Yokukansan Ameliorates Psychiatric Problems in Parkinson’s Disease

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Parkinson’s disease (PD) is a neurodegenerative disorder caused by the loss of dopaminergic neurons. The major clinical features of PD include motor disabilities, such as rigidity, bradykinesia, impaired balance, and resting tremors, as well as non-motor symptoms, such as cognitive decline, psychosis, and autonomic dysfunction. Neuropsychiatric problems seriously affect the activities of daily living and quality of life of PD patients and are caused by a dysfunction not only in dopamine, but also other neurotransmitters, including noradrenaline, serotonin, acetylcholine, and glutamine. Choline esterase inhibitors may improve cognition and visual hallucinations, but not other psychotic symptoms. Although neuroleptics may improve psychiatric problems, these drugs have typically been associated with the deterioration of Parkinsonism. Therefore, the management of hallucinations is an intractable issue for the treatment of PD. Yokukansan, which contains the water extract of a mixture of seven crude drugs, may effectively improve cognition and ameliorate psychiatric problems, such as hallucinations, apathy, and anxiety. We here reviewed yokukansan therapy for and psychiatric problems associated with PD.

Key words: yokukansan, Parkinson’s disease, psychiatric problems, dementia

Introduction

Parkinson disease (PD) is a slowly progressive neurodegenerative disease with typical features such as resting tremors, cogwheel rigidity, bradykinesia, and postural instability. The pathological hallmarks of PD are the marked loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), which depletes dopamine in the striatum, and the presence of intracytoplasmic inclusions known as Lewy bodies in the remaining cells. The pathological changes associated with PD have been observed not only in the SNc, but also in the locus coeruleus (LC), pedunculopontine nucleus, raphe nucleus, dorsal motor nucleus of the vagal nerve, olfactory bulb, parasympathetic as well as sympathetic post-ganglionic neurons, Mynert nucleus, and the cerebral cortex. Widespread neuropathology in the brainstem and cortical regions is responsible for the various motor and non-motor symptoms of PD.

The management of motor dysfunctions in PD is centered on replacement therapy using L-Dopa and dopamine agonists, with the aim of supplementing the reduced levels of dopamine in the substantia nigra and striate body. However, long-term L-Dopa therapy leads to several disabling problems, such as L-Dopa-related motor complications and psychiatric symptoms. Dopamine agonists may also induce or exacerbate hallucinations and sleep disturbance. A previous study reported that 10 to 40% of patients administered antiparkinsonian agents developed hallucinations. Psychiatric symptoms including dementia, depression, anxiety, apathy, hallucinations, and sleep disorders frequently occur and may become debilitating. Once patients have developed psychiatric symptoms, they are more likely to recur and can continue for an extended period. Therefore, general physicians and neurologists should give careful attention to the treatment...
of psychiatric as well as motor symptoms. Although psychiatric symptoms in PD patients can be difficult to treat, several studies have suggested that yokukansan can effectively ameliorate the severity of problems such as hallucinations, apathy and anxiety. We herein reviewed yokukansan therapy for and psychiatric problems associated with PD.

Dementia in Parkinson’s disease

Cognitive dysfunction is one of the most common features of advanced PD. One prospective study reported that the prevalence of dementia was 26% at baseline, 52% at 4 years, and 78% at 8 years, indicating an association between the increasing prevalence of dementia and disease duration. However, cognitive dysfunction, such as dysexecutive function and visuospatial deficits, can occur in the early stages of PD. Furthermore, recent findings have suggested that approximately 40% of PD patients without dementia have mild cognitive impairments. Since cognitive impairments are typically associated with psychiatric symptoms, the prevention and treatment of these symptoms is important for the management of PD. In an autopsy study, midfrontal choline acetyltransferase activity was markedly lower in diseases with Lewy pathology than in controls and Alzheimer disease. Choline esterase inhibitors, such as donepezil and rivastigmine, improve cognitive functions, without serious side effects, in Parkinson’s disease with or without dementia, and dementia with Lewy body. These findings indicate that cholinergic dysfunction plays important roles in the pathogenesis of dementia due to PD and dementia with Lewy bodies.

Hallucinations in Parkinson’s disease

Although the development of hallucinations in PD patients is commonly associated with dementia, several patients without dementia have also been reported to have hallucinations. Hallucinations include the feeling of an abnormal ‘presence’ (a vague and erroneous perception that another person or threat is present) or ‘passage’ hallucinations (transient undefined hallucinations that pass through the periphery of the visual field). Visual hallucinations exist along a spectrum including simple images as well as more complex images of people, animals, or insects. Whereas visual hallucinations are the most frequent among patients with PD, hallucinations in other modalities, such as auditory, olfactory, and tactile hallucinations, have also been reported. Hallucinations are one of most troublesome problems not for only PD patients themselves, but also caregivers, and antiparkinsonian drugs have been suggested to induce and aggravate hallucinations.

The treatment of hallucinations in patients with PD includes reductions in the dose of antiparkinsonian medication and/or the administration of neuroleptics, also known as antipsychotics. Neuroleptics and reduced doses of antiparkinsonian agents have both been reported to deteriorate Parkinsonism. Therefore, the management of hallucinations is an intractable issue for the treatment of PD. Choline esterase inhibitors have been shown to ameliorate the visual hallucinations associated with PD; therefore, these hallucinations may be related to a central cholinergic dysfunction. Manganelli et al recently revealed a significant reduction in short-latency afferent inhibition in PD patients with visual hallucinations, which implied abnormalities in inhibitory cholinergic circuits in the human cerebral motor cortex. Modulating the cholinergic pathway is important for the treatment of visual hallucinations and dementia in PD patients. However, choline esterase inhibitors may not have an effect on other psychiatric symptoms.

Depression, anxiety, and apathy in Parkinson’s Disease

Depression, anxiety, and apathy are highly prevalent neuropsychiatric symptoms in PD patients. Depression is one of the most common problems in PD, with a prevalence of 30–40%. The clinical features of depression include psychomotor retardation, memory impairment, pessimism, irrationality, and suicidal ideation without suicidal behavior, and differ from those of major depression. PD patients with depression typically have less guilt and self-reproach, but are more irritable, sad, and concerned about their health. Mood fluctuations may be associated with motor fluctuations.
motivation in goal-directed behaviors, indifference, and a flattened affect. \textsuperscript{21) 22) This symptom may develop in the early untreated clinical motor stages, has been detected in almost one third of patients, and is independent of depression. A recent study found that 23\% of PD patients without dementia had a combination of depression and apathy, while 28\% had apathy without depression. \textsuperscript{23) 24) This finding indicated that apathy was not the same as depression and/or cognitive decline.

The prevalence of anxiety has been reported to be between 25 and 43\% with a life-time prevalence of 49\%. This symptom has been attributed to dysfunctions in a combination of dopaminergic, serotonergic, and cholinergic pathways in the limbic system. \textsuperscript{3) 11} C-RTI-32–positron emission tomography (PET), which can evaluate the functions of dopamine and the norepinephrine pathway, revealed that a dysfunction in the catecholaminergic pathway in the LC and limbic systems could play a role in the development of depression in PD patients. \textsuperscript{25) Dopaminergic therapy, tricyclic antidepressants, and selective serotonin reuptake inhibitors have been shown to affect the depression, anxiety, and apathy associated with PD.

Yokukansan therapy in Parkinson's Disease

Yokukansan, a traditional Japanese medicine (Kampo medicine), is approved by the Ministry of Health, Labor and Welfare (MHLW) with an official drug price listing, and is in widespread use for the treatment of insomnia, pediatric irritability, and behavioral and psychological symptoms associated with PD. However, its effect on neuropsychiatric symptoms in PD has not been extensively studied. Dr. Hatano and colleagues conducted a randomized controlled trial to evaluate the efficacy of Yokukansan in patients with PD (Hatano et al., 2014).

**Figure 1** Changes in NPI Total Scores and NPI Subscale Scores in Patients with Parkinson’s Disease

(A) NPI Total Scores; Numbers in parentheses indicate the number of subjects with neuropsychiatric symptoms. (B) NPI Subscale Scores; Numbers on the horizontal axis indicate the number of subjects. *** $p < .005$, ** $p < .01$, * $p < .05$, signed rank-sum test. NPI = Neuropsychiatric Inventory. These results indicate that yokukansan ameliorated psychosis in patients with Parkinson’s disease. Reprinted from Hatano et al.\textsuperscript{10} with permission from Springer.

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with dementia. This medicine contains the water extract of the following mixture of seven crude drugs included in the Japanese Pharmacopoeia: 4 g of Atractylodis Lanceae Rhizoma, 4 g of Poria, 3 g of Cnidii Rhizoma, 3 g of Uncariae Uncis Cum Ramulus, 3 g of Angelicae Radix, 2 g of Bupleuri Radix, and 1.5 g of Glycyrrhizae Radix. Yokukansan is used to treat neuropsychiatric problems, such as insomnia, irritability, screaming attacks, dementia, and the behavioral and psychological signs and symptoms of dementia (BPSD). Several studies revealed the effectiveness and safety of yokukansan in the treatment of BPSD with Alzheimer disease and dementia with Lewy bodies. Iwasaki et al conducted a randomized, observer-blind, controlled trial to examine the efficacy and safety of yokukansan medication as a therapy for 52 patients with mild to severe Alzheimer disease. Patients were assessed using the neuropsychiatric inventory (NPI) and the yokukansan treatment significantly improved hallucinations, agitation/aggression, irritability/lability, and aberrant motor activity. Mizukami et al investigated the efficacy of yokukansan medication in patients with Alzheimer disease or dementia with Lewy bodies (DLB), and found that yokukansan affected delusions, hallucinations, agitation/aggression, depression, anxiety, and irritability/lability without severe adverse events. Yokukansan also effectively reduced hallucinations in PD patients and was used to treat psychiatric symptoms in patients with PD or PD with dementia. We recently revealed the efficacy of yokukansan in the treatment of PD patients without dementia. We enrolled twenty-five patients with PD (M: F = 14:11; average age 72 years) without explicit dementia and administered yokukansan (7.5 g/day) for 12 weeks. The median NPI total score significantly decreased from 12 points at baseline to 4.0 points after 12 weeks (p = 0.00003). Within each NPI subscale, significant improvements were observed in hallucinations, anxiety, and apathy. These symptoms were slightly worse after the completion of the yokukansan treatment. Delusions, agitation, depression, euphoria, disinhibition, and aberrant motor activity improved slightly, whereas irritability remains unchanged. The median NPI subtotal scores for positive symptoms (delusions, hallucinations, and irritability) significantly decreased (p = 0.01666) while those for negative symptoms (anxiety and apathy) significantly decreased (p = 0.00391). No significant changes were observed in the UPDRS-III or Hoehn and Yahr scale. Radix glycyrrhizae has been shown to induce hypokalemia; therefore, serum potassium concentra-

**Figure 2** Changes in NPI Subtotal Scores in Patients with Parkinson’s Disease
Effects of yokukansan on PD-specific psychotic problems. The median NPI subtotal scores for positive symptoms (delusions, hallucinations, and irritability) significantly decreased (A) while those for negative symptoms (anxiety and apathy) significantly decreased (B). Numbers in parentheses indicate the number of subjects with neuropsychiatric symptoms. ***p < .005, **p < .01, *p < .05, signed rank-sum test. Abbreviation: NPI = Neuropsychiatric Inventory. Reprinted from Hatano et al with permission from Springer.
tions and edema were evaluated at weeks 0, 4, 8 and 12, and 16 (4 weeks after the completion of its administration). However, sK decreased slightly from 4.26 ± 0.30 mEq/L to 4.08 ± 0.33 mEq/L. Only two patients had hypokalemia lower than 3.5 mEq/L without any corresponding symptoms. We concluded that yokukansan improved neuropsychiatric symptoms in PD patients without dementia, including hallucinations, anxiety, and apathy, without severe adverse events or the worsening of Parkinsonism. Previous studies including ours revealed that yokukansan alleviated BPSD in PD, especially hallucinations, without the deterioration of Parkinsonism. Based on the treatment algorithm for PD, psychiatric symptoms should be controlled by antiparkinsonian agent dose reductions and/or the administration of atypical antipsychotic agents, such as quetiapine and clozapine. However, dose reductions in antiparkinsonian agents negatively impacted on the activities of daily living. Atypical antipsychotic agents have been shown to deteriorate Parkinsonism and may also increase the mortality rate. Furthermore, high dropout rates due to the severe adverse events induced by atypical neuroleptics have been historically reported in studies for the treatment of PD psychosis. On the other hand, yokukansan did not cause severe adverse effects or exacerbation of extrapyramidal symptoms. In our study, serum potassium concentrations significantly decreased; however, the mean value remained within normal ranges.

It currently remains unclear how yokukansan affects psychiatric problems in patients with PD. Several findings supported an association between the psychotic symptoms of PD and imbalance in neurotransmitters, including dopaminergic, cholinergic, serotonergic, and glutamatergic systems. Therefore, the modulation of those neurotransmissions may be important for the treatment of PD psychosis. Yokukansan was previously found to exhibit partial agonist activity against the 5-HT_{1A} receptor in in vitro binding studies; therefore, the alleviation of neuropsychiatric symptoms in PD patients may be due to modulations of the serotonin nervous system. This efficacy has mainly been attributed to geissoschizine methyl ether, which is a component of Uncaria hook, one of the crude drugs in yokukansan. Yokukansan has also been assumed to affect the 5-HT_{2A} receptor based on animal model analyses, which revealed that yokukansan induced the down-regulation of 5-HT_{2A} receptors in the prefrontal cortex and alleviated the head-shaking behavior induced by a 5-HT_{2A} agonist. The 5-HT_{2A}-receptor is known to play a role in the pathomechanisms responsible for visual hallucinations in patients with PD. Therefore, yokukansan may have down-regulatory effects on the 5-HT_{2A} receptor and may, in part, alleviate the hallucinations associated with PD. Mizoguchi et al previously indicated that yokukansan may improve serotonergic and dopaminergic transmissions in the prefrontal cortex in aged animal models. These findings suggest that yokukansan can have an impact on neuropsychiatric problems without deteriorating extrapyramidal symptoms. Yokukansan may also affect the glutamatergic nervous system. Glutamate is the principal excitatory neurotransmitter in the brain and regulates memory and other higher brain functions. Yokukansan has been shown to ameliorate increases in extracellular glutamate concentrations by inhibiting the release of glutamate, and also activated the glutamate-transporter. It has also been found to have a protective effect against glutamate–induced neuronal death. Clinical investigations revealed that yokukansan successfully ameliorate hallucinations in PD patients. Previous studies have suggested an association between visual hallucinations and cholinergic dysfunction; therefore, yokukansan may influence cholinergic neurons. Uchida et al demonstrated using a rat model of early phase Alzheimer disease that yokukansan may improve the release of acetylcholine by modulating dynamin 1. These findings suggest that yokukansan could modulate several neurotransmitters, including serotonin, glutamate, and acetylcholine.

Conclusions

Cognitive decline and psychiatric problems are highly prevalent in PD patients and impact on their QOL. Therefore, physicians and neurologists should pay careful attention to the management of these symptoms. Since several neurotransmitters, including dopamine, serotonin, acetylcholine, and noradrenalin, have been linked to cognitive decline and psychosis, these symptoms may not respond well to
treatment. Yokukansan contains several agents that have been shown to modulate neurotransmitters. Our and several studies demonstrated that yokukansan alleviated neuropsychiatric symptoms in PD patients, and was effective against both positive and negative symptoms, including hallucinations, depression, anxiety, and apathy. Furthermore, it did not induce any serious adverse events or exacerbate extrapyramidal symptoms. Therefore, yokukansan may represent a useful treatment for the neuropsychiatric symptoms associated with PD.

References


