



## **Dementia in Parkinson's disease – a comprehensive review**

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### **ABSTRACT**

Parkinson's disease is neurodegenerative disease characterized by motor and non-motor symptoms. Dementia is one of the most debilitating non-motor symptoms of Parkinson's disease. It affects intellectual and cognitive functioning at various levels. In this regard, this review acts as a comprehensive overview of history, pathology, symptomology, and treatments while suggesting future avenues for further research.

The review assesses disease pathology covering aspects of clinical manifestations, risk factors, morphological changes in the brain, and etiology. Dementia is correlated with increasing age, severity of underlying complications (Hoehn and Yahr Stage), and is more prevalent in males. On average, approximately, 1 in 4 patients with Parkinson's disease will develop dementia.

With better health care and technological advancements, life expectancy has been shown to be on a rise. Also, the baby boomers are reaching retirement age and are most at risk of neurological disorders. As a result, it is estimated that dementia will become as prevalent as affecting 81.1 million individuals

by the year 2040. Parkinson's disease by itself is debilitating and in conjunction with dementia completely hampers independent living. Thus, future avenues for further understanding and preventing dementia in Parkinson's disease are necessary.

### **HISTORY AND BACKGROUND**

Before the end of 19<sup>th</sup> century, dementia was associated with many mental illnesses that led to disturbances in one's ability to reason.<sup>1</sup> Diseases such as psychosis and syphilis were once considered as part of dementia.<sup>1</sup> Furthermore, schizophrenia was classified as dementia praecox (an early onset of dementia).<sup>2</sup> Seniors of age 65 and above, who showed abrupt symptoms of cognitive weakness were assumed to be diagnosed with senile dementia. Since very few individuals managed to reach seniority in the 19<sup>th</sup> century, dementia was thought to be a normal by-product of aging.<sup>3</sup> The first breakthrough in establishing a concrete classification of dementia arose after Robert Katzman suggested identical pathology of Alzheimer's disease (AD) and senile dementia in 1976.<sup>4</sup> Prior to this, both of these illnesses were considered independent of each other. Katzman's paper sparked the concern to characterize dementia's symptomology and etiology.

In recent years, the definition of dementia has been developed as "a syndrome of acquired persistent intellectual impairment that is part of a cognitive continuum regardless of etiology."<sup>5</sup> Evidently, many neurological disorders contribute to a patient's

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dementia. In particular, patients with Parkinson's disease (PD) are six times more likely to develop dementia than controls.<sup>6 7 8 9</sup> In light of this, the aim of this review is to describe dementia in patients already diagnosed with Parkinson's disease (PDD) and provide insight into future research avenues.

## **PATHOLOGY**

PD is clinically characterized as a progressive neurodegenerative disorder which causes a deterioration of substantia nigra, in turn, leading to a deficit of dopamine neurotransmitter.<sup>10 11</sup> As a result, characteristic PD symptoms like rigidity, tremor, bradykinesia, and postural instability become evident.<sup>10 11</sup> Despite being heavily researched upon, the etiology of dementia is still unclear. However, over the past few decades, the symptoms and signs of dementia have been quite well documented.

Dementia is primarily characterized with severe loss of mental activities, particularly in reaction to a progressive loss of cortical tissue perhaps directed by another mental disorder. To ascertain a diagnosis, the patient must exhibit cognitive dysfunction in at least three of the following mental activities: language, memory, visuospatial skills, emotion, and cognition (abstraction, calculation, judgment and executive function).<sup>5 6 12</sup> Due to altered brain structure and physiology as a result of mental disorders, memory and thought processes are impaired in a distinguishable manner. Usually, neurological diagnosis of dementia is ascertained as outlined in DSM-IV (Diagnostic and Statistical Manual of Mental Disorders – IV).<sup>13</sup>

An early symptom for dementia is usually mild forgetfulness which later advances into other cognitive abilities and memory to an extent where the patient is no longer capable of being independent.<sup>12 14</sup> Common symptoms amongst PDD patients include bradyphrenia, impaired planning, lack of organization of goal-directed activity, problems with set shifting, visuospatial deficits, fluctuation in attention and cognition, personality instability and learning and memory difficulties.<sup>15</sup> Because some of these symptoms may arise in the form of a resistance to a particular medication or other underlying illnesses, or as a response to therapeutic agents, the diagnosis of PDD can be challenging.<sup>16</sup> As PD develops with time, the symptoms for PDD accumulate and worsen. However, language and praxis remain stable up until the last stage of the illness.<sup>15</sup> Vulnerability to dementia increases with severity of rigidity and hypokinesia, suggesting the role of subcortical structures in the pathophysiology of dementia in PD.<sup>17</sup>

One of the most important risk factor in developing dementia is the presence of underlying neurological complications. AD is considered to be the most influential factor in developing dementia in elderly adults.<sup>12 18</sup> Independently, AD arises as a result of loss of neurons leading to brain atrophy (shrinkage), neurofibrillary tangles, and amyloid plaques.<sup>19</sup> These conditions subsequently give rise to cognitive (memory, concentration, orientation), functional (shopping, preparing meals, getting dressed), mood, and behavior dysfunctions.<sup>19</sup> As AD progresses through different stages, these symptoms gain severity and take control over the patient's life.

Neuropathological changes during the development of PD, itself, may lead to mild cognitive dysfunctions. As the disease progresses, cognitive impairments due to dementia are more consistent with AD.<sup>16</sup> Recent research suggests the risk for dementia increases by 20-40% in PD patients<sup>16</sup> and the prevalence of dementia may be six times higher in PD patients as compared to age-matched controls.<sup>6 7 8 9</sup> Age has also been suggested as a determining factor for developing PDD by various studies.<sup>9 15 16 20</sup> Furthermore, a retrospective cross-sectional study of 310 patients with PD provides evidence for the development of PDD independent of gender.<sup>15</sup> A H&Y stage greater than 2 has also been implicated as a predicting factor for PDD.<sup>9</sup>

When patients have been diagnosed with PDD, the health condition deteriorates with age. They may show symptoms of slower thinking than before, for additional time to respond. PDD is also progressive; the risk for acquiring the disease and the severity of its symptoms worsens with age and stage of PD.<sup>15 17 21 22</sup>

Depression, Levodopa-induced hallucinations, intake of tobacco, onset of PD at old age, and the stage of the disease assess the degree to which PD has progressed and impacted cognitive impairment.<sup>16 23 24</sup> Severe extrapyramidal symptoms in elderly adults are most vulnerable to developing PDD.<sup>25</sup>

The morphology of brain with PDD is similar in comparison to a brain with dementia with Lewy bodies (DLB).<sup>26 27</sup> Both of these disorders are believed to be phenotypes of a single disease spectrum only to be distinguished by clinical manifestations.<sup>27</sup> The pathological basis of PDD lies in the abnormal accumulation of  $\alpha$ -synuclein ( $\alpha$ Syn) embedded in Lewy bodies and dystrophic neurites of the central and autonomic nervous system.<sup>10 26</sup> PDD can be classified in an autopsy if severe lesions to substantia nigra are present.<sup>27</sup> Better ways of differentiating the disease pathologically is under study. New methods to distinguish between the illnesses are debated.

As people age, they slowly lose the ability to produce and supply their brain with significant dopamine cells at a rate required for normal functioning. The reduction of dopamine levels in brain leaves higher vulnerability for PD.<sup>21</sup> The abnormal accumulation of amyloid  $\beta$  protein in the brain and elevated levels of oxidative stress has been linked to AD.<sup>28</sup> Some studies suggest the presence of both circumstances in PD give rise to dementia.<sup>21</sup>

## TREATMENT OF PDD

Although an efficient medication for PDD is yet to be discovered, there are only palliative treatments which aid patients in coping with the illness. These treatments include appropriate diet and lifestyle, pharmacological treatments, and exercise and physical therapy.<sup>15</sup> Some studies suggest that exercise for these patients will lead to a better mental state, even though exercise and dementia are not directly related.<sup>16</sup> Pharmacological treatments include medication which may help suppress some symptoms (such as depression, or anxiety) accompanied by the disease for a short period, but it does not provide any cure for the symptoms themselves.

The difference in hormonal level between genders and its implication on the risks for PDD is currently under study.<sup>7 20 22 25 29 30</sup> Males have a lower level of estrogen than normal females. By using androgens as antagonists, males recompense for the differences.<sup>30</sup> Some studies conclude gender to be insignificant as a risk factor for PDD while others yet believe that incongruity in hormonal levels may make males more prone to PDD. Folstein, Folstein, and McHugh<sup>29</sup> reported post-menopause females possess a higher risk for developing the illness compared to normal females. Estrogen replacement therapy (ERT) has also been known to decrease the possibility for developing PDD in post-menopause females by increasing the levels of estrogen in the body.<sup>30</sup> Males produce similar levels of estrogen as postmenopausal females and thus, the issue of whether hormones play a part in gender risk factors for developing PDD is debatable.<sup>7 20 22 25</sup> Further research regarding the relationship between hormones and PDD will give a better understanding of these responses.

Maintaining a normal lifestyle with PD can be very challenging. In addition to dementia, it can be very difficult to perform tasks individually. A person diagnosed with both diseases needs additional care and assistance. Due to their severity, patients lose their independence and often rely completely on caregivers.

## FURTHER DISCUSSION

With exclusion to cases of patients with arteriosclerosis, and atypical Parkinsonism the average prevalence of dementia in PD was found to be 24.5%.<sup>31</sup> But this estimate is based on diagnosis of dementia using methods similar to MMSE and it may include a number of misdiagnoses.<sup>31</sup> A majority of these research failed to explain the criteria for assessment and method of diagnosis in detail.<sup>31</sup> As a result, prevalence rates vary quite dramatically (20%-81%).<sup>31</sup> An accurate range of prevalence, in general public, can be anywhere from 15% to 20%.<sup>31</sup> This estimate may increase by 5% for patients above the age of 65. Providing a background of the patient's health condition can also be useful to narrow variables. Furthermore, the differences in numbers can be narrowed by collecting data of patients controlling for medical history.

The patient's age plays a significant factor in the percentage of prevalence of PDD. The cognitive disability worsens with age, leading to higher prevalence of developing dementia and other disorders. This is why it is necessary to group patients with respect to their age, in order to assess them differently, so symptoms of normal aging can be prevented from being misdiagnosed as dementia.

Cholinergic deficiency is a symptom of PDD, which is also present in other mental disorders, such as AD. One study used rivastigmine (an anticholinergic drug) to examine the response of PDD and its motor symptoms.<sup>32</sup> The results concluded with no signs of significant motor dysfunction. However, the drug did not cure the disease but, only reduced the symptoms for a certain period. Future studies can assess the efficacy of anticholinergic drugs in treating dementia; first, in animal models and then, in humans.

As knowledge of dementia and its disorders grows, similarities among the disorders continue to grow. Recent finding of amyloid- $\beta$  in AD and Lewy bodies in PDD and DLB grow in similarity, suggesting synergistic roles.<sup>32</sup> The neuropathology of PDD and DLB are almost identical.<sup>26</sup> The pathogenesis of such neuropathological disorders may be genetic.<sup>10 33</sup> If the cause of a particular disease leading to dementia is prevented, then dementia itself is avoidable. Future studies need to be aimed towards identifying mechanisms underlying the development of dementia and finding an appropriate method to prevent them from developing.

## CONCLUSION

Analysis of data obtained from relevant studies creates noise due to lack of consensus of methods for diagnosing dementia. Thereby, prevalence in some studies rises to a significantly high value while in others it remains relatively low.<sup>34</sup> To get a better grasp at the prevalence of dementia in PD patients, future studies need to develop a clear, explicit method for diagnosing dementia. In particular, researchers should include the procedure followed in differentiating dementia from other closely associated illnesses such as DLB and AD in order to prevent misdiagnosis. Further research should address the issue of discerning PD's and PDD's etiology perhaps through genetic mapping of correlated genes.

Nevertheless, the prevalence of PDD has been reported to be 24.5% on average taking into account misdiagnoses.<sup>31</sup> As time progresses, the prevalence will only increase. A prevalence study of global population predicts that 81.1 million people will be afflicted by dementia by 2040. This, in turn, refers to seven new cases every second.<sup>35</sup> With advancing in technology, countries across the globe see a tremendous rise in their life expectancy at birth and the baby boomer generations are reaching their retirement age shifting the population dynamics. Thus, due to significant correlations with age, PDD prevalence is expected to rise dramatically. This would entail massive costs on the state and the individuals themselves. In turn, extensive planning for an uncertain future must be done from now.

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