Review Article

Challenges in Treating Depression and Dementia in Parkinsonism

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Abstract

The changes in brain caused by Parkinson's disease begin in a region which plays an important role in movement. As changes in brain gradually spread to other parts of brain, they often begin to affect mental functions, including memory [depression] and the ability to pay attention, make sound judgments, plan the steps needed to complete a task and depression. About 50 to 80 percent of those with Parkinson's disease eventually experience Parkinson's disease dementia as per estimation. The average time from onset of Parkinson's to developing dementia is about 10 years. Neuropsychiatric symptoms such as depression and anxiety are common but often goes undiagnosed and untreated in majority of patients. This oversight can lead to overall worsening outcomes in the course of the disease leading to therapeutic failure.

Keywords: Challenges; Depression; Dementia; Parkinsonism

Introduction

Central nervous system [CNS] is a part of the nervous system that integrates the information that it receives from, and coordinates the activity of, all parts of the bodies of bilaterian animals that is, all multicellular animals except radially symmetric animals such as sponges and jellyfish. CNS contains majority of the nervous system and consists of the brain and the spinal cord.

Along with the peripheral nervous system, it has a fundamental role in the control of behavior. There are many central nervous system diseases, including infections of the central nervous system such as encephalitis and poliomyelitis, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease etc [1].

Depression is an affective disorder, defined as disorders of mood rather than disturbances of thought or cognition; it ranges from a very mild condition, bordering on normality, to severe psychotic depression accompanied by hallucinations and delusions [2].

Dementia is a serious loss of global cognitive ability in a previously unimpaired person, beyond what might be expected from normal aging. It may be static, the result of a unique global brain injury, or progressive, resulting in long-term decline due to damage or disease in the body. Although dementia is far more common in the geriatric population, it can occur before the age of 65, in which case it is termed "early onset dementia". A recent survey done by Harvard University School of Public Health and the Alzheimer's Europe consortium revealed that the second leading health concern [after cancer] among adults is Dementia [3,4].

Spirulina is a microscopic and filamentous cyanobacterium that derives its name from the spiral or helical nature of its filaments. It has a long history of use as food and it has been reported that it has been used during the Aztec civilization. Spirulina refers to the dried biomass of Arthrospira platensis, an oxygenic photosynthetic bacterium found worldwide in fresh and marine waters. This alga represents an important staple diet in humans and has been used as a source of protein and vitamin supplement in humans without any

significant side-effects. Apart from the high [up to 70%] content of protein, it also contains vitamins, especially B12 and provitamin A (β-carotenes), and minerals, especially iron. It is also rich in phenolic acids, tocopherols and γ-linolenic acid. Spirulina lacks cellulose cell walls and therefore it can be easily digested [5].

Dementia in Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease. The typical clinical motor syndrome of PD is associated with neurodegeneration and neuronal loss in the substantia nigra and the presence of inclusions that contain the protein α-synuclein (α-syn) known as Lewy bodies.

However, although the clinical phenotype is predominated by motor features, it is now well established that a variety of non-motor features belong to the disease. In particular with regard to cognition, the prevalence of Parkinson's disease dementia (PDD) is roughly estimated to be around 30%, while PDD will occur in over 80% of patients after 20 years of disease [6].

Spirulina is a microalga that can be consumed by humans and animals. It is usually taken by humans as a nutritional supplement and is made primarily from two species of cyanobacteria: Arthrospira platensis and Arthrospira maxima.

Arthrospira is cultivated worldwide; used as a dietary supplement as well as a whole food; and is available in tablet, flake and powder form. It is also used as a feed supplement in the aquaculture, aquarium and poultry industries.

Depression

Mental depression is a chronic illness that affects a person's mood, thoughts and physical and behaviour and may range from very mild condition, bordering on normality to severe depression. Depression is an affective disorder, defined as disorders of mood rather than disturbances of thought or cognition; it may range from a very mild condition, bordering on normality, to severe psychotic depression accompanied by hallucinations and delusions. The primary clinical manifestations of major depression are significant depression of mood and impairment of function. Some features of depressive disorder overlap those of the anxiety disorders, including panicagoraphobia syndrome, severe phobias, generalized anxiety disorder, social anxiety disorder, posttraumatic stress disorder, parkinsonism and obsessive-compulsive disorder.

Along with the classical theory of decrease in the neurotransmitter levels in the brain leading to the pathogenesis of clinical depression, recent studies have also shown the involvement of oxidative stress in the phenomenon [7,8]. Recent evidence suggests that depression may be associated with neurodegeneration and reduced neurogenesis in the hippocampus [8, 9]. Despite the development of new molecules for pharmacotherapy of depression, it is unfortunate that this disorder goes undiagnosed and untreated in many patients. Although the currently prescribed molecules provide some improvement in the clinical condition of patients, it is at a cost of having to bear the burden of their adverse effects [9-13].

Mood disorders are one of the most common mental illnesses, with a lifetime risk of 10% in general population. Prevalence of depression alone in general population is estimated to be around 5% with suicide being one of the most common outcomes. Commonly used Antidepressants often cause adverse effects, and difficulty in tolerating these drugs is the most common reason for discontinuing an effective medication, for example the side -effects of Selective Serotonin Reuptake Inhibitor (SSRIs) include: nausea, diarrhea, agitation, headaches. Sexual side-effects are also common with SSRI's. The Food and Drug Administration requires Black Box warnings on all SSRIs, which state that they double suicidal rates (from 2 in 1,000 to 4 in 1,000) in children and adolescents [14-16].

Dementia

Dementia [taken from Latin, originally meaning "madness", from de- "without" + ment, the root of mens "mind"] is a serious loss of global cognitive ability in a previously unimpaired person, beyond what might be expected from normal aging. It may be static, the result of a unique global brain injury, or progressive, resulting in long-term decline due to damage or disease in the body. Although dementia is far more common in the geriatric population (about 5% of those over 65 are said to be involved), it can occur before the age of 65, in which case it is termed "early onset dementia" [17,18].

Dementia is not merely a problem of memory. It reduces the ability to learn, reason, retain or recall past experience and there is also loss of patterns of thoughts, feelings and activities. Additional mental and behavioral problems often affect people who have dementia, and may influence quality of life, caregivers, and the need for institutionalization. As dementia worsens individuals may neglect themselves and may become disinhibited and may become incontinent. Behaviour may be disorganized, restless or inappropriate. Some people become restless or wander about by day and

sometimes at night. When people with dementia are put in circumstances beyond their abilities, there may be a sudden change to tears or anger (a "catastrophic reaction"). A common symptom of dementia is for dementia sufferers to deny that relatives, even relatives in their immediate family, are their own relatives [19].

There are many other medical and neurological condition in which dementia only occurs late in the illness. For example, a proportion of patients with Parkinson's disease develop dementia, though widely varying figures are quoted for this proportion. (citation needed) When dementia occurs in Parkinson's disease, the underlying cause may be dementia with Lewy bodies or Alzheimer's disease, or both [20].

Dementia in parkinson's disease

PDD can exacerbate the disabilities caused by motor symptoms in PD, and the presence of cognitive impairment or dementia in patients with PD is associated with a loss of independence, a lower quality of life, and a shorter survival time than PD patients without dementia. The course of decline in PDD is progressive over time with periods of rapid worsening [21,22].

Age is the most prominent risk factor for PDD independently from the age of PD onset [23-25]. PDD also correlates with the severity of motor disability, and the aging factor may be additive to the severity of the motor dysfunction [24,26]. Other factors such as visual hallucinations, and the PD phenotype [e.g., prominent axial rigidity and bradykinesia as opposed to tremor], confer risk for the development of PDD [22,27,28]. Mild cognitive impairment [MCI] has also been associated with an increased risk of developing PDD [24,29].

The most common cognitive deficits in PDD include those in attention, executive functioning, and visuospatial processing. Attentional performance may fluctuate, leading to a variable level of function and a major impact upon activities of daily living [30].

In PDD, short-term memory is impaired, both for initial learning and immediate recall. Traditionally, amnesic deficits in PD have been considered to be mainly of retrieval, rather than encoding and storage. However, memory loss in PDD has been associated more with a frontally mediated retrieval deficit thus again a deficit in executive functioning, than to an intrinsic defect [22].

Neuropsychiatric symptoms, including hallucinations and delusions, depression, anxiety, and apathy, are well reported in PD [32]. Dysphoria and depression occur with approximately the same frequency in PDD and AD (40–58%) patients [31,32].

Etiopathogenesis of PDD

Neuropathology

Several lines of evidence from studies using α-syn immunohistochemistry in postmortem brains implicate cortical α-syn pathology as the strongest correlate of dementia in PDD demonstrating higher levels of cortical α-syn pathology than do cases of PD without dementia [33-38]. The Braak hypothesis states that Lewy body pathology progresses in a sequence from the pons and brainstem via the forebrain and limbic system to the neocortex. These stages might progress in parallel with cognitive decline [39]. Indeed, many studies have found that the level of global cortical and limbic α-syn pathology or the levels of α-syn pathology in specific brain regions, such as the parahippocampal or anterior cingulate gyrus, can discriminate between PD without dementia and PDD and are the strongest correlate to PDD when compared with other possible factors such as genetic [35,36,40]. Neurochemically, cholinergic deficits occur in patients with PDD, attributed to neuronal loss in basal forebrain cholinergic nuclei, and are associated with the transition of α-syn pathology into limbic and neocortical regions [41-45].

However, despite the crucial role of a-syn in PDD, the hallmark pathologies of AD, that is, mainly the levels of Aβ plaques and less the tau neurofibrillary tangles [NFTs], have been found to inversely correlate with the cognitive status in a subset of PDD patients [33,40,46]. Cortical α-syn, tau, and Aβ pathologies together have been shown to more accurately predict dementia than any single marker alone [34-36,47,48]. Thus, AD pathology [and in particular Aβ plaque pathology] may have an important role in the pathogenesis of PDD and a possible synergy with α-syn pathology [49,50]. Indeed, clinically, patients with PDD and AD pathology have shorter disease duration, older age at onset of motor symptoms, and shortened survival times compared to PDD patients without concomitant AD pathology [51-53]. In summary, the progression of Lewy body and neurite pathology from subcortical areas into limbic and cortical structures seems to be the major determinant of the development of dementia in most individuals with PDD; however, other pathologies such as that of AD may be implicated in the underlying neuropathology of PDD [36-53].

Genetics

Genetic factors may also play an important role in the development of cognitive impairment in PDD. Some monogenic forms of PD have been associated with dementia such as those resulting from pathogenic mutations of the α-synuclein gene (SNCA), whereas others such as mutations in leucine-rich repeat kinase 2

(LRRK2) or the parkin gene do not seem to be as strongly linked to PDD and DLB. Heterozygous mutations in the b- glucocerebrosidase (GBA) gene are associated with an increased risk of PD or DLB, and GBA-linked [54,55].

PD is associated with a higher risk and an earlier age of onset of dementia, as well as higher levels of cortical and limbic α-syn pathology than noncarrier patients with PD. Moreover, polymorphisms of DYRK1A, which encodes a kinase that phosphorylates proteins such as α-synuclein and amyloid precursor protein, have been associated with PDD and DLB [56-61].

The APOE ε4 allele has been established as a risk factor for AD and may also confer an increased risk of dementia in PD, but further studies are needed [62-64]. The H1/H1 haplotype of the MAPT gene, encoding for protein tau, has been associated with an increased risk of some tauopathies, for example, progressive supranuclear palsy [65]. Interestingly, this variation in MAPT has been associated with PD as well; however, the risk for PDD as associated with the H1/H1 haplotype in PD has been less well studied [59,60,64,65]. Other possible associations such as the BDNF [Met/Met] homozygote genotype need further confi rmation [66].

Conclusion

Even though many drugs are available to treat parkinsonism, but it is quite challenging to treat depression and dementia in parkinsonism. However judicious use of pharmacological agents in combination with dose titration may offer beneficial results in parkinsonism with depression and dementia.

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