Clinical Complexities Of Parkinson's Disease: An Updated View

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Abstract

Parkinson's disease (PD) is one of the neurodegenerative diseases of which we can by certainty identify its pathology; however, this confidence disappears when we talk about the cause and clinical complications of the disease. Dopamine deficiency, caused by the degeneration of nigrostriatal dopaminergic neurons, is the cause of the major clinical motor symptoms of PD and these symptoms can be treated successfully with a range of drugs that include levodopa, inhibitors of the enzymatic breakdown of levodopa and dopamine agonists. However, PD involves degeneration of non-dopaminergic neurons and result in broad spectrum of clinical manifestations, extending beyond movement disorders. These include cardiovascular, olfactory, gastrointestinal, sleep, autonomic, sensory, cognitive dysfunction, as well as psychiatric manifestations. Thus treatment of the resulting predominantly non-motor features remains a multifaceted challenge for the physicians. Clinical complications mentioned in this review deserve a special address and attention by the research community as well as by the clinicians as they may help to understand the complexity of disorder as well as may serve to diagnose and manage PD.

Introduction

INTRODUCTION
Parkinson's disease (PD) is the second most common neurodegenerative disease and its prevalence is increasing such that over the next 25 years the number of individuals over 50 years of age with PD can be expected to double in the world's 10 most populous nations [1]. Parkinson's disease was first described in 1817 by the physician James Parkinson [2] even prior to this, accounts of the symptoms were remarkably scarce, which led many researchers to theorize whether this disease may have been a product of the beginning of the early 19th century and the industrial revolution in England[3]. Earlier than James Parkinson, many physicians have picked up some of the features of Parkinson's disease and described them in their writings, for example, Franciscus de le Boe (1614–1672) who described tremors and Francois Boissier de Sauvages de la Croix (1706–1767) who described patients with “running disturbances of the limbs”[4].

Even though its incidence is higher in individuals of 50 to 70 years of age, with a peak at the age of 60, the onset of PD can also occur, before the age of 40 (early-onset Parkinson) or 20 (juvenile Parkinson) [5,6]. The term “Parkinson’s disease” refers to a neurodegenerative disease that affects several regions of the brain, including the pigmented nuclei in midbrain and brainstem, the olfactory tubercle, the cerebral cortex, and elements of the peripheral nervous system [7]. Parkinson's disease (PD) is the most common disease of motor system [3] and takes a heavy toll in mental anguish, lost productivity, and health care expenditures. Parkinson's disease is now recognized to be a widespread degenerative illness that affects not just the central nervous system, but also the peripheral and enteric systems [8].
PD is marked by the degeneration of the dopaminergic neurons of the substantia nigra, thyrosine hydroxylase deficiency and the presence of intracytoplasmatic inclusions rich in α-synuclein, named Lewy’s bodies [9]. In this disease, the dopaminergic areas of the central nervous system are not equally affected. Initially, neuronal loss tends to occur mainly in the ventrolateral layer of the substantia nigra (estimated at 60% to 70%), progressing towards the medial ventral and dorsal layers. An extensive loss of neurons is also observed in the brain stem, in the hypothalamus, in the cortex and in Meynert's basal nucleus [10]. Dopaminergic cell loss in Substantia niagra (SN) directly leads to dopaminergic deficiency in the substantia nigra pars compacta (SNpc) [11]. Formerly the disease was typecast as motor system degeneration, yet sensory fields, association areas, and premotor fields become damaged throughout the brain. The limbic, autonomic, and neurosecretory control fields (hypothalamus) all show micro-anatomic damage [6].

The variable presentations of PD often cause diagnostic confusion and a delay in treatment. In the early stages, Parkinsonian symptoms are often mistaken for simple arthritis or bursitis, depression, normal aging, Alzheimer's disease, or stroke [12]. A prodromal phase 4–6 years characterized before the main manifestation in PD patients. During this period,
PD patients, compared with normal controls, had a higher frequency of mood disorder, "fibromyalgia," and shoulder pain [4]. Parkinson's disease (PD) may involve skeletal abnormalities including extreme neck flexion ("dropped head") and truncal flexion (camptocormia) [13]. Pathology of PD can be associated with a very broad spectrum of clinical manifestations, extending beyond movement disorders. These include olfactory, gastrointestinal, sleep, sensory, and cognitive dysfunction, as well as psychiatric manifestations such as depression and anxiety. Many of these features predate the development of the classic motor disorder, and thus may serve as early markers of the disease, but are also common in the general population. It may be possible to identify individuals in the earliest stages of neurodegeneration using these early premotor features of PD in combination with other novel biomarkers [14, 15].

Review

TREMORS

Resting tremor is a characteristic of Parkinsonism and in fact, begins on one side of the body, most commonly in the hand and then spreads, over months and years, to the other side of the body [16]. Classic Parkinsonian tremor is a rest tremor of 4-5 Hz affecting the limbs, asymmetric or unilateral in the early stages of the disease. The combination of postural deformity and tremor can produce the unique tremor which Charcot described as follows: "The patient closes the fingers on the thumb as though in the act of spinning wool" or "crumbing bread". In the limbs it is distal. Arms are affected more commonly than legs. Less commonly it is present in lips, chin and tongue. Tremor is abolished during sleep [17]. The tremor of Idiopathic PD can affect the eyelids (blepharoclonus), jaw, and legs, while essential tremor targets the head, voice, and upper limbs. Parkinsonian tremor is increased by anxiety, and abolished by sleep. Limb activity attenuates rest but increases postural tremor. Around 50% of rest tremors respond well to dopaminergic and anticholinergic agents [18].

RIGIDITY

Rigidity is of the extrapyramidal "plastic" or "lead-pipe" type, i.e. not dependent on the velocity of passive muscle stretch. Many patients, particularly those with tremor have cog-wheeling but anyone with tremor (e.g. a patient with severe essential tremor) may have cog-wheeling [17]. The rigidity initially targets limbs but later spreads axially. A predominant involvement of limb and trunk flexors leads to characteristic “dystonic” posturing with trunk, neck, and arm flexion, and foot inversion. The rigidity is abolished by sleep and in 80% of cases responds well to dopaminergic agents [18].

SLOWNESS

Fifty per cent of IPD patients complain of slowing up at presentation. Writing becomes progressively smaller (micrographia). Difficulty in chewing and swallowing are common. [19]. Later on they develop difficulty washing, feeding, dressing, and turning in bed, but reveals slowing [18].

VOICE CHANGES AND SIALORRHEA

This initially becomes quiet and speech loses its natural cadence and prosody. Later lingual and labial bradykinesia leads to problems with articulation and speech becomes indistinct. Pallilalia is a feature of end stage disease. Sometimes sialorrhea appears when saliva is not swallowed as fast as it is produced, although increased saliva production may also occur as an autonomic symptom of Parkinsonism.

DYSTONIA

Dystonia is characterized by slow or sustained involuntary muscle contractions, frequently causing twisting and repetitive movements or abnormal postures [20, 21]. The muscles involved are usually localized in the head (mouth and eyes), neck, trunk and limbs. When dystonia becomes irreversible (which is often the case in tardive dystonia), it is one of the most disabling and untreatable adverse events in psychiatry [22].

Younger onset IPD cases (including genetic Parkinson's disease associated with parkin mutations) are particularly prone to exhibit limb dystonia. This can be early morning or wearing off dystonia with a predilection for painful foot inversion, but can also manifest as a variety of segmental syndromes. Levodopa and dopamine agonists may worsen rather than improve dystonia in some of these young onset IPD cases and anticholinergic treatment or amantadine can be helpful [4, 17, 18].

BRADYKINESIA

Bradykinesia(Slowed movement), hypokinesia (reduced movement), and akinesia (loss of movement) may be seen in a progressive decrement in the speed and amplitude of rapid succession movements e.g. finger tapping or fist opening and closing. These are the most common and disabling features of Parkinsonism. It also manifests in other ways. Reduction of arm swing during walking and micrographia are other examples. Ulnar deviation of the hands, extension of the interphalangeal joints and flexion of the metacarpophalangeal joints may
stimulate the changes of rheumatoid arthritis. Many patients find this to be the most frustrating aspect of their disease. It results in a loss of independence as it progresses, due to difficulties performing everyday functions, such as getting dressed, using utensils, and rising from chairs or bed.

**CAMPTOCORMIA**
Camptocormia is a relatively common sign in PD and present therapeutic regimens, including drug therapy, surgical therapy and rehabilitation, have limited effect on camptocormia[23]. Camptocormia in PD is defined by marked anteroflexion of the trunk, which abates in the recumbent position, with no or minimal response to levodopa [13, 24, 25]. The condition is exacerbated by walking and is relieved by sitting, lying in the supine position or by volitionally extending the trunk when the patient leans against a wall or a table. Although early reports often attributed camptocormia to a conversion disorder, it is now accepted as an axial feature of Parkinson’s disease [26, 27, 28]

**COGNITIVE DEFICITS AND DEMENTIA**
Nowadays Parkinsonism is not only recognised as a movement disorder but a multisystem disease affecting cognitive functions even in the earlier stages of disease [29].

The prevalence rate of dementia in PD patients can range from 17-43 % [29] and increases up to 83% after 20 years follow up [30]. Patients with Parkinson’s disease are impaired in cognitive tasks. A likely source of these deficits is depleted levels of the neuromodulator dopamine in the basal ganglia of Parkinson’s patients [31] because dopamine plays a key role in reinforcement learning processes in animals. Dementia commonly accompanies late-stage Parkinson’s disease can be associated with nocturnal confusional episodes and vocalizations and awakenings [32].

**INSOMNIA**
Based on the National Center for Sleep Disorders Research Classification [33] insomnia symptoms can be defined as subjective complaints of difficulty falling asleep, difficulty maintaining sleep, early awakening and non refreshing sleep despite an adequate opportunity to sleep. Sleep disturbances tend to increase with age and is particularly common in Parkinson’s disease. Difficulty falling asleep and difficulty remaining asleep are the most common complaints. Loss of dopaminergic neurons of the substantia nigra is responsible for most of the daytime features of Parkinson’s disease. Other neurochemical changes affecting cholinergic, serotonergic and noradrenergic systems are also involved and have been implicated in the sleep-wake disturbances in Parkinson’s disease. The precise role of these neurotransmitters in the disruption of the sleep-wake cycle is as yet unclear. Depression and anxiety may be the prime reasons for early awakening and difficulty in falling asleep. The on-off phenomena and presence of hallucinations can result in severe sleep disruption [32]. Sleep disorders are common in patients with Parkinson’s disease. They consist of insomnia, excessive daytime sleepiness, parasomnias, sleep breathing disorders and abnormal movements during sleep [34].

**BLADDER DISORDER**
In Parkinsonism beside several clinical disabilities, complaints of bladder and bowel dysfunction may add considerably to the patients’ disabilities. In some patients, urinary symptoms were the sole presenting complaints and these included difficulties in voiding, nocturnal urinary frequency of more than twice, sensation of urgency, urge incontinence, daytime frequency of more than eight times, nocturnal enuresis and urinary retention[35,36,37]. Urinary dysfunction in PD may reflect pathology of the disease. Detrusor hyperreflexia has been found cause of filling disorder [37]. The responsible sites for the detrusor hyperreflexia seem to be the nigrostriatal lesions in PD. Experimental studies showed that electrical stimulation of the basal ganglia inhibits micturition reflex in the cat [38] probably by activating striatal GABAergic neurons which descend to the locus ceruleus (PMC). Bladder hyperreflexia occurs in MPTP (1-methyl-4-phenyl- 1, 2, 3, 6-tetrahydropyridine)-induced Parkinsonian animals. There is experimental evidence that D1 receptors have an inhibitory and D2 a facilitatory effect on the micturition reflex [39]. Therefore, it seems likely that bladder hyperactivity in PD is associated with a reduction in the central dopamine D1 receptors.

**BOWEL DISORDER**
Patients’ symptoms of anorectal dysfunction are common with PD, and constipation appears to be increasingly common with advancing disease [40]. Constipation occurs in 29-77% of PD patients compared to 10-13% of age-matched controls. Difficulty in defecation occurs in 67-94% of PD patients compared to 10-13% of age-matched controls. Difficulty in defecation occurs in 67-94% of PD patients compared to 28% of a control group [41]. Megacolon in PD patients has severe fecal impaction (intestinal pseudo-obstruction) and rectal transit times were also prolonged, indicating reduction of rectal contractility. Immunostaining of biopsied colonic musculature and the submucosa showed a reduction of dopamine containing neurons and there has also been a report showing Lewy bodies in the myenteric plexus of the colon [42]. These findings suggest that not only central, but also peripheral dopamine dysfunction in the colon account for the prolonged...
transit time and constipation in PD. Rectoanal manometry has shown reduced resting and defecating pressures [35,40]. These probably reflect dysfunction of the internal anal sphincter innervated by lumbosacral sympathetic nerve. Other possible causes include over extension injury of the myenteric plexus due to severe fecal impaction, and an adverse effect of anticholinergic agents in PD. Defecography and anal sphincter EMG showed paradoxical contraction of the puborectal muscle in PD as a cause of rectal constipation [43].

**SEXUAL DYSFUNCTION**

Estimates of the prevalence of erectile dysfunction (ED) in patients with PD show that it is a significant problem, affecting 60% of a group of men compared with an age-matched healthy group without PD in whom the prevalence was 37%. ED and premature ejaculation was a complaint in a significant proportion. In general terms, however, sexual dysfunction appeared to be multifactorial with no simple single cause identified [44].

**PSYCHOSIS IN PARKINSON’S DISEASE**

Patients with Parkinson’s disease (PD), particularly those exposed to dopaminergic agents such as levodopa, have a high incidence of psychiatric symptoms. Common symptoms are hallucinations [45,46] delusions [46,47,48], depression, euphoria (48,49] agitated confusion, sleep disturbances, and delirium [50]. Visual hallucinations are the most common psychotic symptom exhibited by PD patients. Typical hallucinations have been described as nocturnal, nonthreatening images of people or animals, which the patient recognizes, or comes to recognize, as imaginary [46]. Delusions are less common in PD patients than hallucinations. Both hallucinations and delusions are serious complications of PD [51]. Risk factors for psychosis in PD patients include advancing age [52], increased dosage of levodopa [53, 54] long-term treatment with levodopa [55] anticholinergic therapy, multiple drug therapy [45] dementia [47], cerebral atrophy [53] and pre-existing psychiatric conditions [54].

**EPILEPSY**

In literature, there is brief information about the presence of epileptic seizures in patients with Parkinson’s disease but epileptic seizures are not very rare in patients with Parkinson’s disease. In their etiopathogenesis probably are included common pathophysiological mechanisms. These epileptic seizures are symptomatic, maybe a consequence of degenerative brain process and respond well to antiepileptic therapy [56].

It’s hard to imagine two diseases more different than Parkinson’s and cancer but Parkin as a tumor suppressor gene was the latest-discovered link between the two diseases. Parkin mutations cause up to half of early-onset hereditary cases of Parkinson’s disease. Another early onset Parkinson’s gene, DJ-1, has been implicated in cancer, and a third gene, LRRK2, has features that strongly hint at cancer like effects. In the 1980s researchers reported that Parkinson’s patients had an overall decreased incidence of cancer, with some important exceptions, mainly melanoma. People with Parkinson’s disease had a twofold increased risk of melanoma and also of breast cancer and there is a huge body of epidemiological data to support these conclusions [57].

**OTHERS**

Patients have impaired sense of smell [19].Increased sweating “seborrhoea” and facial flushing are late disease features (18,58). Further, A group of neurobehavioral abnormalities can be found in PD such as apathy, fearfulness, emotional liability, social withdrawal, increasing dependency, depression., bradyphrenia, a type of anaomia termed the “tip-of-the-tongue phenomenon,” visual-spatial impairment and other psychiatric problems [14]. Hypomimia (masked facies), Speech disturbance (hypokinetic dysarthria), Hypophonia. Dysphagia, Respiratory difficulties, Loss of associated movements, Shuffling, short-step gait, Festination, Difficulty turning in bed, Slowness in activities of daily living, Stooped posture, kyphosis, scoliosis, orofacial dyskinesia and decreased blink rate are also experienced by the patients depending on the status and progress of disease [59]. Myerson’s sign is the inability to resist blinking when the glabella (area above the nose and between eyebrows) is tapped with finger; it can be seen early in PD [60]. Other autonomic abnormalities include cardiovascular disorders and gastrointestinal dysfunction [19].

**Conclusion(s)**

Variety of motor and non motor complications signifies the involvement of several neurotransmitters and signaling pathways involved in the neurobiology of Parkinsonism. Thus a multicentered and multitargeted approach must be applied by research community to understand the molecular mechanisms involved in pathogenesis of disease so that we can have a drug that can stop the progression of disease rather than provide symptomatic relief only.
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