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REVIEWS

Ageing, neurodegeneration and Parkinson's disease

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Abstract

Age is the largest risk factor for the development and progression of Parkinson's disease (PD). Ageing affects many cellular processes that predispose to neurodegeneration, and age-related changes in cellular function predispose to the pathogenesis of PD. The accumulation of age-related somatic damage combined with a failure of compensatory mechanisms may lead to an acceleration of PD with age. The formation of Lewy bodies may represent a marker for protective mechanisms against age-related dysfunction and degeneration of the nervous system. Mild parkinsonian signs may be present in older people, which are associated with reduced function. These may be due to age-related decline in dopaminergic activity, incidental Lewy body disease, degenerative pathologies (early PD and Alzheimer's disease) or vascular pathology. Ageing may affect the clinical presentation of PD with altered drug side effects, increased risk of developing dementia and an increased likelihood of admission to a nursing home. Progression of PD, including the development of dementia, and hallucinations is related to the age of the patient rather than the age of disease onset. PD may reflect a failure of the normal cellular compensatory mechanisms in vulnerable brain regions, and this vulnerability is increased by ageing. PD is one of the best examples of an age-related disease.

Keywords: *ageing, Parkinson's disease, neurodegenerative disease, Lewy bodies, α-Synuclein, elderly*

Introduction

We all age, our brains age, but only some of us develop neurodegenerative diseases such as Parkinson's disease (PD). There has been a debate as to whether the pathological processes of PD are exaggerations of those processes involved in ageing, making us all liable to develop PD if we live long enough, or whether the ageing process makes us vulnerable to diseases such as PD or whether the pathology of PD is independent of ageing. The pathogenesis and clinical presentations of PD result from complex interactions between ageing and other susceptibility factors, making PD one of the best examples of an age-related disease.

Epidemiology of PD

The prevalence of PD increases with increasing age, and this age-specific prevalence is remarkably similar in the majority of countries in Europe. It is likely that variations in prevalence around the world reflect variations in life expectancy and case ascertainment. Age-adjusted prevalence rates in the UK are around 150 (105–168) per 100,000 population with an age-specific incidence of 10.8 cases of PD and 16.6 cases of parkinsonism per 100,000 population per year [1]. Most studies suggest a mean age of onset in the 70s.

Ageing and neurodegeneration

Ageing is thought to be a stochastic process combining predictable and random effects that lead to the accumulation of unrepaired cellular damage, weakening cellular repair and compensatory mechanisms [2]. Much of the individual variation in ageing is accounted for by lifestyle and the effects of the environment, with genes accounting for only 25% of variability [2]. Although brain cells are particularly susceptible to the accumulated effects of ageing, neuronal death is not programmed to occur at a particular time. Cellular and molecular changes of ageing interact with genes and environmental factors to determine which cells age successfully and which succumb to neurodegeneration. It is not clear how the selective vulnerability comes about, giving rise to different differing patterns of neurodegeneration in different diseases.

Compensatory strategies protective against cell damage and death include mitochondrial oxygenation, ubiquitiniza-

tion and proteolysis by proteasomes and activity of chaperones and lysosome-mediated autophagy. Ageing is associated with mitochondrial dysfunction, increased free radical production and oxidative stress, which may lead to genomic instability and DNA mutations, with shortening of telomeres associated with reduced survival [3]. There is an age-related decline in activity of proteasomes that degrade damaged or ubiquitinated proteins leading to an increase in abnormal deposition of cellular brain proteins [4]. There is some age-related deposition of α-synuclein, although post-mortem studies show that it is much less in age-matched controls compared with PD brains. These studies also show the co-existence of beta amyloid and α-synuclein pathology possibly suggesting common underlying pathogenic mechanisms between Alzheimer's disease and PD [5]. The sirtuins are members of the histone deacetylase family of proteins that play a role in the regulation of the cell cycle and the promotion of cell survival. Inhibition of sirtuins has been shown to rescue the toxicity of α-synuclein in animal models, suggesting a link between ageing and neurodegeneration [6]. Ageing is associated with a reduced efficiency of chaperones and imbalanced autophagic recycling, changes in inflammation, complement activation, activation of microglia and an impaired response to neurotrophic factors impairing the brain's ability to recover from damage [7]. Iron progressively accumulates in the brain with age, including in the substantia nigra, rendering the cell more susceptible to toxins [8]. Optimum functioning of the insulin signalling pathway maximises longevity, with each tissue having its own critical level. Lower levels of activity interfere with metabolism producing diabetes while higher levels in the brain with ageing predispose to neurodegeneration [9].

There are age-related genetic changes in the substantia nigra due to an accumulation of deletions of mitochondrial DNA in ageing with functional impairment of neurons. Such deletions are also prevalent in PD and affect the functioning of neurons [10].

Other age-related changes include reductions in striatal tyrosine hydroxylase and dopamine, a reduction in the number of pigmented neurons in the substantia nigra and reduced dopamine receptor density. Although there is loss of pigmented neurons with age, there is evidence that remaining neurons hypertrophy, possibly as a compensatory mechanism [11]. All of these age-related changes are relevant to the aetiology and pathogenesis of PD.

Aetiology of PD

Ageing is the largest single independent risk factor for the development of PD. Environmental risks for PD include exposure to pesticides, rural living, drinking well water, heavy metal and solvent exposure, welding and mining. There are also some possible protective factors including a history of cigarette smoking, caffeine use and use of anti-inflammatory agents [12].

There is a positive family history of PD in 10–15% of PD patients. At least 13 different PD gene groups have been described, which are mostly associated with rare forms of younger onset disease that have clinical features distinguishing familial from sporadic cases [13]. The leucine-rich repeat-kinase-2 gene defect (LRRK2) or park 8 is an example of a gene defect causing late-onset PD [13]. LRRK2 PD is the most common autosomal dominant parkinsonism accounting for 1–2% of patients with sporadic late-onset PD. The clinical signs and symptoms are heterogeneous but can resemble sporadic PD with an average age of onset in the late 50s and 60s but with a more benign prognosis and less dementia. Pathological changes are variable and it is suggested that the mutation leads to a cascade of neurodegeneration with differing pathology [13].

Pathogenesis of PD

The pathogenesis of PD consists of a cascade of events leading to cell death (Figure 1). This cascade includes oxidative stress, impaired mitochondrial function, excitotoxicity via glutamate pathways, protein misfolding and aggregation due to ubiquitin–proteasomal system dysfunction, impaired lysosome and chaperone-mediated autophagy, and the development of cytoplasmic inclusion bodies called Lewy bodies that contain neurofilament proteins and ubiquitinated α-synuclein. Inflammation and humoral immune reactions may contribute to the processes linked to cell death through apoptosis. Many of these mechanisms parallel the changes of ageing. Many environmental agents may be inhibitors of proteasomal function and, in rat models, proteasomal inhibition alone can reproduce the key features of PD [14].

The main areas to consider in reviewing the relationship between ageing and the pathological processes in PD are the presence and distribution of Lewy bodies, the specific distribution of cell loss and the pattern of protein deposition.

Lewy bodies

Braak staged PD according to the progression of the pathological changes from the brain stem to the cortex, in an ascending course, based on the presence of Lewy bodies [15]. In Braak Stage 1, changes are confined to the dorsal motor nucleus and olfactory bulb associated with loss of olfactory function, commonly seen in pre-clinical PD. Loss of the sense of smell should, therefore, reflect the underlying disease course rather than an age-related change. PD patients have a more rapid decline in the sense of smell when compared with age-matched controls with an onset of decline many years before the motor syndrome [16]. Using a predicted age-related rate of decline in the sense of smell, PD would only develop due to 'normal ageing' considerably beyond the normal human lifespan. Braak Stage 2 involves Lewy body formation in the pons and medulla, Stages 3 and 4 produce clinical motor symptoms and Stages 5 and 6 involve neocortical areas, producing cognitive problems and dementia. Early involvement of the brain stem in PD may correlate with early autonomic symptoms which are more common with increasing age and can precede the motor symptoms [17].

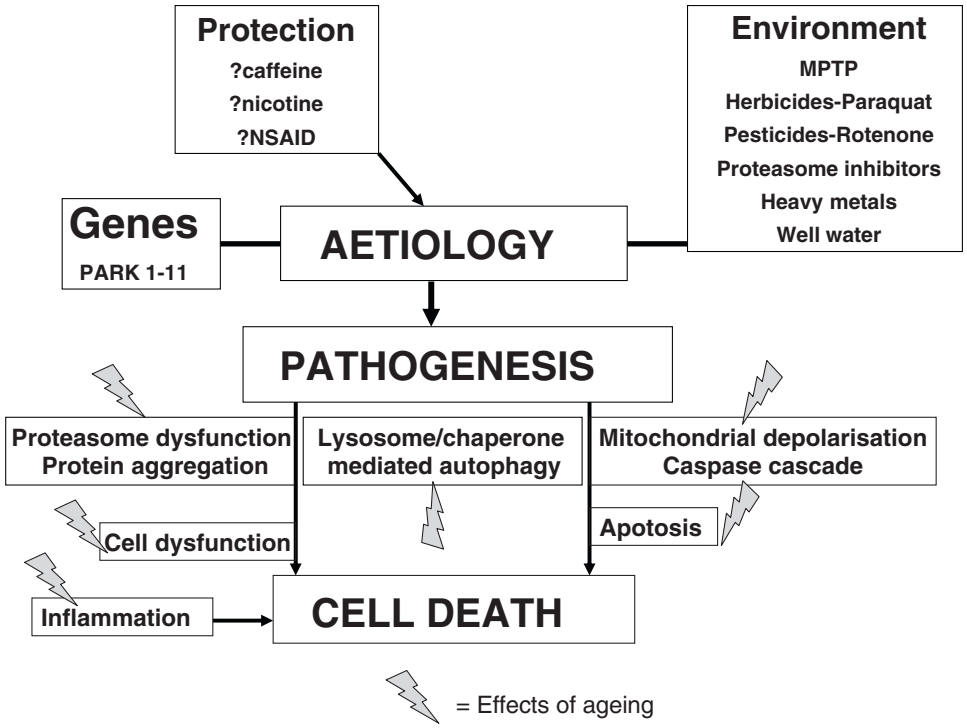

Figure 1. Aetiology and pathogenesis of Parkinson's disease.

Accumulation of α-synuclein at the synapse leads to a loss of synaptic proteins and synaptic pruning with loss of connectivity [18]. Retrograde transport of α-synuclein in the axon to the cell body to form the Lewy body may be protective. A post-mortem study which included people with no dementia or PD in life showed that 50% of brains in which diffuse cortical Lewy bodies were found had no history of dementia in life and the pattern of Lewy body formation only partially confirmed Braak's staging [19]. Some Lewy body-related α-synucleinopathy is found in up to 50% of Alzheimer's disease brains and 30% of controls, with >10% having significant Lewy body disease but no parkinsonism [20]. This 'incidental Lewy body disease' (ILBD), which may represent pre-clinical PD, is more common with increasing age, and is associated with cell loss to a degree intermediate between that found in PD and in normal ageing. There is evidence that PD progressing to PD dementia, and dementia with Lewy bodies progressing to parkinsonism, end in similar clinical and pathological patterns, suggesting that the pattern observed by Braak is part of a spectrum of conditions ranging from those commencing in the brain stem through to those commencing in the cortex. It is possible that the Lewy body represents a marker of protective mechanisms against age-related dysfunction and degeneration of the nervous system.

Cell loss

Cell loss occurs not only in the dopaminergic cells in the substantia nigra (SN) but also in many other non-dopaminergic areas of the brain including the noradrenergic locus coeruleus, the cholinergic nucleus basalis of Meynert, the serotonergic raphe nucleus and the autonomic nervous system. In the very early stages of PD where Lewy bodies are found in the brain stem, there is already cell loss without Lewy bodies in the SN. The SN has two divisions, the pars reticulata and the pars compacta (SNc), with the SNc subdivided into ventral and dorsal tiers. Cell loss in PD mainly occurs in the ventral tier of the SNc. At post mortem, only a quarter of cells in the SNc remain in PD compared with normal, with the surviving cells being in the dorsal tier [21]. In normal ageing, the dorsal tier is preferentially affected by a ratio of over 3:1 [11] with a 5% loss per decade after the age of 40 years. The pattern of cell loss seen in PD does not occur in other neurodegenerative diseases or in normal ageing. The causes of the selective vulnerability of cells affected in PD (SNc, medium spiny neurons in the striatum and lower motor neurons in the spinal cord) are unclear. Selective vulnerability may be related to changes in cellular excitotoxicity and calcium homeostasis in cells which have altered levels of calcium-binding proteins [22]. It has also been proposed that vulnerability may be due to the size of dopaminergic neurons which have many connections. Synapses are particularly prone to damage and the production of dopamine may increase oxidative stress and damage in the pre-synaptic nerve terminals. This dysfunction may affect neurons with which they communicate leading to a spread of degeneration throughout the brain.

Protein deposition

PD is associated with abnormal protein deposition, especially α-synuclein, although the areas of accumulation do not always coincide with the areas of cell death. The toxicity

Table 1. Clinical relationships Parkinson's disease, mild parkinsonian signs and age-related gait disturbance

	Parkinson's disease	Mild parkinsonian signs	'Age-related' gait disturbance
Tremor	Rest	Absent in 90%	Absent
Rigidity	Typical cogwheel and lead pipe	Variable	Musculoskeletal
Bradykinesia	Typical with fatigue	Variable	General slowness
Gait and balance disturbance	Late	Early	Axial impairment gait and posture
Symmetry	Asymmetrical	Symmetrical	Symmetrical
Dementia risk	Increased	Slightly increased	Age related
L-dopa response	Good	Poor	None

of α-synuclein may be related to a perturbation of dopamine storage and release or through a massive increase in apolipoprotein-E levels and accumulation of insoluble amyloid (Ab) [23]. Predisposition to cell loss in PD may relate to increased pigment density and α-synuclein precipitation under oxidative conditions, precipitating a cascade leading to cell death. Accumulation of proteins such as α-synuclein leads to the formation of precursors of protein fibrils called protofibrils which may promote cell death.

Clinical symptoms of PD and ageing

Extra-pyramidal symptoms and signs can sporadically occur in older people. Mild parkinsonian signs characterised by an absence of rest tremor, symmetrical signs and lack of response to dopaminergic therapy have been attributed to normal ageing. Mild parkinsonian signs include rigidity, bradykinesia, tremor and problems of gait and balance found commonly during the clinical examination of older people who have no definite neurological disease [24]. These mild parkinsonian signs can predispose to functional difficulties, a loss of capacity to perform activities of daily living, impaired gait and balance, increased risks of mild cognitive impairment, dementia and increased mortality. Older people with mild parkinsonian signs fall short of established research criteria for PD such as the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria [25]. The clinical differences between PD and mild parkinsonian signs include the number and severity of parkinsonian signs, the presence of rest tremor, the symmetry of signs and likelihood of responsiveness to levodopa therapy (Table 1). Although there is an association between olfactory loss and mild parkinsonian signs suggesting early brain stem involvement, the pathogenesis of mild parkinsonian signs remains unclear. The origins are likely to be multi-factorial, with possibilities including age-associated decline in dopaminergic activity, ILBD, degenerative pathologies (early PD and AD) or vascular pathology in the basal ganglia or deep white matter [24].

Ageing can produce axial impairment of gait and postural control in PD due to the combined effect on non-dopaminergic and dopaminergic pathways. Older PD patients are more liable to suffer side effects of anti-cholinergic medications, such as confusion and hallucinations, because of the increasing cholinergic deficit in PD with age. Levodopa-induced dyskinesia may reduce with age, possibly because younger onset patients demonstrate a higher rate of dopamine turnover relative to production when compared with older patients. One of the difficulties extrapolating the evidence base for the use of many anti-parkinsonian medications to older people is the exclusion of older people from trials, which may lead to an over- or underestimation of the efficacy of treatments in older people [26].

Non-motor symptoms may be present at diagnosis of PD with many patients having consulted their general practitioner for non-motor symptoms before the diagnosis of PD was made. As PD progresses, the impact of the non-motor symptoms dramatically increases with the development of constipation, incontinence, falls, orthostatic hypotension, sweating abnormalities, dysphagia, dribbling and psychiatric disorders including dementia and hallucinations. Long-term studies have shown that disability in PD largely relates to the emergence of non-motor symptoms that are not improved by treatment with levodopa [27]. Factors increasing the risk of falls include being female or having a symmetrical onset, postural instability or autonomic dysfunction, with the shortest latency to the onset of falls occurring in older age.

Some evidence of cognitive impairment may be present in patients even at diagnosis of PD, with more global impairment in older age. There is slowing of motor learning with age, but sequenced motor learning and executive function are much more significantly impaired in PD. There are significant impairments of visuo-spatial tasks in PD compared with both young and age-matched controls. PD patients have a 5-fold increase in the risk of developing dementia with the risk increasing with advancing age. Age itself is the single largest risk factor for the development of dementia in PD [28]. A later age of onset of PD, longer duration of symptoms, the presence of hallucinations and impaired memory or language function also predict the development of dementia. The motor subtype of postural instability and gait disorder may be associated with faster cognitive decline and is also a risk factor for dementia. A family history of PD, rather than dementia, may increase the risk of developing dementia in PD. Pathologically, dementia may be due to the development of cortical and parahippocampal Lewy bodies but may also be due to the development of Alzheimer's pathology and superimposed vascular pathology.

Dementia is a significant predictor for institutional placement. With increasing age and the development of dementia

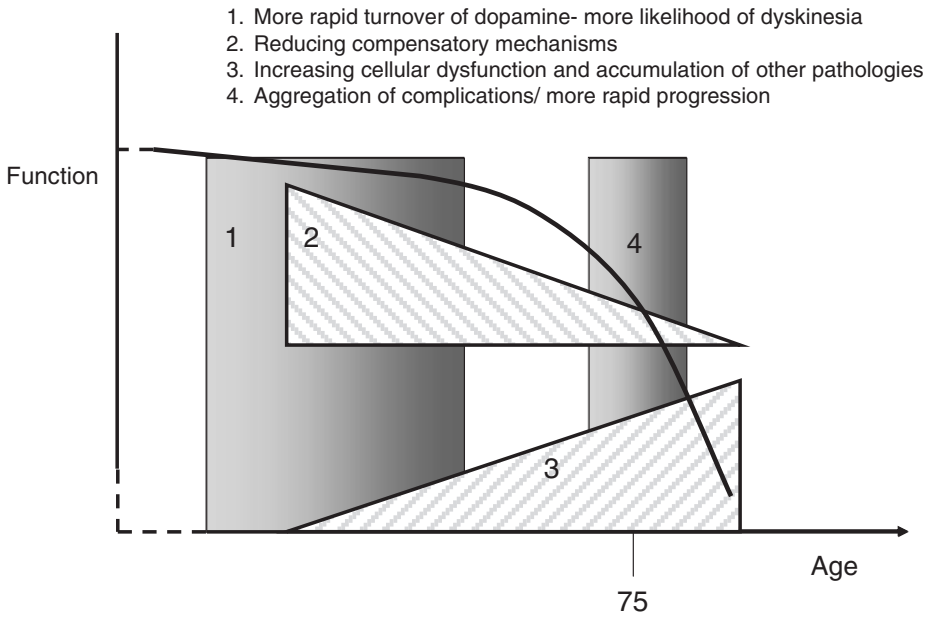

Figure 2. A model of ageing and progression of PD.

and psychosis, there is an increasing likelihood of admission to a nursing home with subsequent increased mortality. Increasing social care and admission to a nursing home are the largest economic burdens in PD. Comorbidity increases with age and may be a predictor of an increased use of primary care services. Comorbidity of other age-related diseases, including other neurodegenerative diseases, cerebrovascular disease, cardiac disease, respiratory disease, diabetes, falls and incontinence, is likely to contribute to frailty in older patients. The psychosocial effects of ageing including retirement, social isolation, poor housing, poor nutrition and poverty may have additional effects on PD in older patients.

Compensatory mechanisms and progression

Compensatory mechanisms maintain apparently normal motor function over many years from disease onset to clinical diagnosis. These mechanisms include increased striatal dopamine turnover and receptor sensitivity, up-regulation of striatopallidal enkephalin levels, increased sub-thalamic excitation of the globus pallidus pars externa and maintenance of cortical motor area activation [29]. A marked loss of nigrostriatal compensatory mechanisms with age has been shown in primates, and it may be that this age-related loss of plasticity makes it less possible to recover from accumulated insults with advanced age.

With increasing age, polygenic influences and the accumulation of other insults, there is an increased likelihood of failure of these mechanisms leading to the development of or the acceleration of PD. A recent post-mortem study of levodopa-responsive PD patients who came to autopsy showed three groups of pathological patterns. A younger group had Lewy body pathology consistent with the Braak staging of disease. A second group had early malignant dementia symptoms and pathology consistent with dementia with Lewy bodies. The final group had an older disease onset and a more complex course, a shorter survival with higher Lewy body loads and higher prominence of other pathologies including plaques. This study was not consistent with a unitary cause of all Lewy body pathologies but raises the importance of the more malignant older onset disease [30].

Most authors have used a linear progression model suggesting that the onset of complications, such as dementia and hallucinations, would be dependent on the age of onset, i.e. the younger the onset, the younger the presentation of complications. A recent study, however, has shown that these complications aggregate according to the age of the patient rather than age of onset of PD with a rapid accumulation in the eighth decade of life [31]. PD may have a complex progression with a more linear initial progression in younger patients with the development of a quadratic progression with age and with an older age of disease onset (Figure 2).

Conclusions

The mechanisms of ageing and neurodegeneration are complex and inter-related. Ageing is the single most significant factor influencing the clinical presentation and course and progression of PD. Normal ageing may be associated with very mild parkinsonian signs, whereas PD has a distinct clinical picture. PD reflects a failure of the normal cellular compensatory mechanisms in vulnerable brain regions, and this vulnerability is increased by a genetic susceptibility acted upon by other genetic and environmental factors and most importantly by age. The accumulation of age-related somatic damage combined with a failure of compensatory mechanisms may lead to an increased prevalence and an acceleration of PD with age. Ageing is, therefore, the main modifying factor on the phenotypic presentation of PD. PD is an outstanding example of an age-related disease.

Key points

- The mechanisms of ageing and neurodegeneration are inter-related.
- Ageing is the single most significant factor influencing the clinical presentation, course and progression of PD.
- Age-related changes in cellular function and a reduced compensatory capacity predispose to the pathogenesis of PD.
- The formation of Lewy bodies may represent a marker of protective mechanisms against age-related degeneration of the nervous system.
- PD is one of the best examples of an age-related disease.

Conflicts of interest

Nothing to declare.

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