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Research Article

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Parkinsonian Consequences in Patients Treated with Psychotropics-Why Does It Affect the Elderly More so than the Young?

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Abstract

Introduction: *Psychotropics may provoke medication induced parkinsonism (MIP). Age is its most common risk factor and predictor for idiopathic PD. This paper reviews these relationships.*

Background: *MIP may result from a trigger evoking subclinical idiopathic PD and idiopathic PD may represent an expression of aging.*

Discussion: *Aging may play a substantive role in the pathogenesis of idiopathic PD, involving nondopaminergic structures, causing a cascade of stressors within the substantia nigra, reducing capacity to respond to insults. Mitochondrial dysfunction and altered protein degradation may be more detrimental to these neurons than elsewhere within the brain. The neurons, degenerating in idiopathic PD, are the same as in aging. Despite epidemiology identifying aging, as the PD risk factor, biological correlates remain elusive. Midbrain dopamine neurons, from aging nonhuman primates, show markers of known correlates of dopamine neuron degeneration, found in PD. Pang et al claim most octogenarian do not have PD, challenging age in its aetiology. Idiopathic PD remains a clinical diagnosis, questioning how detailed was their physical examination. Raghunathan et al evaluated glycosaminoglycans and proteins in PD brains, compared with controls, finding idiopathic PD differed from controls, casting doubt that PD is an expression of aging. Environmental or genetic factors may be important but age remains pivotal with treatment started as soon as the diagnosis of PD is made.*

Conclusions: *Age is more relevant to the prognosis of idiopathic PD than is disease duration. MIP may result from a trigger allowing the expression of pre-existing idiopathic PD, requiring treatment and further investigation.*

Keywords: Psychotropics, Parkinsonian features, Aging, Indiopathic Parkinson's Disease, Diagnostic Dilemma

Introduction

Psychotropic medications have long been known to cause the potential unwanted effect of producing extrapyramidal features of parkinsonism which may be indistinguishable from Parkinson's disease (PD) [1-3]. While these features may resolve after discontinuation of the offending medication, they may continue long after its cessation, raising questions why this should be so [1-5]. The clinical manifestations of medication induced parkinsonism (MIP) are said to be bilateral and symmetric parkinsonism, devoid of tremor at rest. This is far from universal, with about half of these patients, with MIP, having asymmetrical parkinsonism and tremor at rest, making it difficult to differentiate MIP from idiopathic PD [1]. MIP was first reported with the use of chlorpromazine (Largactil®), a member of the phenothiazine group of medications but MIP was subsequently recognised to occur with a range of psychotropic medications, including antidepressants as well as gastrointestinal motility medications, calcium channel blockers and antiseizure medications [1-4].

Age is the most prominent risk factor for MIP evoking the question, why is this so? The role of age, within this scenario, has been the focus of further investigation [5-8]. MIP is identified as a strong predictor for idiopathic PD which is the underlying motivation for the current paper which offers an alternative hypothesis for the interaction and relationship between age, MIP and idiopathic PD [9].

Background

The pathophysiology of MIP is said to be related to medication induced changes in the basal ganglia motor circuit secondary to dopaminergic receptor blockade [1]. It is often caused by lipophilic drugs that "block" dopamine D2 receptors in the brain, although presynaptic dopamine depletion, false transmitters, mitochondrial respiratory chain dysfunction and over activity in the gamma-aminobutyric acid (GABA) ergic system or cholinomimetic action have also been postulated as possible mechanisms [7].

In a study of almost 450 patients with MIP, with a 4-year follow up, there was a significant increase of subsequent idiopathic PD, when compared to patients with diabetes mellitus, (adjusted hazard ratio, HR: 18.88, 95% CI, 9.09-39.22, adjusting for comorbidities and causative drugs) [9]. It occurred mostly within the first year of follow-up [mean days 453 (SD 413.36)] [9]. Other medications, impugned to cause MIP, included calcium channel blocker (Verapamil®, Diltiazem®, and Flunarizine®) associated with increased idiopathic PD risk (HR: 2.24, 95% CI, 1.27-3.93). Jeong et al. postulate that the greater prevalence of idiopathic PD, in those with MIP, might not be caused by the toxic effects of antidopaminergic medications but rather that they act as a trigger for people who already have subclinical idiopathic PD pathology. They argue that MIP may "serve as a strong proxy for I(idiopathic) PD incidence. Subjects who develop DIP (MIP) should be monitored carefully for potential I(idiopathic)PD incidence." [9].

The hypothesis, proffered by Jeong et al., adds strength to that by Beran which argues that idiopathic PD may not be a specific disease per se but rather it may represent an alternative, specific expression of the aging process, affecting those cells which are involved in both aging and the evolution of idiopathic PD [10-12]. It is hypothesised that the expression of MIP, provoked by the identified medications, and others not set out in the above discussion, but equally known to provoke MIP, provides the trigger (as suggested by Jeong et al.) to amplify the subtle early signs of idiopathic PD and initiate the clinical manifestations thereof.

Discussion

There is a growing number of researchers who question the relationship between aging and idiopathic PD [13-15]. In the 20th Century, there were prominent hypotheses attributing a substantive role to aging, in PD pathogenesis, which included "accelerated aging" and normal aging-related neuronal attrition, following a suspected subclinical environmental insult to the substantia nigra in early or middle adult life [16,17]. Levy argued that aging may still play a substantive role in the pathogenesis of idiopathic PD involving the nondopaminergic structures [15]. He cited Dauer and Przedborski and Greenamyre and Hastings to claim that the pathogenic cascades, involved in PD, should explain the relative selectivity of PD for the substantia nigra pars compacta as well as the widespread involvement of monoaminergic and cholinergic structures in late stages of the disease [18,19]. He relied on experiments, designed to investigate whether the susceptibility of non-dopaminergic structures or cell types to the disease process was synergistically influenced by molecular mechanisms related to the aging process. He raised the hypothesis of there being a biologic interaction between the disease process and aging in non dopaminergic structures. He also questioned if further investigation, into this hypothesis, might eventually provide opportunities to modify the clinical progression in idiopathic PD, with the potential to delay the non-levodopa-responsive motor and cognitive manifestations of PD [15].

Reeves et al. argued that the effects of aging cause a cascade of stressors within the substantia nigra which affects the neurons and their capacity to respond to further insults which may contribute to the disease process [13]. They also argue that mitochondrial dysfunction and alterations in protein degradation pathways are subsequently far more detrimental to the neurons of the substantia nigra than they would be to neurons elsewhere within the brain [13]. This concept may be highly relevant to the emergence of MIP in which it could be argued that medications, in a variety of different pharmacological categories, may constitute the imputed insult. This might evoke idiopathic PD that was sub-clinically present due to underlying aging process recognised as a major factor in MIP. Rodriguez et al. hypothesised that aging may be critical for PD, arguing that those neurons degenerating in idiopathic PD are the same that degenerate in normal aging [14]. They further claimed that the different agents, involved in the evolution of idiopathic PD, are similarly involved in aging [14]. They acknowledge that, *"Senescence is a wider phenomenon affecting cells all over the body, whereas Parkinson's disease seems to be restricted to certain brain centers and cell populations"* and they concluded that idiopathic PD *"may be a local expression of aging on cell populations which, by their characteristics (high number of synaptic terminals and mitochondria, unmyelinated axons, etc.), are highly vulnerable to the agents promoting aging."* [14]. This philosophy underpins the similar ideology adopted by Beran which acknowledges the possibility that idiopathic PD is an expression of aging and hence a novel treatment algorithm was adopted to provide a rationale which advocated very early introduction of treatment, starting with very low dose L-dopa, as soon as there are features of PD, while the aging brain receptors are still receptive to replacement therapy, using dopa which is converted to dopamine in the brain, before the receptors degenerate to necessitate increased dosages with compensable proclivity to adverse consequences [10-13,20].

Collier et al. supported the concept that idiopathic PD and aging were the two faces of the same coin [21]. Their argument entailed that, despite abundant epidemiological evidence identifying aging as the primary risk factor for idiopathic PD, the biological correlates of a connection have been elusive [21]. They presented evidence, from work on midbrain dopamine neurons, of aging nonhuman primates, which showed markers of known correlates of dopamine neuron degeneration, found in idiopathic PD, including impaired proteasome/lysosome function, oxidative/nitrative damage and inflammation, all increase with advancing age. They demonstrated that these markers were *"exaggerated in the ventral tier substantia nigra dopamine neurons most vulnerable to degen-*

eration in PD". They concluded that their findings supported the hypothesis that aging-related changes, within the dopamine system, approached the biological threshold for parkinsonism, actively producing a vulnerable pre-parkinsonian state [21]. This lends further weight to the supposition that MIP may be the expression of an environmental factor, superimposed on the age-related predisposition to idiopathic PD.

Age remains the single, largest risk factor for idiopathic PD, affecting many cellular processes that predispose to neurodegeneration and age-related changes in cellular function which predispose to idiopathic PD [22]. Hindle recognised that mild parkinsonian signs may be present in older people with associated reduced function. He hypothesised that these may relate to age-dependant decline in dopaminergic activity, incidental Lewy body disease, degenerative pathologies (involved in both early PD and Alzheimer's disease) or vascular pathology [22]. He stated that *"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"*. This may have particular relevance when considering the role of age, the possible presence of subclinical idiopathic PD and the expression of MIP. He further concluded that *"PD may reflect a failure of the normal cellular compensatory mechanisms in vulnerable brain regions, and this vulnerability is increased by ageing (making) PD ...one of the best examples of an age-related disease"* [22].

Countering the argument that idiopathic PD is simply an expression of aging, Pang et al. claimed that the majority of those, over the age of 80, do not have PD, thereby refuting the claim of age as the aetiology of its expression [23]. The diagnosis of idiopathic PD remains a clinical diagnosis for which there is no reliable antemortem, objective testing and the clinical diagnosis remains dependent upon expert opinion as the 'gold standard' [24-26]. The diagnosis remains reliant on the cardinal features of bradykinesia, rigidity and resting tremor, requiring at least two out of these three features [10, 24-26]. Various primitive reflexes, such as the glabellar tap, grasp reflexes and palmar mental/naso-palpebral reflexes, when present, assist in the clinical diagnosis of PD but are not obligatory [10,26]. It is unclear the extent to which Pang and colleagues examined patients, to arrive at the statement which excluded idiopathic PD in most octogenarians, but their claim is far from a universal impression when patients are diligently examined for the cardinal feature, especially rigidity and bradykinesia [10,11,20,23].

A more impressive counter argument is provided by Raghu Nathan et al. who reviewed previous studies of idiopathic PD which showed dysregulated extracellular transport of α-synuclein and growth factors in the extracellular space [27]. They sought to evaluate alterations to structure of glycosaminoglycans and proteins occurring in PD brains when compared with similar aged controls and reported that the brains of those with idiopathic PD differed markedly from controls in upregulation of extracellular matrix structural components, such as collagens, proteoglycans and glycosaminoglycan binding molecules. Levels of haemoglobin chains, possibly related to defects in iron metabolism, were found to be enriched in idiopathic PD brains. They argued that these findings cast serious doubt on the hypothesis that idiopathic PD is simply an expression of aging. As stated by Hindle, progression of idiopathic PD, is related to the age of the patient rather than the duration since the disease onset [22]. It may reflect a failure of the normal cellular compensatory mechanisms in vulnerable brain regions, which is increased by ageing, making idiopathic PD one of the best examples of an age-related disease. What is unclear is whether, by the time Raghu Nathan et al. received their post mortem samples, there were other confounding factors, such as comorbidities and other issues which may have influenced or altered the findings.

What this review has demonstrated is that the jury is still out on the true relationship between idiopathic PD and aging, with pathological studies raising some concern regarding the hypothesis that idiopathic PD is merely a selective expression of aging. It is unclear if the aging process, for those who develop idiopathic PD, is, in any way, different to that of those who do not develop PD but the high prevalence of this degenerative disease makes that unlikely. One of the arguments favouring this suggestion is that the features of PD have been reported as long ago as Babylonian times and were noted in ancient China and Greece as well as India, thereby demonstrating its ubiquitous nature, transcending various ethnicities, cultures and societies [10,28]. The question of environmental or genetic factors may well play a more pivotal role than has thus far be attributed to them but that role, in relationship with aging, is unclear. This would provide fertile ground for further research. The fact that age is a pivotal factor in the expression of idiopathic PD, as well as MIP, also does still raise unresolved questions of MIP being a trigger for the expression of subclinical idiopathic PD in an aging or susceptible population and that idiopathic PD may be more ubiquitous than is currently accepted. This underpins the novel approach to the management of PD, with the introduction of treatment for PD, namely starting medications as soon as the clinical diagnosis is established, based on 2 of the 3 cardinal signs (Rigidity, bradykinesia and tremor). Such treatment is started immediately upon diagnosis with very low dosage of either L-dopa/carbidopa (Kinson® or Sinemet®) or L-dopa/benserazide (Madopar®), adopting the 100/25 combination strength, a half twice daily, and very slowly titrating to need (11,12,20). This is followed by the addition of other medications, such as monoamine oxidase (MAO) A and B inhibitors, selecting either selegiline (Eldepryl ®), rasagiline (Azalect ®) or safinamide (Xadago®), again titrated to the patient's need (11,12,20) and added to the existing L-dopa. When it is apparent that the patient needs further adjunctive therapy, dopamine agonists, as required, such as pramipexole (Sifrol ®) can be added and titrated to requirement, followed by the replacement of the L-dopa/carbidopa or L-dopa/beserazide combined medication with the triple combination of L-dopa/carbidopa/entacapone (Stalevo®), introduced in incremental fashion and as a further adjunctive treatment to the MAO A and B inhibitors and the dopamine agonist [11,12,20].

Conclusion

There remains the unresolved question whether idiopathic PD is merely an expression of the aging process, acknowledging that age is more relevant to the prognosis of PD than is the duration thereof. There is a viable argument that MIP may be the manifestation of the offending medication acting as a trigger to allow the expression of idiopathic PD, especially in those for whom the signs and symp-

toms of idiopathic PD do not resolve, following cessation of that medication. This is further amplified when acknowledging that age is also the principal aetiological factor in the expression of MIP. Autopsy is generally not a viable option in those experiencing MIP as the majority have a remedial disease, especially those with psychiatric diagnoses such as psychosis or depression. This provides fertile soil for further investigation.

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