MEDICINE

432 Team

3

Extra: Parkinson's disease And Motor Neurone Disease

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COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

Objectives

My goal from these extra lectures is to cover the deficiency that my college and I have noticed in our curriculum so please read these lectures and be familiar with these diseases

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MOVEMENT DISORDERS

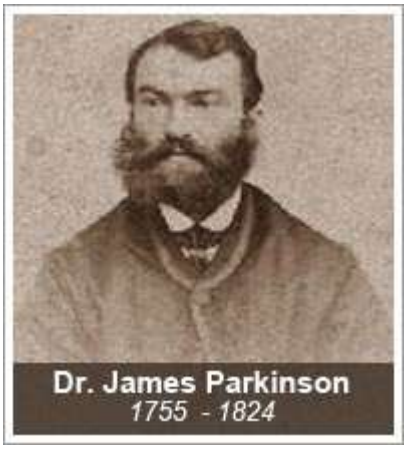
Disorders of movement divide broadly into two categories:

- Hypokinesias – characterized by slowed movements with increased tone (Parkinsonism)
- Hyperkinesias – excessive involuntary movements.

Both types may co-exist, for example in Parkinson's disease where there are both slowed movements and tremor. Many of these disorders (not all) relate to dysfunction of the basal ganglia.

Parkinsonian disorders:

Idiopathic Parkinson's disease:



In 1817, James Parkinson, a physician in Hoxton, London, published The Shaking Palsy, describing this common worldwide condition that has a prevalence of 150/100 000. Parkinson's disease is clinically and pathologically distinct from other parkinsonian syndromes. The causes of idiopathic Parkinson's disease (PD) is still not fully understood. The relatively uniform worldwide prevalence suggests that a single environmental agent is not responsible. There may be multiple interacting risk factors including genetic susceptibility:

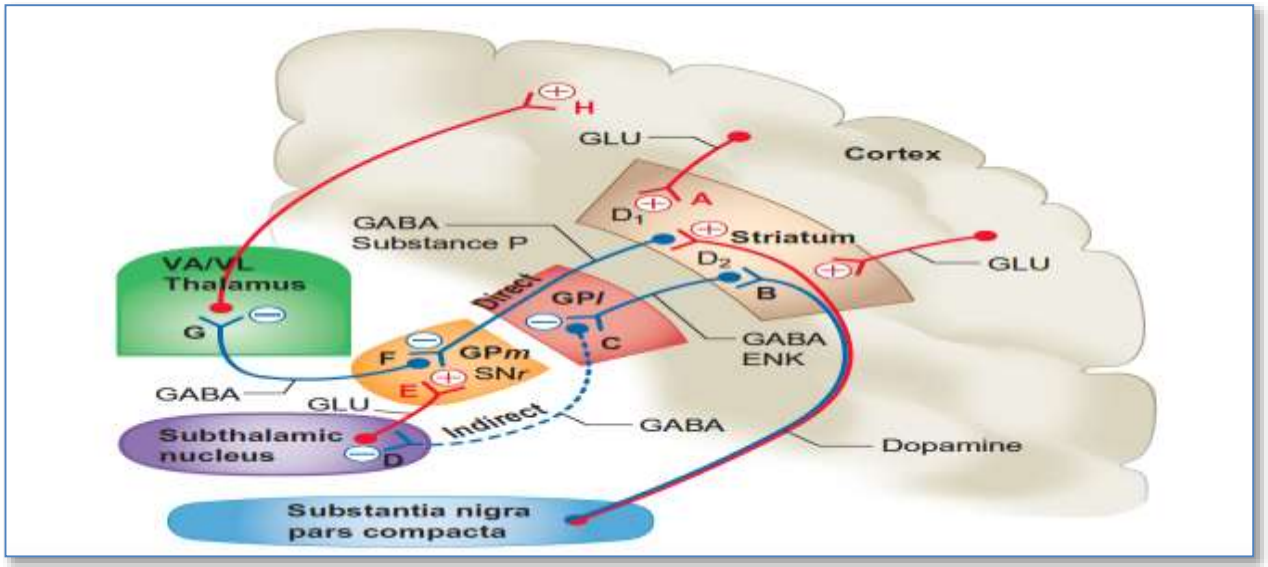
Age and gender: Prevalence increases sharply with age, particularly over 70 years with prevalence of 1 in 200 over age 80. Ageing changes are likely to be an important factor in causation. Prevalence is higher in men (1.5:1-M:F)

Environmental factors: Epidemiological studies consistently show a small increased risk with rural living and drinking well water. Pesticide exposure has been implicated and pesticide-induced rodent models of PD exist, which increases biological plausibility of a link. The chemical compound MPTP, a potent mitochondrial toxin, causes severe Parkinsonism, leading to suggestions that oxidative stress may be a factor leading to neuronal cell death in idiopathic PD. Studies consistently show that non-smokers have a higher risk of PD than smokers (even after controlling for shorter life expectancy in smokers), an observation that is difficult to explain.

Genetic factors: Idiopathic PD is not usually familial, but twin studies show there is a significant genetic component in early onset PD (onset before 40). Several genetic loci for Mendelian inherited monogenic forms of PD have now been identified (Table 22.18), designated PARK 1–11. Most of these are rare but together they account for a large proportion of early onset and familial PD, and a small proportion (perhaps 1–2%), of sporadic late onset cases. The main significance of the PARK genes is that they provide insights into the pathophysiological mechanisms underlying PD that may be relevant to sporadic cases. Research is ongoing to determine whether polymorphisms in these and other genes may, in combination, constitute a susceptibility to PD which can be triggered by environmental factors or the ageing process.

Pathology:

The pathological hallmarks of PD are the presence of neuronal inclusions called Lewy bodies and loss of the dopaminergic neurones from the pars compacta of the substantia nigra in the midbrain that project to the striatum of the basal ganglia. Lewy bodies contain tangles of α - synuclein and ubiquitin and become gradually more widespread as the condition progresses, spreading from the lower brainstem, to the midbrain and then into the cortex. Degeneration also occurs in other basal ganglia nuclei. The extent of nigrostriatal dopaminergic cell loss correlates with the degree of akinesia.



Extrapyramidal system: connections and neurotransmitters. The inhibitory pathways are in blue (B, C, D, F, G) and excitory in red (A, E, H). VA/VL, ventral anterior and ventrolateral thalamic nuclei. GPl, lateral globus pallidus. GPm: medial globus pallidus. SNr, substantia nigra pars reticulata. GLU, glutamate; ENK, enkephalin; GABA, γ -aminobutyric acid.

Symptoms and signs:

PD almost always presents with the typical motor symptoms of tremor and slowness of movement but it is likely that the pathological process starts many years before these symptoms develop. By the time of first presentation, on average 70% of dopaminergic nigrostriatal cells have already been lost.

Prodromal premotor symptoms:

Patients develop a variety of nonspecific non-motor symptoms during the approximately seven years, sometimes longer, before the motor symptoms become manifest. These include:

- Anosmia (present in 90%) – the olfactory bulb is one of the first structures to be affected
- Depression/anxiety (50%)
- Aches and pains
- REM sleep behaviour disorder

- Autonomic features – urinary urgency, hypotension
- Constipation
- Restless legs syndrome.

Motor symptoms:

These develop slowly and insidiously and are often initially attributed to 'old age' by patients. The core motor features of PD are:

- Akinesia
- Tremor
- Rigidity
- Postural and gait disturbance.

Slowness causes difficulty rising from a chair or getting into or out of bed. Writing becomes small (micrographia) andspidery, tending to tail off. Relatives often notice other features slowness and an impassive face. Idiopathic PD is almost always initially more prominent on one side. The diagnosisis usually evident from the overall appearance.

The clinical evolution of PD

PD worsens slowly over the years as more neuronal cells become affected by the pathological process. Initial symptoms may be trivial, especially if affecting the non-dominant hand, but worsening akinesia and tremor eventually cause significant disability if untreated. Symptoms which are initially unilateral eventually spread to the opposite side, and axial symptoms such as walking difficulty and postural instability develop. Most patients respond well to treatment and there is generally a period of several years in which symptoms are well controlled with relatively little disability. Response to dopaminergic drugs is never lost but treatment-related fluctuations may develop (see below) which can be limiting, especially for patients with early age at onset. Eventually, usually by mid-70s, late stage, treatment-unresponsive, features such as cognitive impairment, swallowing difficulty, loss of postural stability and falls start to emerge.

The rate of progression is very variable, with a benign form running over several decades. Usually the course is over 10–20 years, with death resulting from bronchopneumonia and immobility.

Diagnosis:

There is no laboratory test; diagnosis is made by recognizing physical signs and distinguishing idiopathic PD from other Parkinsonian syndromes. Patients with suspected PD should be referred to a specialist without initiation of treatment. MRI imaging is normal and not necessary in typical cases. Dopamine transporter (DaT) imaging makes use of a radiolabelled ligand binding to dopaminergic terminals to assess the extent of nigrostriatal cell loss. It may occasionally be needed to distinguish PD from other causes of tremor, or drug-induced Parkinsonism, but it cannot discriminate between PD and other akinetic-rigid syndromes.

Treatment:

Education about the condition is necessary and physical activity is beneficial and should be encouraged. Dopamine replacement with levodopa or a dopamine agonist (DA) improves motor symptoms and is the basis of pharmacological therapy. Treatment of non-motor symptoms such as depression, constipation, pain and sleep disorders is also necessary and significantly improves quality of life. Dopamine replacement may not always be needed in early stage PD and is only started when symptoms start to cause disability.

Levodopa:

Levodopa remains the most effective form of treatment and all patients with PD will eventually need it. It is combined with a dopa decarboxylase inhibitor – benserazide (co-beneldopa) or carbidopa (co-careldopa) – to reduce the peripheral adverse effects (e.g. nausea and hypotension); 50 mg of L-dopa (e.g. co-careldopa 62.5 mg) three times daily, increasing after 1 week to 100 mg three times daily is a typical starting dose. The response is often dramatic.

Dopamine agonists:

Dopamine agonists (DA) may be used in combination with levodopa or as initial monotherapy in younger patients (below age 65–70) with mild to moderate impairment. Although less efficacious in symptom control than levodopa and generally less well tolerated, DAs are associated with fewer motor complications over a 5 year period.

Other drugs used in PD

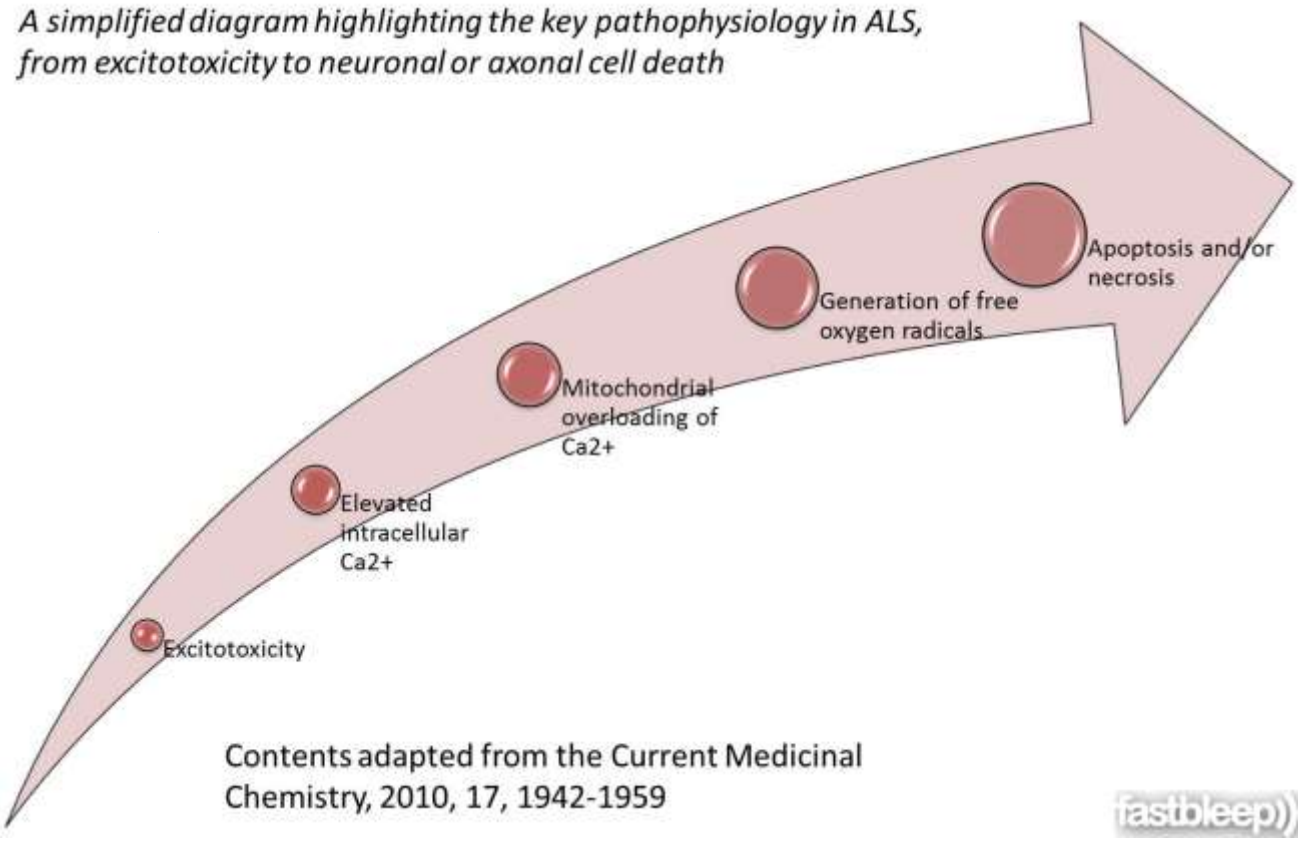
- ***Selegiline*** 5–10 mg once daily (a monoamine oxidase B inhibitor) reduces catabolism of dopamine in brain. Mild symptomatic effect. Rasagiline is another MAOB inhibitor.
- ***Amantadine*** has a modest anti-Parkinsonian effect but is mainly used to improve dyskinesias in advanced disease.
- ***Anticholinergics*** (e.g. trihexyphenidyl) may help tremor but are now rarely used in PD except in younger patients. High propensity to cause confusion in older patients.
- ***Apomorphine*** is a potent, short-acting, DA administered subcutaneously by an autoinjector pen as intermittent 'rescue' injection for off periods or by continuous infusion pump. Used in advanced PD.

Motor Neurone Disease (MND)

Motor neurone disease is a devastating condition causing progressive weakness and eventually death, usually as a result of respiratory failure or aspiration. It is relatively uncommon with an annual incidence of 2/100 000. Presentation is usually between ages 50 and 75. Below age 70 men are affected more often than women. ALS (amyotrophic lateral sclerosis) is the term more commonly used for MND in some countries.

Pathogenesis:

MND predominantly affects upper and lower motor neurones in the spinal cord, cranial nerve motor nuclei and cortex. However, other neuronal systems may also be affected – 5% of patients also develop frontotemporal dementia (p. 1087) and up to 40% have some measurable frontal lobe cognitive impairment. MND is usually sporadic and of unknown cause with no known environmental risk factors. Ubiquinated cytoplasmic inclusions containing the RNA processing proteins TDP-43 and FUS are the pathological hallmarks found in axons, indicating that protein aggregation may be involved in pathogenesis as with other neurodegenerative disorders. Oxidative neuronal damage and glutamate mediated excitotoxicity have also been implicated in pathogenesis. 5–10% of cases of MND are familial and mutations in the free radical scavenging enzyme superoxide dismutase (SOD-1) and in a number of other genes including TDP-43 and FUS have been identified. A hexanucleotide GGGGCC repeat expansion in the C9ORF72 gene on chromosome 9 accounts for a significant proportion of familial cases of MND-FTD overlap.



Clinical features

Four main clinical patterns are seen. These different presentations usually merge as MND progresses. The sensory system is not involved so sensory symptoms such as numbness, tingling and pain do not occur.

- *Amyotrophic lateral sclerosis (ALS).* Most common one
- *Progressive muscular atrophy*
- *Progressive bulbar and pseudobulbar palsy*
- *Primary lateral sclerosis*

Amyotrophic lateral sclerosis (ALS):

The classic presentation with simultaneous involvement of upper and lower motor neurones, usually in one limb, spreading gradually to other limbs and trunk muscles. The typical picture is of progressive focal muscle weakness and wasting (e.g. in one hand) with muscle fasciculations due to spontaneous firing of abnormally large motor units formed by surviving axons branching to innervate muscle fibres that have lost their nerve supply. Cramps are a common but nonspecific symptom. Examination often reveals upper motor neurone signs such as brisk reflexes (a brisk reflex in a wasted muscle is a classic sign), extensor plantar responses and spasticity. Sometimes an

Stephen Hawking

asymmetric spastic paraparesis is the presenting feature with lower motor neurone features developing months later. Relentless progression of signs and symptoms over months allows a diagnosis that may initially be suspected to be confirmed.

Diagnosis:

Diagnosis is largely clinical. There are no diagnostic tests but investigations allow exclusion of other disorders and may confirm subclinical involvement of muscle groups, e.g. paraspinal muscles. Denervation of muscles due to degeneration of lower motor neurones is confirmed by EMG. Cervical spondylosis causing radiculopathy with myelopathy (upper and lower motor neurone signs), can cause diagnostic difficulty. Motor neuropathies such as multifocal motor neuropathy can also appear like motor neurone disease.

Prognosis and treatment:

Survival for more than 3 years is unusual, although there are rare MND cases who survive for a decade or longer. No treatment has been shown to influence outcome substantially. Riluzole, a sodium-channel blocker that inhibits glutamate release, slows progression slightly, increasing life expectancy by 3–4 months on average. Non-invasive ventilator support and feeding via a gastrostomy help prolong survival. Patients should be supported by a specialist multidisciplinary team with access to palliative care and a clinical nurse specialist.