Chapter 12: Parkinson's Disease and Huntington's Disease

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Parkinson's disease

1 Introduction

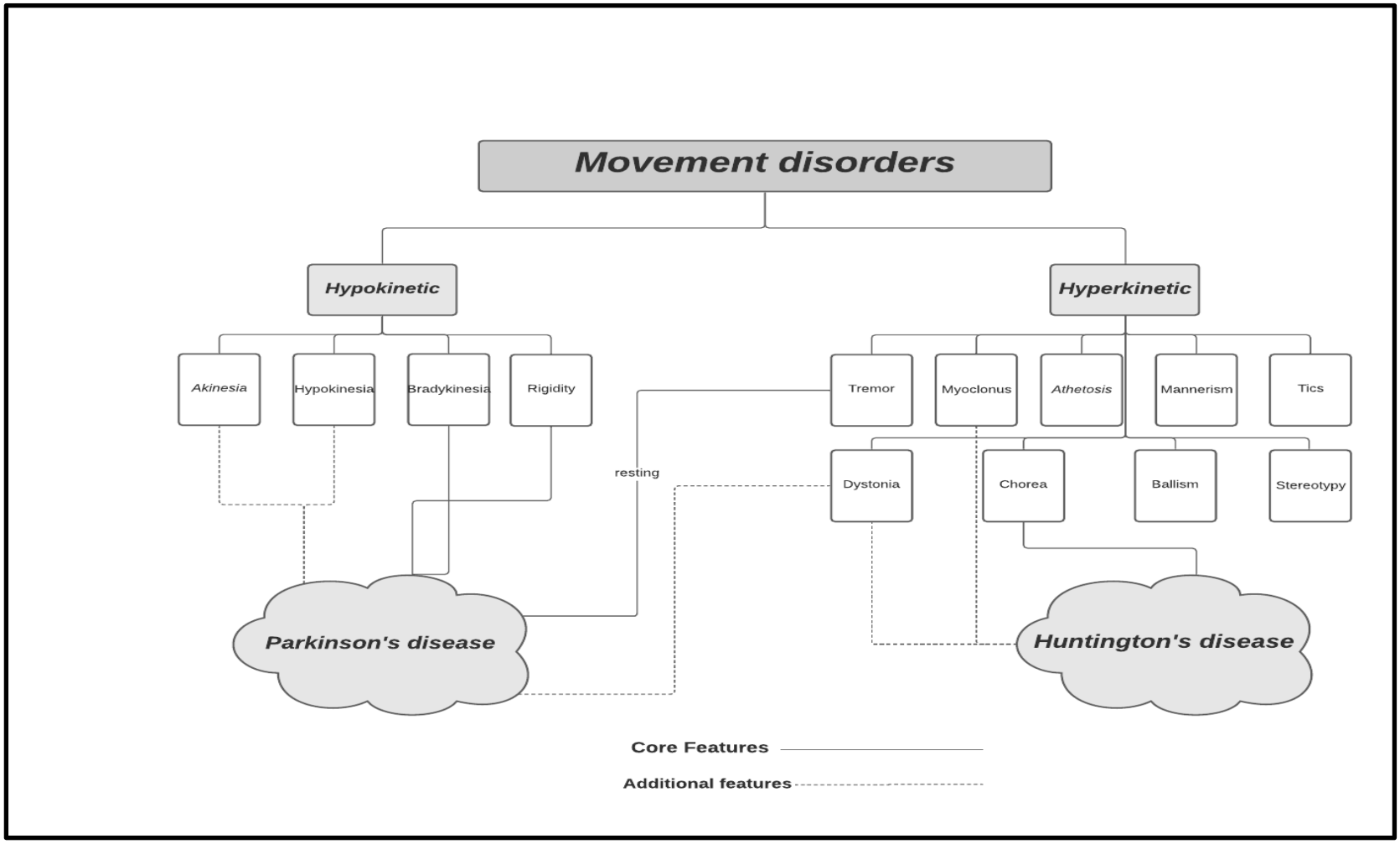
Parkinson's disease (PD) is a neurodegenerative disease that affects people over 40 years of age, incidence increases with age, and the mean age of diagnosis is 71 years. Traditionally, it was described as a hypokinetic motor disorder (Figure 1). However, PD has a diverse clinical profile that includes neuropsychiatric and several nonmotor manifestations (see Figure 2). The cardinal features of PD are tremor, bradykinesia, and rigidity (and postural instability).

2 Clinical manifestations

2.1. Motor Features

The tremor is a resting tremor at 3 to 7 Hz, typically affecting the hands, but it can affect the legs, lips, jaw, tongue and rarely the head. The tremor is the presenting symptom in more than 2/3 of patients. Clinically, it is best seen when the patient is relaxed with hands on the lap, and usually, one side is affected more than the other. Bradykinesia is the major cause of disability and is present in most patients early in the disease. Bradykinesia is generalized slowness of body movements and is assessed clinically by evaluating the speed, rhythm, and amplitude of finger tapping, hand opening & closing, and heel or toe-tapping. Rigidity is increased resistance to passive movement, often begins unilaterally, and remains asymmetric throughout the disease. Patients can have both cogwheel and lead-pipe rigidity. Postural instability, the feeling of imbalance and tendency to fall, appears late in the course of PD.

Figure 1: Classification of movement disorders – Parkinson's disease and Huntington's disease



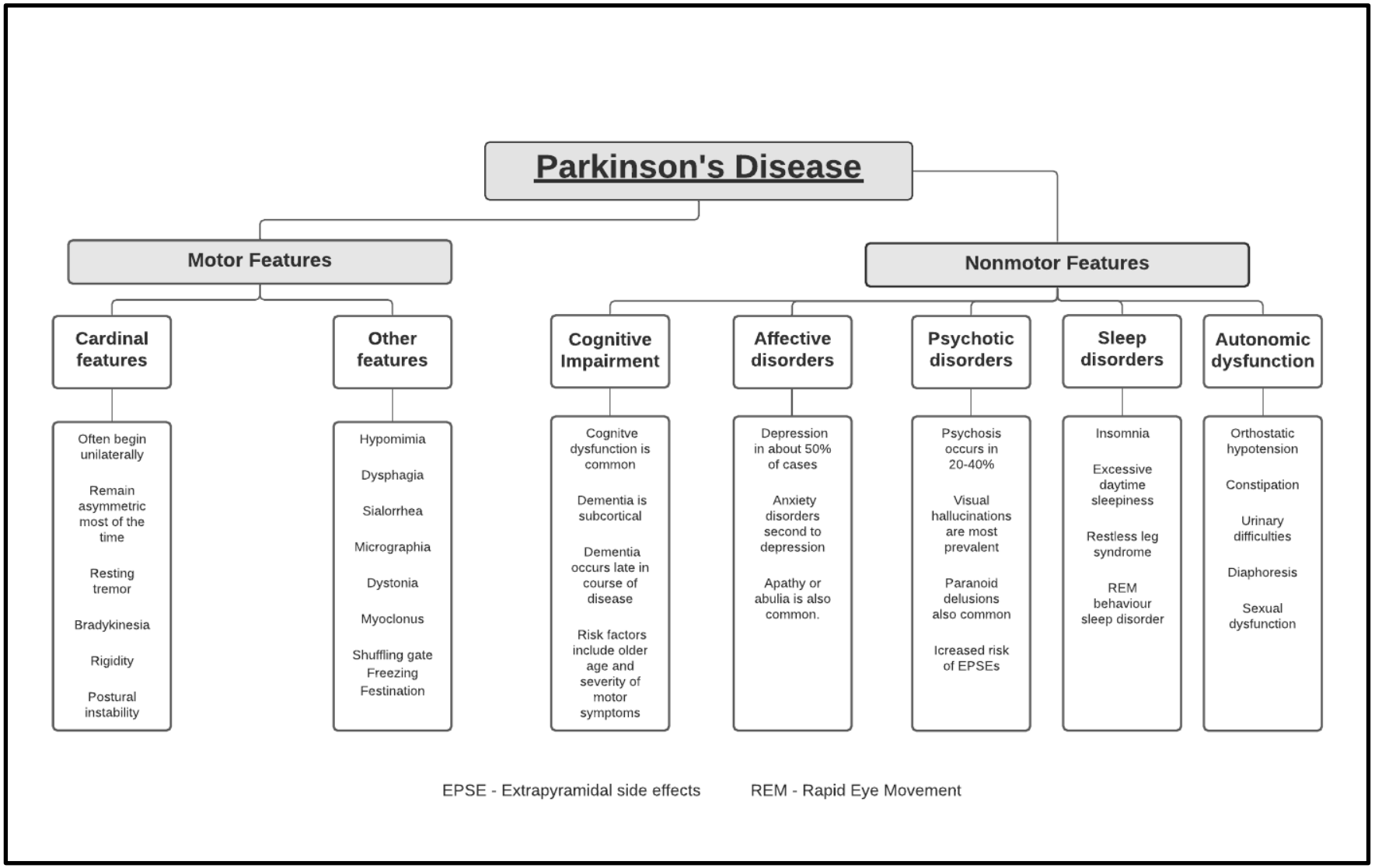
2.2. Nonmotor features

Almost all patients with PD will experience several nonmotor symptoms early on in the course of the disease. Of these, psychiatric features are the most common and may cause more disability than motor symptoms. Nonmotor features such as olfactory dysfunction, constipation, depression, and REM sleep behaviour disorder may precede motor symptoms.

2.3. Cognitive impairment

Cognitive impairment is common in patients with PD and varies from mild cognitive impairment to clinical dementia. Risk factors for dementia include older age, duration of PD, and severity of motor features. The neuropsychological profile of dementia is typically subcortical, involving executive dysfunction, impaired psychomotor speed, impaired visuospatial function, impaired memory retrieval that improves with cueing, and relatively preserved language function. Psychiatric symptoms are more prevalent in patients with PD dementia than those without dementia. Dementia usually occurs late in the course of PD.

Figure 2: Clinical manifestations of Parkinson’s disease



2.4. Mood disorders

About a half of PD patients will experience depression, and depression is associated with increased motor disability and decreased quality of life. However, depression is often not detected because PD and depression share many clinical features such as blunted affect, psychomotor slowing, reduced appetite, impaired concentration, and sleep disturbances. However, the experience of sadness, anhedonia, decreased interest in usual activities, guilt, or feelings of worthlessness are more in keeping with depression. In addition, apathy is quite common in PD and can add to the complexity in diagnosing depression in patients with PD. Lastly, anxiety disorders are also common in PD and are often comorbid with depressive disorders.

2.5. Psychotic experiences

Psychotic experiences are not uncommon in patients with PD and visual hallucinations are the most prevalent psychotic features. Paranoid delusions such as people stealing money, spousal infidelity, or harmful intentions towards the patient are also common. In addition, psychosis is common with dementia, high doses of antiparkinson drugs, older age, severe disease, impaired vision, and sleep disturbances.

2.6. Sleep disorders

The majority of patients with PD experience sleep difficulties in the course of their disease. The sleep disturbances could be due to several factors such as PD symptoms (tremor, rigidity, or dystonia), pain, nocturia, vivid dreams, restlessness, or depression. In addition, sleep disturbances in PD include excessive daytime sleepiness, insomnia, REM sleep behaviour disorder, restless leg syndrome, and periodic limb movement disorder.

2.7. Autonomic dysfunction

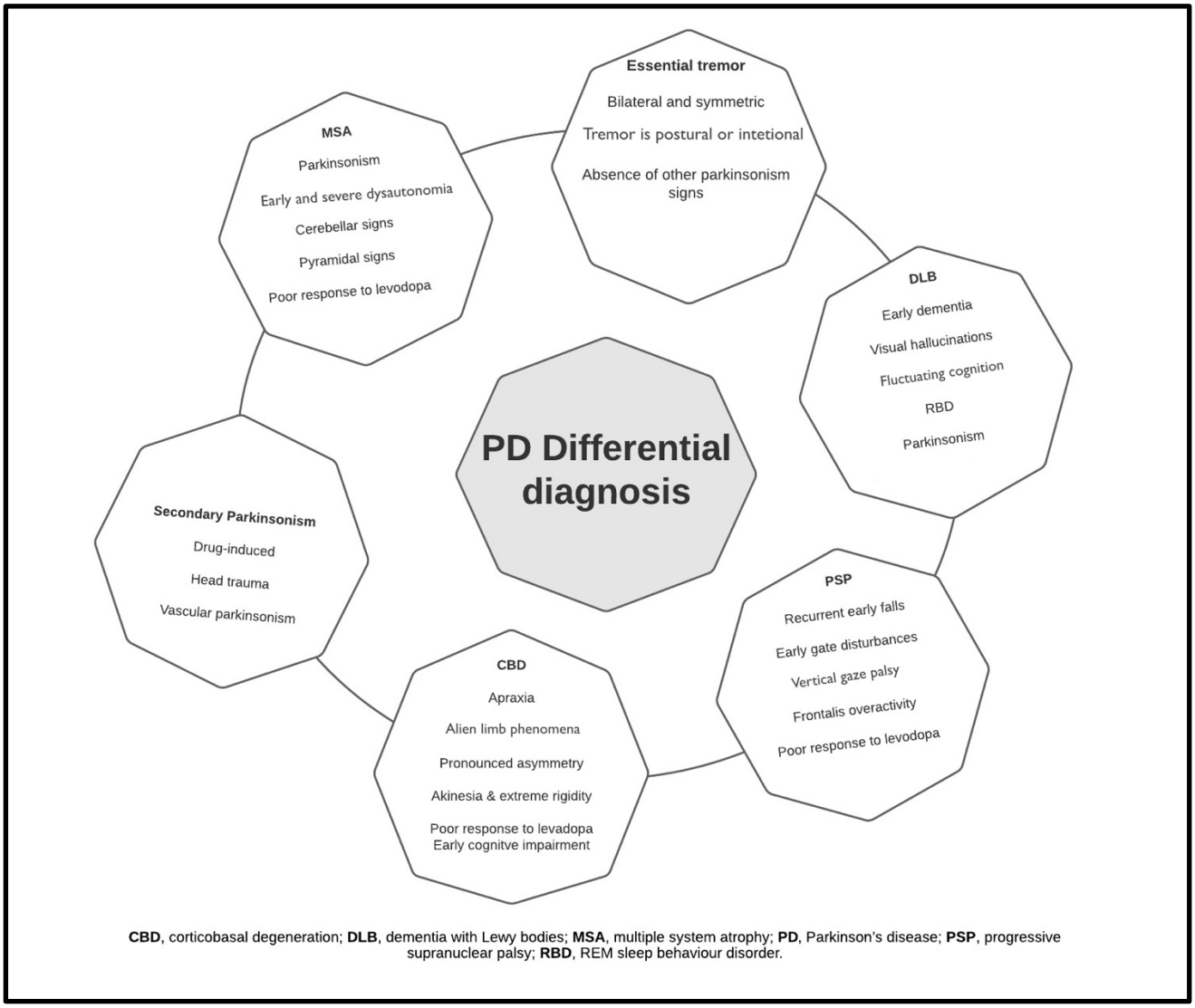
Autonomic dysfunction is common in patients with PD and usually occurs late in the course of the disease. In contrast, autonomic difficulties arise early in multiple system atrophy (MSA), and they are more severe than in PD. The autonomic disturbances could include orthostatic hypotension, constipation, diaphoresis, urinary problems (frequency, urgency, urge incontinence), and sexual dysfunction (mostly hyposexuality).

3 Parkinson’s disease diagnosis

Parkinson's disease is a clinical diagnosis as there are currently no physiologic, serum, or confirmatory radiological tests. Parkinsonism is a clinical syndrome consisting of at least two of the following features: bradykinesia, resting tremor, rigidity, and postural instability. PD is the most common cause of parkinsonism. Therefore, the diagnosis of PD requires the presence of both bradykinesia and resting tremor or rigidity. Other features supporting a diagnosis of PD include a direct benefit from dopaminergic drugs, the presence of levodopa-induced dyskinesia, or olfactory loss on functional imaging. Features suggesting an alternate cause of the parkinsonism include bilateral symmetric parkinsonism, rapid progression of

gait impairment, severe autonomic dysfunction in the first five years, early bulbar dysfunction, or early onset of recurrent falls (see Figure 3).

Figure 3: Differential diagnosis for Parkinson's disease



CBD, corticobasal degeneration; **DLB**, dementia with Lewy bodies; **MSA**, multiple system atrophy; **PD**, Parkinson's disease; **PSP**, progressive supranuclear palsy; **RBD**, REM sleep behaviour disorder.

4 Management of Parkinson’s disease

The treatment of Parkinson's disease is mainly symptomatic as there are no disease-modifying or neuroprotective therapies to date. Drug treatment for motor symptoms includes dopamine replacement (levodopa), dopamine agonists, amantadine, drugs that decrease dopamine breakdown (monoamine oxidase B inhibitors), and drugs that reduce dopamine antagonism (anticholinergic drugs). The decision when to start and the choice of pharmacotherapy is individualized based on characteristics of the individual, the disease, and the available drugs. The high doses and long duration of antiparkinsonian therapy required may lead to several complications such as dyskinesias, psychotic experiences, dopamine dysregulation syndrome, impulse control disorders, or increasing anxiety.

The management of nonmotor symptoms of PD is essential and at times of greater priority than attending to motor features. The treatment of depression and anxiety disorders includes antidepressants, cognitive behaviour therapy (CBT), or both. The treatment of psychosis includes reducing antiparkinsonian medication, a trial of cholinesterase inhibitors (e.g., donepezil), and antipsychotics (quetiapine, pimavanserin, or clozapine) if psychosis persists. The treatment of dementia is symptomatic and involves a trial of cholinesterase inhibitors with or without memantine.

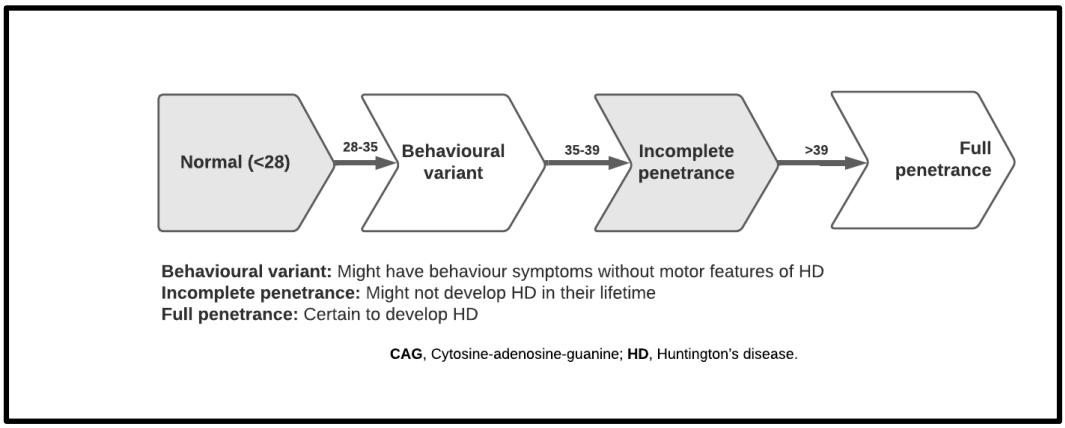
The management of excessive daytime sleepiness may include reducing dopamine agonists or levodopa and a trial of stimulants (modafinil or methylphenidate) if it persists. The management of insomnia and circadian sleep-wake rhythm disturbances is mainly through non-pharmacological approaches such as sleep hygiene, sleep scheduling, light therapy, behavioural components of CBT for insomnia, addressing polypharmacy, and as a last resort, the use of sedating antidepressants such as trazodone.

Huntington’s disease

5 Introduction

Huntington's disease (HD) is an inherited neurodegenerative disorder. Its exact pathophysiology is not fully understood, but it is characterized by cytosine-adenosine-guanine (CAG) trinucleotide repeat expansion in the huntingtin (HTT) gene that codes for Huntington protein located on chromosome 4. HD is inherited in an autosomal dominant pattern, and the expected number of CAG repeats is 28 or less (see Figure 4). However, an increasing number of CAG repeats raises the chance of developing HD, earlier age of onset, and faster disease progression. In addition, the CAG repeat may expand with each subsequent generation leading to earlier onset of symptoms or manifestation of disease in children of asymptomatic parents (anticipation).

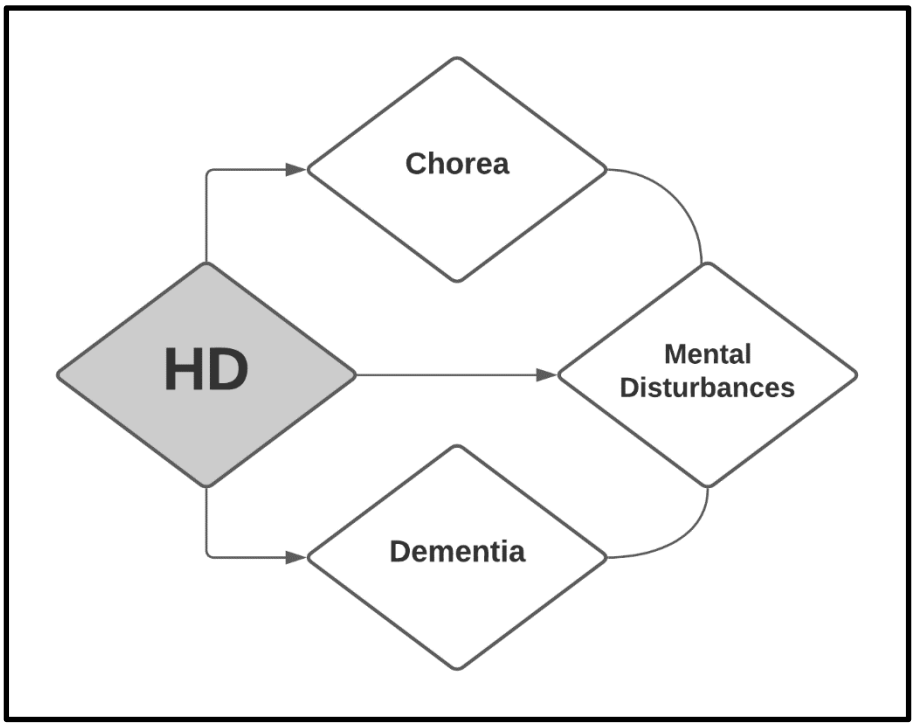
Figure 4: Number of CAG repeats in Huntington's disease



6 Clinical manifestations

HD is characterized by choreiform movements, psychiatric disturbances, and cognitive impairment (Figure 5). Symptoms begin insidiously with any of the core features and are inevitably progressive. Chorea is the critical feature of HD, but other motor disturbances may be present, including hypotonia with hyperreflexia, dystonia, motor persistence, loss of voluntary motor control, dysphagia, and later on, the akinetic-rigid state develops. Psychiatric disturbances are common in patients with HD and may precede motor symptoms by years. These include individual symptoms like irritability, low mood, delusional thinking, and hallucinations or psychiatric disorders, such as major depressive disorder, anxiety disorders, obsessive-compulsive disorders, or less commonly psychotic disorders. In addition, there is an increase in suicide among patients with HD and their family members. Almost all patients with HD will experience significant cognitive decline. The dementia is typically subcortical with mainly executive dysfunction, impaired psychomotor speed, less commonly memory deficits, and rarely cortical dysfunctions such as aphasia or apraxia.

Figure 5: Huntington's disease – core features



7 Huntington's disease diagnosis

Neuroimaging typically shows caudate atrophy, which correlates with cognitive dysfunction, and functional imaging also reveals abnormal changes in the caudate nucleus. However, the diagnosis of HD is made based on typical clinical features, positive family history, and genetic confirmation of the CAG expansion. For asymptomatic individuals with a positive family history, predictive genetic screening for HD can be done at genetic clinics after thorough counselling has been done.

8 Management of Huntington's disease

The treatment of HD remains symptomatic as disease-modifying drugs are yet to be discovered. Patients with HD are best managed in multidisciplinary settings, including neurologists, psychiatrists, social workers, physiotherapists, dieticians, etc. Like in many progressive neurodegenerative disorders, advanced care planning should be discussed early in the disease process while patients can still communicate their intentions.

Occupational therapy and physiotherapy are beneficial in helping the patient adapt to the ensuing motor disability. Speech therapists and dieticians may help with dysphagia and weight loss.

Chorea that is interfering with function or is notably bothersome to the patient should be treated. The treatment can be non-pharmacological with assistive equipment and behavioural interventions to address the accompanying anxiety. The chorea can also be treated with dopamine-depleting drugs like the vesicular monoamine transporter type 2

inhibitors (tetrabenazine or deutetrabenazine) or antipsychotics. If dystonia is present, it may respond to benzodiazepines, baclofen, or dopaminergic agents.

The management of neuropsychiatric disturbance in HD also involves symptomatic treatment. If behavioural measures are not effective, atypical antipsychotics can treat disruptive behavioural symptoms and psychotic experiences. Second-generation antipsychotics have a safer side effect profile and are preferred over the typical neuroleptics. Antidepressants such as selective serotonin reuptake inhibitors can be used to treat both depressive and anxiety disorders. There are no effective therapies for cognitive impairment, and cholinesterase inhibitors have not demonstrated apparent beneficial effects in these patients.

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