neurotransmitter release has now been identified. Treatment with low-dose anticonvulsant therapy such as carbamazepine or phenytoin is advised when the attacks are frequent and interfere with daily life activities and is effective in about 80% of patients. Some clinical features of PKD (abrupt and short-lasting attacks preceded by an "aura") and its favorable response to anticonvulsant drugs have led to speculation that it is epileptic in origin, but this has not been established.

Paroxysmal nonkinesigenic dyskinesia (PNKD) involves attacks of generalized dyskinesias precipitated by alcohol, caffeine, stress, or fatigue. In comparison to PKD, the episodes have a relatively longer duration (minutes to hours) and are less frequent (one to three per day). PNKD is inherited as autosomal dominant with incomplete penetrance pattern in some 80% of cases. A missense mutation in the myofibrillogenesis regulator (*MR-1*) gene has been identified in several families. Recognition of the condition and elimination of the underlying precipitating factors, where possible, are the first priority. Tetrabenazine, neuroleptics, dopamine-blocking agents, propranolol, clonazepam, and baclofen may be helpful. Treatment may not be required if the condition is mild and self-limited. Most patients with PNKD do not benefit from anticonvulsant drugs, but some may respond to clonazepam or other benzodiazepines.

## RESTLESS LEGS SYNDROME

Restless legs syndrome (RLS) is a neurologic disorder that affects approximately 10% of the adult population (it is rare in Asians) and can cause significant morbidity in some. It was first described in the seventeenth century by an English physician (Thomas Willis), but has only recently been recognized as being a bona fide movement disorder. The four core symptoms required for diagnosis are as follows: an urge to move the legs, usually caused or accompanied by an unpleasant sensation in the legs; symptoms that begin or worsen with rest; partial or complete relief by movement; and worsening during the evening or night.

Symptoms most commonly begin in the legs, but can spread to or even begin in the upper limbs. The unpleasant sensation is often described as a creepy-crawly feeling, paresthesia, or burning. In about 80% of patients, RLS is associated with periodic leg movements (PLMs) during sleep and occasionally while awake. These involuntary movements are usually brief, lasting no more than a few seconds, and recur every 5–90 s. The restlessness and PLMs are a major cause of sleep disturbance in patients, leading to poor-quality sleep and daytime sleepiness.

RLS is a heterogeneous condition. Primary RLS is genetic, and several loci have been found with an autosomal dominant pattern of inheritance, although penetrance may be variable. The mean age of onset in genetic forms is 27 years, although pediatric cases are recognized. The severity of symptoms is variable. Secondary RLS may be associated with pregnancy or a range of underlying disorders, including anemia, ferritin deficiency, renal failure, and peripheral neuropathy. The pathogenesis probably involves disordered dopamine function, which may be peripheral or central, in association with an abnormality of iron metabolism. Diagnosis is made on clinical grounds but can be supported by polysomnography and the demonstration of PLMs. The neurologic examination is normal. Secondary RLS should be excluded, and ferritin levels, glucose, and renal function should be measured.

Most RLS sufferers have mild symptoms that do not require specific treatment. General measures to improve sleep hygiene and quality should be attempted first. If symptoms remain intrusive, low doses of dopamine agonists, e.g., pramipexole (0.25–0.5 mg) or ropinirole (1–2 mg), are given 1–2 h before bedtime. Levodopa can be effective but is frequently associated with augmentation (spread and worsening of restlessness and its appearance earlier in the day) or rebound (reappearance sometimes with worsening of symptoms at a time compatible with the drug's short half-life). Other drugs that can be effective include anticonvulsants, analgesics, and opiates. Management of secondary RLS should be directed to correcting the underlying disorder; for example, iron replacement for anemia. Iron infusion may also be helpful for severe primary RLS but requires expert supervision.

## DISORDERS THAT MAY PRESENT WITH A COMBINATION OF PARKINSONISM AND HYPERKINETIC MOVEMENTS

### WILSON'S DISEASE

Wilson's disease (WD) is an autosomal recessive inherited disorder of copper metabolism that may manifest with neurologic, psychiatric, and liver disorders, alone or in combination. It is caused by mutations in the gene encoding a P-type ATPase. The disease was first comprehensively described by the English neurologist Kinnier Wilson at the beginning of the twentieth century, although at around the same time the German physicians Kayser and Fleischer separately noted the characteristic association of corneal pigmentation with hepatic and neurologic features. WD has a worldwide prevalence of approximately 1 in 30,000, with a gene carrier frequency of 1 in 90. About half of WD patients (especially younger patients) manifest with liver abnormalities. The remainder present with neurologic disease (with or without underlying liver abnormalities), and a small proportion have hematologic or psychiatric problems at disease onset.

Neurologic onset usually manifests in the second decade with tremor and rigidity. The tremor is usually in the upper limbs, bilateral, and asymmetric. Tremor can be on intention or occasionally resting and, in advanced disease, can take on a wing-beating characteristic. Other features include parkinsonism with bradykinesia, dystonia (particularly facial grimacing), dysarthria, and dysphagia. More than half of those with neurologic features have a history of psychiatric disturbances, including depression, mood swings, and overt psychosis. Kayser-Fleischer (KF) rings are seen in 80% of those with hepatic presentations and virtually all with neurologic features. KF rings represent the deposition of copper in Descemet's membrane around the cornea. They consist of a characteristic grayish rim or circle at the limbus of the cornea and are best detected by slit-lamp examination. Neuropathologic examination is characterized by neurodegeneration and astrogliosis in the basal ganglia, particularly in the striatum.

WD should always be considered in the differential diagnosis of a movement disorder in the first decades of life. Low levels of blood copper and ceruloplasmin and high levels of urinary copper may be present, but normal levels do not exclude the diagnosis. A computed tomography (CT) scan usually reveals generalized brain atrophy in established cases, and ~50% have signal hypointensity in the caudate head, putamen, globus pallidum, substantia nigra, and red nucleus on T2-weighted MRI. However, correlation of imaging changes with clinical features is not good. It is very rare for WD patients with neurologic features not to have KF rings, and therefore when the diagnosis is considered, examination by slit-lamp is essential. Liver biopsy with demonstration of high copper levels remains the gold standard for the diagnosis.

In the absence of treatment, the course is progressive and leads to severe neurologic dysfunction and early death. Treatment is directed at reducing tissue copper levels and maintenance therapy to prevent reaccumulation. There is no clear consensus on treatment, and all patients should be managed in a unit with expertise in WD. Penicillamine is frequently used to increase copper excretion, but it may lead to a worsening of symptoms in the initial stages of therapy. Side effects are common and can to some degree be attenuated by coadministration of pyridoxine. Tetrathiomolybdate blocks the absorption of copper and can be used instead of penicillamine. Trientine and zinc are useful drugs for maintenance therapy. Effective treatment can reverse the neurologic features in most patients, particularly when started early. Some patients stabilize, and a few may still progress, especially those with hepatocerebral disease. KF rings tend to decrease after 3–6 months and disappear by 2 years. Adherence to maintenance therapy is a major challenge in long-term care.

### NEURODEGENERATION WITH BRAIN IRON ACCUMULATION

Neurodegeneration with brain iron accumulation (NBIA) represents a group of inherited disorders characterized by iron accumulation in the basal ganglia. Clinically, they can manifest as a progressive neurologic disorder manifesting a variety of features including parkinsonism,