkinsonism**

Vascular (arteriosclerotic) parkinsonism (ASP) is probably one of the most debated entities in the study of parkinsonism. 36 **The term was introduced more than 100 years ago, when a syndrome of gait disorder of the elderly, characterized by a small step gait, march a petit pas, mild hemiparesis, dementia, dysarthria and urinary incontinence was ascribed to arteriosclerotic cerebrovascular disease. The clinical syndrome was correlated with the pathologic findings of multiple basal ganglia cavitations (etat crible) and infarcts (etat lacunaris). In 1929, Critchley** 17 **defined the syndrome in a landmark monograph on the subject. Despite the lack of PD-defining pathology at the time, he separated vascular parkinsonism from PD, based on clinical features. He described gegenhalten (lead-pipe) rigidity, lack of tremor, shuffling gait with freezing, acute/step wise progression of the symptoms in the setting of hypertensive disease as characteristic features separating ASP from PD. Despite great advances in the knowledge of the pathology and treatment of PD, researchers have added little to the clinical description of ASP.** 116 **The introduction of levodopa in the late 1960s revolutionized the treatment of PD. The presence of a clear response to levodopa is an obligatory diagnostic criteria of PD and, a lack of response separates patients with atypical parkinsonism, including ASP, in the majority of cases.** 103 **The advent of computed tomography (CT) scanning and magnetic resonance imaging (MRI) contribute to the evolving definition of ASP. Imaging studies allow correlation between the degree and distribution of**

vascular changes and ASP. 35,159

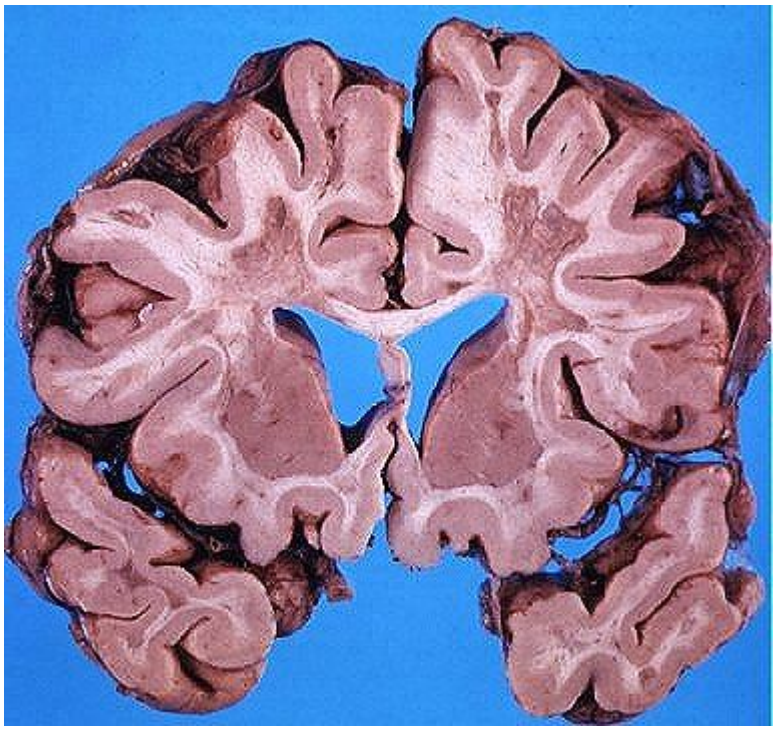

Figure 8. Postmortem specimen. Note the topographically extensive periventricular white matter changes in a hypertensive case with evidence of leukoaraiosis on MRI study

The periventricular distribution of vascular changes is implicated as the reason for the marked gait dysfunction caused by involvement of the pathways leading to the legs. 24,144 **The term "lower body parkinsonism" was introduced in the 1980s to stress that relationship.** 38,64 **A considerable overlap exists between that syndrome and the "pure" gait disorder of the elderly without clinical evidence or known risk factors for vascular disease.** 60 **Elderly subjects with gait dysfunction are more likely than asymptomatic people of the same age to have periventricular white matter changes on imaging studies.** 20,75 **With widespread use of MR imaging, it is now clear that periventricular white matter changes (leukoaraiosis) in no way can be diagnostic of ASP: they can be seen in asymptomatic individuals and may be nonspecific markers of aging,** 24,35 **In summary, short of pathologic confirmation of the diagnosis, clinicians still have to rely on clinical diagnostic criteria of ASP, making an attempt to rule out other potential causes of gait dysfunction in the elderly.** 98 **Hurtig** 60 **has outlined strict diagnostic criteria of "true" vascular parkinsonism, as follows:**

1. Acute or subacute, preferably stepwise, evolution of an akinetic- rigid syndrome, usually without tremor.

2. The presence of vascular risk factors, especially hypertension or prior strokes.

3. Brain imaging studies (CT scanning or MRI) showing two or more infarcts in the basal ganglia.

4. Clinical improvement without anti-PD therapy, and specifically no deterioration after withdrawal of PD therapy.

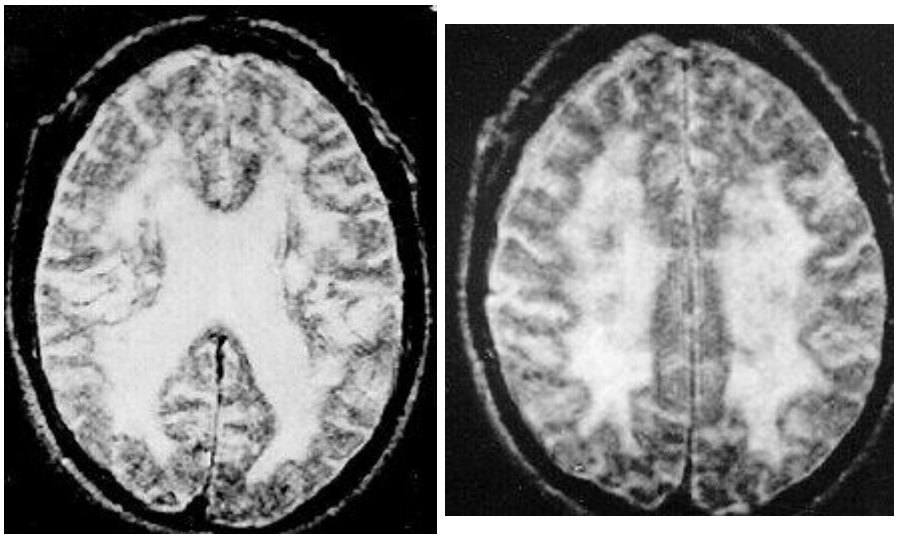

Figure 8. leukoaraiosis, MRI T2 image. The MRI T2 periventricular hyperintensities are mainly due to astrogliosis and interstitial edema.

Adherence to these criteria might exclude some "true" cases of vascular parkinsonism but at the same time will minimize the chance for a false-positive diagnosis. There is no specific therapy for vascular parkinsonism other than aggressive gait physiotherapy. Measures aimed at stroke risk reduction may slow progression.

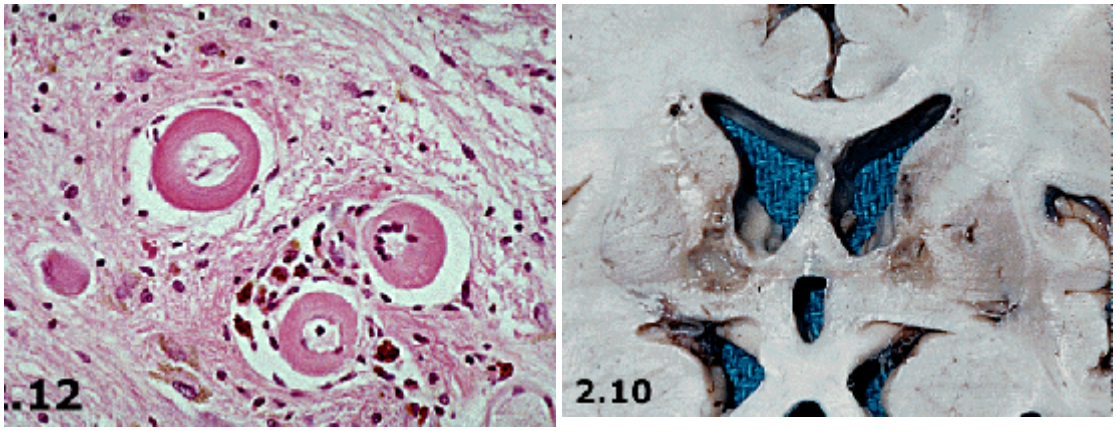

Figure 10. A, lipohyalinosis, B, lacunar infarction

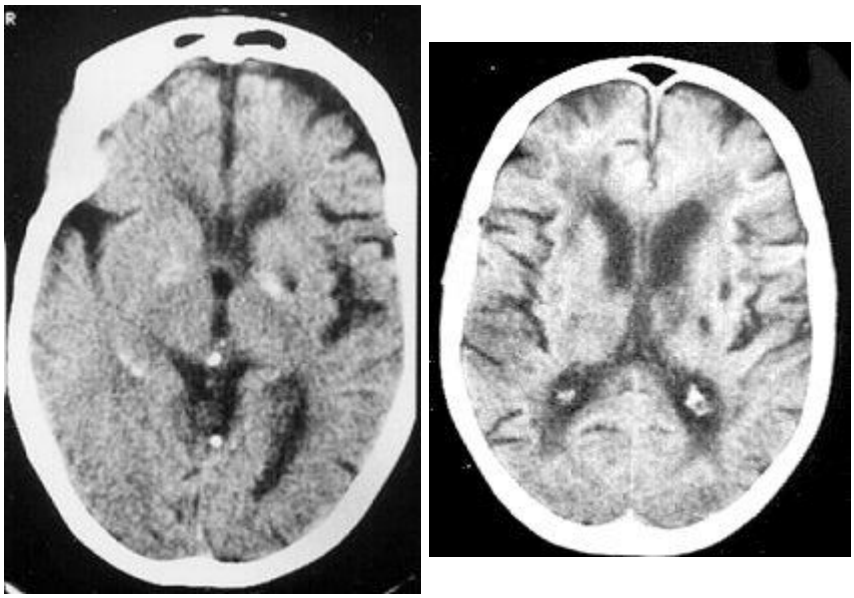

Figure 11. **Periventricular lacunar infarctions and calcifications**

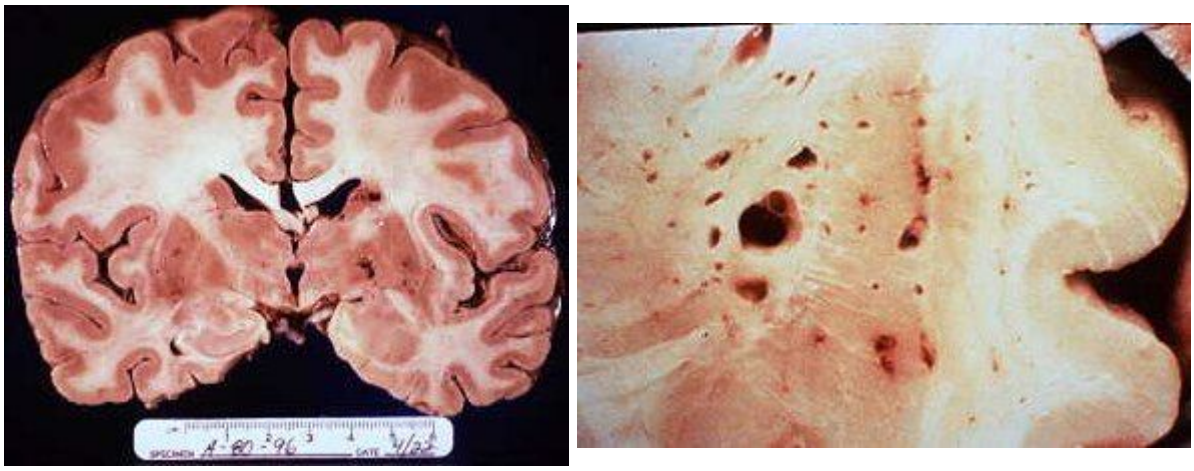

Figure 12. **Lacunes. Small cavitary infarcts, resulting from hypertension, most frequently involving the basal ganglia (caudate nucleus, globus pallidus, putamen, and amygdala) and basis pontis. Compare right with left.**

- **Trauma as a Cause of Parkinsonism**

The relationship between trauma and parkinsonism has been a subject of debate since James Parkinson 104 first implicated trauma as the cause of the syndrome that now bears his name. There is now a unanimous consensus that trauma does not cause PD; however, the notion of post-traumatic symptomatic parkinsonism has evolved. 30,65,76 In the present understanding of the term, post-traumatic parkinsonism is a syndrome that occurs as a result of a significant head trauma, which results in structural damage to the basal ganglia or midbrain. 32 The diagnosis of post-traumatic parkinsonism should not be made in the absence of such findings on brain imaging studies (CT scanning or MRI) . 76,82 The neurologic sequelae of trauma usually is not limited to the signs of basal ganglia dysfunction, but also reflective of global encephalopathy, pyramidal, and cerebellar changes. 32 A bradykinetic-rigid syndrome usually evolves shortly after the injury; however, symptoms can be progressive despite an otherwise static encephalopathy. Symptoms can start unilaterally, and subsequently generalize. Considering the high incidence of head trauma, post-traumatic parkinsonism is rare. jellinger 66,67 reported that of 520 patients with

parkinsonism evaluated pathologically, only three cases were caused by head trauma.

Dementia pugilistica (chronic encephalopathy of boxers) represents a distinct post-traumatic parkinsonian syndrome. 68 It usually has an insidious onset, and is attributed to the cumulative effect of multiple concussive head injuries. 51 Clinical manifestations include dementia, parkinsonism, ataxia, and dysarthria. Resting tremor, unlike other parkinsonian syndromes, is very common. The syndrome is irreversible. 41 Imaging studies demonstrate a variable degree of diffuse cerebral atrophy, ventricular dilatation, and frequently, cavum septum pellucidi. 68 Neuropathologic findings correlate with the clinical manifestations, and demonstrate cell loss in the substantia nigra, hippocampal gyrus, and amygdala. 113 Neurofibrillary tangles are present but Lewy bodies are characteristically absent." Parkinsonian symptoms may respond to dopaminergic therapy, and a trial is warranted. 68

No causality between PD and trauma has been established; however, the concept of head trauma as a risk factor for PD has been debated. 58,140 Data on the effect of head trauma on the time of onset of clinical manifestations of PD and the rate of progression of symptoms is controversial. 31,48, 82,136 Most of the studies are retrospective. A single prospective study of 821 patients did not demonstrate a relationship between PD and head trauma, however, a transient worsening of pre-existing PD symptoms, sometimes occurred, but was reversible three months after the injury. 153 It is possible that head trauma might exacerbate PD symptoms that prior to the insult were clinically compensated, producing a slightly earlier age of disease onset.

- **Hemiparkinsonism-Hemiatrophy**

Hemiparkinsonism-hemiatrophy syndrome is a rare condition characterized by the combined appearance of atrophy and parkinsonism on one side of the body. 74 The cause of the syndrome is believed to be an early perinatal brain injury, usually of anoxic etiology. Patients typically are neurologically normal until middle age. The hallmark of the syndrome is the presence of unilateral or markedly asymmetric parkinsonism in conjunction with ipsilateral body atrophy Hemiatrophy is evident with smaller extremities on one side of the body; typically, the arm and hand are affected and it may be subtle or more significant. Dystonia frequently is the initial manifestation, which then progresses to parkinsonism involving the atrophic side of the body. The mean age of onset of parkinsonism is 43.7 years. 10 Symptoms are slowly progressive, and therapy may not be needed for more than ten years.

The diagnosis is supported by radiologic findings of significant brain asymmetry on CT scanning or MRI. Brain hemiatrophy can be present even in the absence of clinical signs of body hemiatrophy. 10 FDG PET scanning also shows asymmetric metabolism. There is hypometabolism in the basal ganglia and the medial frontal cortex. ^{18} F fluorodopa PET scanning reveals decreased striatal ^{18}F levodopa uptake. 111

- **Machado-Joseph Disease, Spinocerebellar Ataxia 3**

Some of the inherited spinocerebellar ataxias (SCA) present with parkinsonian features. Typically, as the disease progresses, ataxia becomes a more prominent feature. The rate of progression compared to that of PD is more rapid. Machado-Joseph disease (MJD), SCA-3, is an autosomal dominant disease transmitted through an expanded CAG trinucleotide repeat on chromosome-14. The CAG trinucleotide codes for the protein Ataxin-3. Because of the long polyglutamine stretch in the abnormal form of Ataxin-3, the protein adapts an abnormal confirmation within the nucleus of the affected cells. 107 The rate of disease progression in MJD correlates with the CAG repeat length.

MJD was initially described in families of Azorean ancestry. 53 The mean age of onset is 37.4

years. Typical initial symptoms involve problems with balance, difficulty walking, dysarthria, and impaired dexterity. Vision may be impaired early in the course of the disease. Ocular motor findings include nystagmus, vertical gaze palsy, absent saccadic eye movements, lid retraction, and blepharospasm. 5 The speech becomes dysarthria with a spastic pattern. Dysphagia is common fairly early in the course of the illness. Most patients are found to have some component of cerebellar ataxia which eventually progresses leaving the patient nonambulatory. There are some patients who present with more of a spastic rigid or akinetic-rigid syndrome. There may be components of dystonia seen as well. Some patients exhibit the typical resting tremor seen in PD and, when ambulatory, also have freezing episodes. 53

Gradual cognitive decline is part of this disease. Affective changes also are prominent, and sleep disturbance is an issue. Restless legs syndrome (RLS), which is also commonly found in patients with PD, is a fairly common sleep disturbance in patients with MJD. In one study by Schols et al, 127 45% of patients with MJD studied had RLS. Peripheral nerve problems are also evident. There may be muscle atrophy, sensory loss, and loss of deep tendon reflexes. 158 There is significant phenotypic variability with this disorder even within families with the same genetic mutation. The course of the disease is progressive. The rate of progression is faster than PD. The majority of patients become nonambulatory within five to fifteen years. The median survival time is approximately twenty years from diagnosis.

MRI findings in patients with MJD typically reveal decreased width of the superior cerebellar peduncles, atrophy of the frontal and temporal lobes, and decreased diameter of the globus pallidus, and the pons. 97 MR images reveal more severe brain stem and cerebellar atrophy with longer repeat length when adjusted for age. 1 In MJD patients with extrapyramidal signs, 99mTc-TRODAT-1 brain single positron emission tomography (SPECT) scanning shows decreased binding, reflecting decreased presynaptic dopamine availability. 156 Fluorine-18-fluorodeoxy-glucose (FDG) positron emission tomography (PET) scanning is abnormal in both symptomatic and asymptomatic gene carriers with MJD. There is decreased FDG usage in the cerebellar hemispheres, occipital cortex, brain stem, and increased FDG metabolism in the parietal and temporal cortices. 134

Pathology involves cell loss in the pons, substantia nigra, anterior horn cells, and Clarke's column. 123 There is degeneration of the spinocerebellar tract and the cerebellar white matter. Pathologically, there is aggregation of the polyglutamine containing fragments of Ataxin-3. Internuclear inclusions are seen in neurons in affected brain regions. 105 Ocular motor neurons are lost. The vestibular nuclei are frequently involved. There is also significant cell loss or gliosis in the dentate, caudate, and putamen. The olives are spared. The striatum typically is minimally affected.

- **Hallervorden-Spatz Syndrome**

Hallervorden-Spatz syndrome (HSS) is a rare autosomal recessive disease that has been mapped to chromosome 2Opl2.3-pl3. 124 The symptoms usually start in childhood. Symptoms involve the cognitive, speech, and motor domains. Children demonstrate signs of cognitive and motor regression, the speech becomes dysarthric, and extrapyramidal symptoms appear. Typical symptoms at onset involve difficulty walking or postural abnormalities. Personality changes and cognitive changes infrequently are the presenting symptoms. Rigidity gradually progresses. Spasticity associated with hyperreflexia is seen in over half of the cases. Dysarthria becomes evident in all cases. Dystonia, chorea, and tremor are also seen. Optic abnormalities are seen in HSS patients including pigmentary retinopathy and optic atrophy. Movement disorders associated with HSS include rigidity which can involve half of the body, axial structures, arms, legs or be generalized . 22,27 Dystonia is also seen typically involving the facial musculature and the feet. 129 Chorea is seen, and has recently been described as the presenting feature in a woman with adult

onset of symptoms. 50 Resting or action tremor can be another symptom. Parkinsonism as an initial manifestation is rare, and usually occurs in adult onset cases. 62 In rare adult- onset cases presenting symptoms can be indistinguishable from PD with signs of bradykinesia, rigidity, resting tremor, hypomimia and stooped posture as well as gait impairment. Patients quickly develop other features, like lid apraxia, profound dementia, and aphonia, suggesting an alternative diagnosis. In juvenile HSS, parkinsonism as a presentation is rare although some features of the syndrome, mainly rigidity, can occur over the course of the disease. The cognitive abnormalities are common in HSS: they can be present from birth or start as time goes on. They may precede the motor symptoms of the disease. 62 Seizures can also be seen in this disorder. The disease usually starts between the ages of seven and twelve. The disorder typically progresses and leads to death within twenty years.

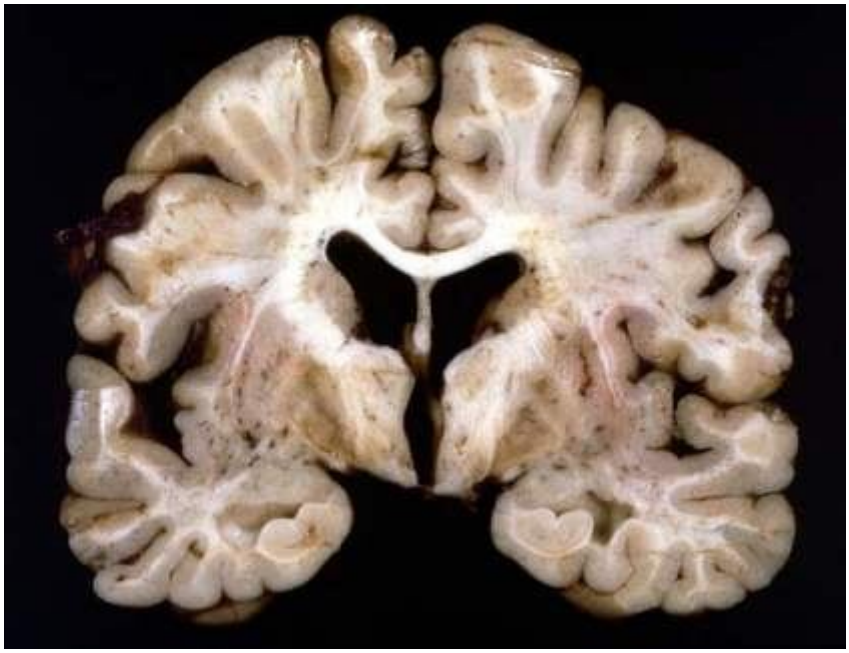

Figure 13. Coronal section of the brain at the level of the lenticular nuclei and mamillary bodies in a case of Hallervorden-Spatz Syndrome shows a brown-bronze discoloration of globi pallidi, diffuse cerebral atrophy and moderate ventricular dilatation.

Definitive diagnosis of HSS can only be made histologically. Presumptive clinical diagnosis is based on the constellation of the clinical signs, supported by the neuroimaging data. CT scanning may reveal cerebral atrophy with increased ventricular size. Mineralization of the globus pallidus is also seen. 6 Hyperlucency of the putamen and globus pallidus is seen on CT scanning. MR imaging is more sensitive. There is decreased T-2 weighted and proton density signal in the globus pallidus, which is caused by iron deposition. 122 In some patients there is a hyperintense area within the area of hypointensity, "the eye of the tiger sign. "129

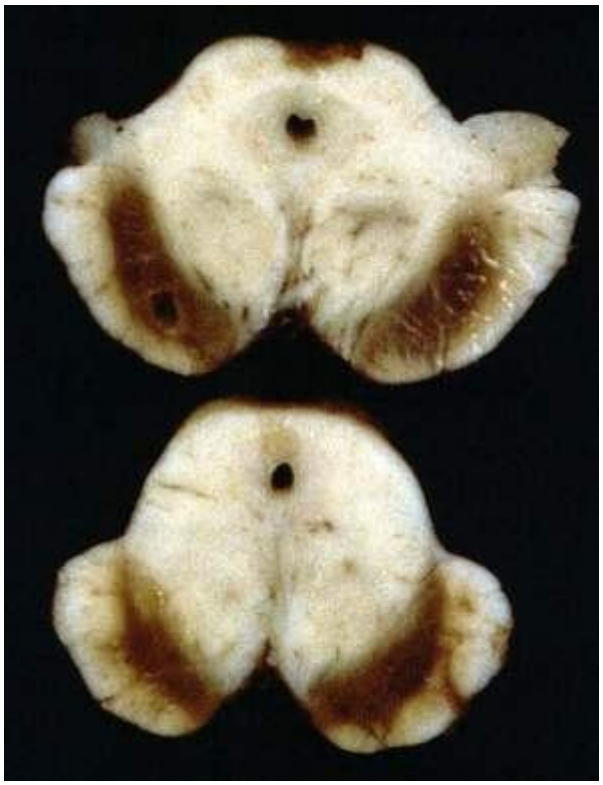

Figure 14. Cross section of the midbrain in a case of Hallervorden-Spatz Syndrome shows a dense brown-bronze discoloration of the substantia nigra.

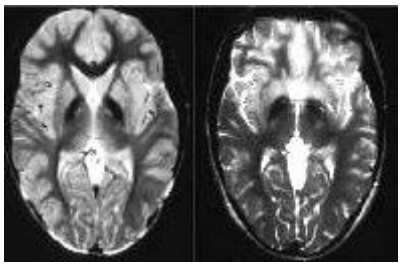

Figure 15. MRI has increased the likelihood of antemortem diagnosis of Hallervorden-Spatz (HSD)disease. The typical MRI appearance is of bilaterally symmetric hyperintense signal changes in anterior medial globus pallidus with surrounding hypointensity in the globus pallidus on T-2 weighted images. These imaging features are fairly diagnostic of HSD and have been termed the “eye-of-the-tiger” sign. The hyperintensity represents pathologic changes including gliosis, demyelination, neuronal loss, and axonal swelling, and the surrounding hypointensity is due to loss of signal secondary to iron deposition.

Pathologically, the hallmark of the disease, is rust-brown discoloration of the pars reticulate of the substantia nigra and the internal segment of the globus pallidus. The pigmentation is caused not only by the abnormal iron deposition, but also high concentration of the organic pigments, lipofuscin, and neuromelanin. 102 Histologically, distal axonal swellings are seen on electron microscopy. When large, these swellings are termed "spheroids". 27 Spheroids are found diffusely within the central nervous system in the striatum, cortex, thymus, subthalamus, and brain stem. 22 The cerebellum may be involved as well. The contents of the spheroids are variable including mitochondria, myelin fragments, filaments, vescicles, lipofuscin, and amorphous material. 108 The pathogenesis of spheroid formation is unclear. Theories invoke pseudoperoxidation, because of the iron accumulation and dying back of axons because of neuronal pathology. 72,108 Lewy bodies are occasionally seen in HSS. These are typically located in the substantia nigra, but can be seen diffusely as well. Alphasynuclein is also seen in the Lewy bodies in HSS. 149 Neurofibrillary tangles also can be seen and are ultrastructurally and immunocytochemically identical to those seen in Alzheimer's disease but are not typically cortical. 27 They are seen in the substantia nigra, and subthalamic nucleus, areas not typically affected in AD.

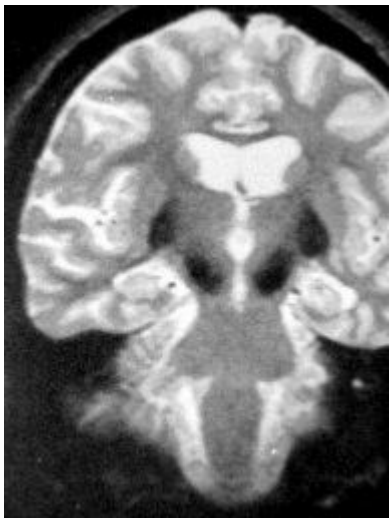

Figure 16. Hallervorden-Spatz disease. Prominent abnormal signal hypointensity in the globus pallidus and substantia nigra with associated atrophy in a 9-year- old child.

- **Amyotrophic Lateral Sclerosis/ Parkinsonism-Dementia Complex**

Amyotrophic lateral sclerosis (ALS)/parkinsonism-dementia complex is a unique disorder found in Guam. The etiology of this disorder remains unknown, however, one theory links it to a dietary toxin exposure. Cycad flour was used extensively in the diet of the Chamorro people of Guam during World War 11. This flour, made from the plant Cycas circinalis contains BMAA, beta-N-methyayoaminos-L-alanine. This is an excitatory neurotoxin. Defective glutamate transport may lead to increased levels of extracellular glutamate and neurotoxic nerve cell death. Clinically, patients can present with either a pure ALS type picture or a pure parkinsonian syndrome. With the latter presentation, the initial signs are typically dementia or bradykinesia, less often rigidity and tremor. In the ALS presentation the first sign is typically atrophy in combination with spasticity. The age of onset of the predominantly parkinsonian syndrome is later than the ALS type syndrome: fifth versus fourth decade, respectively. 80 Men are more often affected than women, with a ratio of greater than two to one. The clinical course of the parkinsonian syndrome is rapid with progression of bradykinesia, gait disturbance, and balance problems eventually leading to immobility. Forty percent (40%) of the patients presenting with parkinsonism at the onset eventually developed signs of motor neuron disease and a minority of them developed muscle atrophy. 115 Aside from motor disability, ocular motility problems including abnormalities of saccades, pursuit, nystagmus, and vestibular ocular reflexes may be present. 141 pigmentary retinopathy has also been found in this population. 16 Olfactory dysfunction is seen in all subtypes of Guamanian ALS-Parkinsonism dementia complex. 4

Pathologically, the ALS form shows neurofibrillary tangles and granulovacuolar degeneration in the cortex as well as findings of motor neuron disease. Hirano bodies are present in the amygdala, hippocampus, the basal ganglia, the reticular formation, the dentate nucleus of the cerebellum, and the posterior and anterior horns of the spinal cord. 115 Parkinsonism pathology shows cortical atrophy and ventricular dilatation. 54 Again, neurofibrillary tangles and granulovacuolar inclusion bodies are seen. 55 The distribution of NFrs is similar in the parkinsonian and the ALS forms, but there is a higher NFT density in the PD form. 56 Lewy bodies are rare. 55

Parkinsonism is seen with amyotrophy in cases outside of Guam. It has been reported to occur in both sporadic and familial forms. 56,126 The majority of patients become symptomatic in their fifth decade of life. There is equal appearance of parkinsonism and amyotrophy, and about one-third of patients develop both simultaneously As in the Guamanian syndrome, the male to female ratio is approximately two to one. 59 The occurrence of dementia in the syndrome is variable. It

can occur at any point in the disorder, overall, affecting over half of the patients. Other parkinsonian syndromes may have amyotrophy in addition to the more typical features. These include olivopontocerebellar atrophy, Shy-Drager syndrome, postencephalitic parkinsonism, Creutzfeldt-jakob disease, pallidoluysionigral atrophy, neuroacanthocytosis, MJD, and Gerstmann- Strdussler-Scheinker disease. 133

Pathologically, cell loss is seen in the substantia nigra and anterior horn cells of the spinal cord. There are areas of cell loss within the striatum, globus pallidus, thalamus, red nucleus, and dentate nucleus. 59 **Spongiform changes are seen in the frontal and temporal cortices.** 47,57

- **Huntington's Disease**

Huntington's disease (HD) is typically a hyperkinetic movement disorder. The juvenile form of HD can present with an akinetic rigid syndrome at its onset. HD is an autosomal dominantly inherited disease, associated with an abnormal CAG trinucleotide repeat expansion, localized on chromosome 4. Age of onset of symptoms is inversely proportionate to the number of repeats with significantly expanded repeat lengths resulting in juvenile onset HD. In general, the majority of patients who develop juvenile onset HD have inherited the gene from their fathers.

Figure 17. Huntington's Disease: A coronal section through a brain in a case of Huntington's disease reveals dilatation of the lateral ventricles due to degeneration and shrinkage of the caudate nucleus. Histologically, there is marked loss of neurons in both the caudate and the putamen

Clinical features of HD vary. It can begin with a movement disorder, mood disturbance, or cognitive decline. Predominance of the symptoms changes over the course of the disease. In adult onset cases, chorea is the prominent initial motor manifestation. Few adult onset cases present with rigidity as their initial symptom. 34 **Late in the course of adult onset HD the chorea will typically wane, and rigidity and spasticity will be evident.** 34 **juvenile onset HD begins with bradykinesia and rigidity. Seizures are seen in half of the patients. Dysarthria and dementia are also seen fairly early in the course of this disease. Cerebellar signs, as well as myoclonus, may also be seen in the juvenile form of HD. The diagnosis of the juvenile variant of HD is not difficult, if a clear family history is available. The diagnosis can be challenging if the family history is questionable; however, the presence of associated features, like seizures, early dementia, and myoclonus will distinguish juvenile HD from young onset PD.**

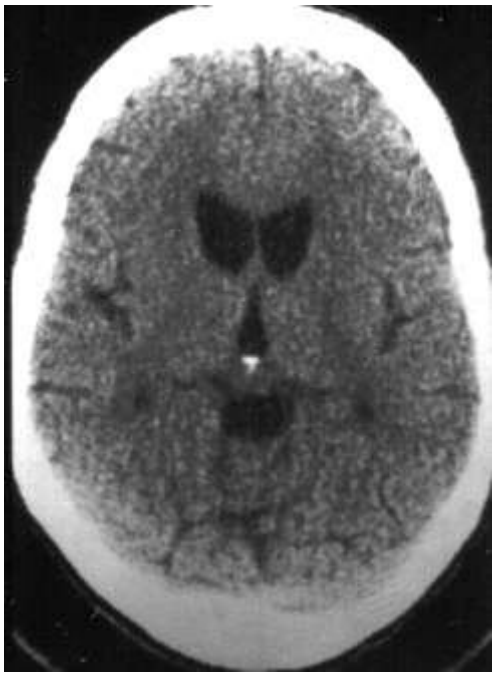

Figure 18. CT - Huntington's disease: A 59-year-old long-term female resident of a local psychiatric center was referred for involuntary jerking movements. Examination revealed oculomotor apraxia, dementia and diffuse chorea. This CT scan without contrast demonstrates bilateral caudate atrophy, with loss of the usual protrusion of the head of the caudate into the lateral aspect of each lateral ventricle. Her clinical and x-ray features are strongly suggestive of Huntington's disease, an autosomal dominant disorder characterized by psychiatric illness, dementia and chorea.

The expanded CAG repeat codes for the protein Huntington. This protein contains an expanded polyglutamine stretch that impairs the normal folding of the protein. The toxic folding caused by the expanded polyglutamine repeat at the N-terminal leads to aggregation of the abnormal protein. These aggregates are deposited in the cell nucleus and perinuclear region of neurons, causing neuronal death. The entire mechanism of cell death is not completely understood, but it is believed that caspace activation and apoptosis are involved. 120 Pathologically, there is loss of medium spiny neurons in the striatum, and less so in the cortex. Gliosis is present both in the striatum and cortex.

- **Hydrocephalus**

Hydrocephalus occurs when cerebrospinal fluid circulation within the brain is abnormal. This may be caused by decreased absorption of CSF (most common) versus increased CSF production (rare). In either case, the ventricular system dilates. If there is an obstruction to CSF flow, the ventricular enlargement is seen proximal to the site of obstruction. Symptoms depend on the rate of development of the hydrocephalus, presence of increased pressure within the ventricular system, and the age of the patient. Children whose sutures have not fused together can have more severe hydrocephalus before symptoms become apparent because of the compliance of the skull. In general, symptoms of hydrocephalus include lethargy, headache, seizures, gait disturbance, papilledema, ataxia, nystagmus, and pyramidal tract dysfunction.

Parkinsonism is rarely associated with hydrocephalus. Nevertheless, parkinsonism has been described in the setting of hydrocephalus of various etiologies including aqueductal stenosis, 157 shunt obstructions,70 tumor, normal pressure hydrocephalus, 18,77 posterior fossa cyst, Paget's disease, 61 head trauma 63, metastatic disease, and posterior fossa tumors. The most common

initial manifestation is gait disturbance, but resting tremor may be seen as well. 70 The pattern of gait can be the typical shuffling, short-stepped gait seen in PD. Bradykinesia, facial masking, and rigidity are seen commonly in this population. The neurologic dysfunction typically involves more than the basal ganglia with pyramidal dysfunction and cerebellar findings. In many cases, parkinsonism resolved after shunting. 18,63,70 Levodopa therapy produces symptom relief in some cases 3,157 but is ineffective in others. 18

The mechanism of parkinsonism related to hydrocephalus may be explained by pressure on nigral neurons and thus impaired dopamine transport. 131 Decreased blood flow in the basal ganglia, left caudate and putamen, based on 99mTc-hexamethylpropylenamine oxime SPECT scanning, was seen in a 17-year-old with shunt obstruction, parkinsonism, and Parinaud's syndrome. 130

- **Psychogenic Parkinsonism**

In general, the diagnosis of a psychogenic movement disorder (PMD) is one of the most challenging problems even for an experienced movement disorders neurologist. There are three major errors in dealing with such patients, all of which could lead to devastating consequences: 1. Misdiagnosis of psychogenic disorder in the setting of organic pathology; 2. Attributing psychogenic symptoms to an organic cause; and 3. Failure to provide appropriate care and therapy. 39 The prevalence of psychogenic parkinsonism is unknown, however it is believed to be the least common type of all PMD. 29,41,81 The diagnosis is based on the systematic evaluation of history, clinical exam, and response to treatment. It is a diagnosis of exclusion; however a systematic approach in the majority of cases will avoid unnecessary testing. 48 Clues to the diagnosis of PMD have been published. 33,43,154 The same criteria are applicable to psychogenic parkinsonism and are summarized in Table 5.

It should be noted that the above criteria are only clues, and are in no way diagnostic. Until a biological marker or a reliable diagnostic tool for PD is available, the diagnosis relies on the judgment of a clinician experienced in the field. The evolving role of the dopamine transporter ([jl2l 1 beta-CIT) SPECT for the early diagnosis of PD could make the task easier. The scans have been shown to reliably separate subjects with presynaptic dopaminergic dysfunction from age-matched controls . 128 This tool remains investigational and additional data are necessary. Once the diagnosis is made, careful nonconfrontational counseling, ideally done by a psychologist with expertise in managing psychogenic movement disorders, is essential. Generally, earlier intervention correlates with better prognosis for recovery. 84

Table 5. GENERAL CLUES SUGGESTING PSYCHOGENIC NATURE OF A MOVEMENT DISORDER

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1. Historical

- **Abrupt onset**
- **Static cause/spontaneous remission**
- **Obvious psychiatric disturbance**
- **Somatizations**
- **Pending litigation or compensation**

- **Secondary gain**

2. Clinical

- **Inconsistent character of the movement disorder**
- **Distractability**
- **Ability to trigger or relieve symptoms with provocation/nonphysiologic intervention**
- **(tuning fork, alcohol swab)**
- **Presence of nonphysiologic weakness, sensory loss on examination**
- **Functional disability out of proportion to examination findings**

3. Therapeutic response

- **Unresponsiveness to the appropriate therapy**
- **Response to placebo**
- **Remission with psychotherapy**

SUMMARY

The etiology of parkinsonism is varied. Symptomatic parkinsonism is seen in the setting of genetic disorders, infectious processes, structural lesions, and as a result of concomitant medications. A thorough history and good examination will differentiate PD from the diverse group of conditions that can mimic it.

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