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Risks and Triggers of Psychosis in Parkinson Disease

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Abstract

Psychosis is a common non-motor complication in Parkinson disease, and affects the quality of life of patients and their care-givers. This psychosis is caused by intrinsic (pathological and genetic) and extrinsic factors. Pathological factors include the severity of Lewy body pathology, degeneration of cholinergic neurons and overstimulation of serotonin receptors. Genetic factors include apolipoprotein ε4, cholecystokinin genotyping, and glucocerebrosidase mutations. Extrinsic factors that trigger psychosis include systemic inflammation and medication of risky drugs. To prevent such psychosis, it is important to examine systemic infection, cease high-risk drugs, and then consider prescription of anti-psychotic drugs. This review is to discuss pathogenesis and therapeutic strategy of psychosis in Parkinson disease.

Keywords: C-reactive protein; Cognition; Psychosis; Hallucination; Delusion; Lewy body

Abbreviations: PD: Parkinson's Disease; REM: Rapid Eye Movement; GBA: Glucocerebrosidase; 5-HT: 5-Hydroxytryptamine

Introduction

Parkinson disease (PD) is characterized by steadily progressive motor disturbance such as bradykinesia, muscular rigidity, and tremor. Pathologically, it is characterized by death of nigral dopaminergic neurons and the presence of Lewy bodies. Majority of motor symptoms and signs are caused by striatal dopamine deficiency due to nigral dopaminergic neuronal loss, and relieved by dopamine replacement therapy. In addition to motor symptoms and signs, cognitive decline [1], anxiety [2], depression, sleep disturbance, apathy [3], psychosis, orthostatic hypotension and sweating attacks [4] are recognized as non-motor problems. Among them, psychosis reduces the quality of life of patients and their care-givers [5]. Importantly, medications against psychosis can often worsen motor symptoms and signs. Serious psychosis often occurs in advanced stages of PD and requires use of dopaminergic antagonists. Dopamine antagonists exacerbate extrapyramidal signs, and as a result, elevate the risk of aspiration pneumonia by swallowing disturbance or bone fractures because of falling, which can increase psychosis [6]. Therefore, psychosis is a key problem in advanced stages of PD, and it is important to develop therapeutic strategies for psychosis in PD.

Prevalence

The prevalence of psychosis is reported as only 3% in initial untreated patients with PD [7]. However, with long-term pharmacological treatment, the prevalence of hallucinations is elevated to 40%-50% [8-10]. Simple visual hallucination with retained insight is common, occurring in approximately 50%. It can occur even in early stages of the disease [11] and often disappears spontaneously without any antipsychotic medications. However, hallucinations can sustain in some cases, and reduce the quality of life of patients especially without insight. Further, delusions usually sustain and require medical treatment. Comparing with hallucinations, delusions are rare, with a prevalence of approximately 7% [12,13]. The contents of the delusion are variable, delusions of poisoning, jealousy or infidelity; although rare but impressive is Capgras syndrome, whereby a patient believes that a familial person will be replaced by an identical imposter [14].

Sleep Disturbances and Hallucinations

Sleep disturbance is one of the most common non-motor symptoms of PD, and includes insomnia, fragmented sleep, daily excessive sleepiness, REM (rapid eye movement) sleep behavior disturbance, and sudden onset sleep. Daytime sleepiness is more common in patients taking dopamine agonists, although sleepiness is observed in patients without dopamine replacement therapy [15]. Sleepiness is thought to be caused by degeneration of neurons of the arousal system, locus coeruleus (noradrenergic), pendunculopontine nucleus and the basal forebrain (cholinergic), the raphe nucleus (serotoninergic), and the lateral hypothalamus (hypocretinergic) [15].

Sleep disturbances are associated with visual hallucinations [15,16]. However, pharmacological interventions against daytime sleepiness have low efficacy [17] and it remains unclear whether interventions against sleep disturbances also improve psychosis.

Cognition and Hallucinations

Cognitive function is often disturbed, especially in advanced stages of PD, and is characterized by reduced attention or difficulty in concentrating. Psychosis is associated with cognitive functional decline in language, memory, attention, executive function and visuospatial ability [18]. Although cognitive function is improved by inhibitors of brain cholinesterase, it is uncertain whether psychosis including hallucinations is improved or prevented [19].

Genetic Factors in Psychosis

Previous studies of genetic factors in psychosis have mainly focused on dopamine transporters and receptors, apolipoprotein E and cholecystokinin genotyping [20]. Monsell et al. investigated the association of apolipoprotein genotypes with development of clinical phenotype in 423 patients with PD, and found that apolipoprotein ε4 carriers were prone to developing dementia and that the risk of hallucinations was

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significantly higher (odds ratio of 5.29) [21]. By contrast, ε4 was not associated with motor function in PD in that study. An association of apolipoprotein ε4 with psychosis was also reported in non-demented PD patients [22], although this remains controversial [23].

Cholecystokinin is a gastrointestinal neuropeptide, and is found in dopaminergic neurons and regulates dopamine release. Polymorphisms in cholecystokinin were reported to be associated with development of psychosis [24,25]. Genetic mutations in glucocerebrosidase (GBA) are responsible for Gaucher disease and also represent a genetic risk factor for sporadic PD. Functional prognosis of PD patients with GBA mutations is poorer than of those without mutations. We also recently demonstrated that psychosis is more frequent and develops earlier in PD patients with GBA mutations than those without [26].

Pathological Background

Williams and colleagues investigated the pathological findings and clinical records of 787 patients presenting Parkinsonism, including PD and other symptomatic Parkinsonism and reported that vivid visual hallucinations were strongly associated with Lewy body pathology [10]. The concentration of β amyloid peptide in the cerebrospinal fluid is also associated with hallucinations [27]. As described above, there are several reports of associations of hallucinations with apolipoprotein ε4 that is a strong genetic risk for Alzheimer disease. Overall, these results suggest that Alzheimer pathology, including senile plaques and neurofibrillary tangles, is also among the pathological background of PD psychosis.

Acetylcholine and Hallucinations

Hallucinations can be a clinical hallmark of Lewy body pathology [10] and acetylcholine alterations are a biochemical feature of dementia with Lewy bodies [28,29]. As described, acetylcholine is a neurotransmitter involved in the arousal system and disruption of the arousal system is associated with psychosis. There are some reports of improvement in psychotic symptoms with use of donepezil and rivastigmine [30,31]. However, further studies examining the effect of cholinesterase inhibitors against psychotic symptoms in PD are required.

Serotonin and Hallucinations

Pathological studies of PD patients show degeneration of serotonergic raphe nuclei as well as nigral dopaminergic neurons, and as a result, serotonin 5-HT2A receptors are upregulated – upregulation of 5-HT2A receptors in the temporal cortex was also reported to be associated with visual hallucination [32,33]. The hypothesis of 5-HT2A receptor overactivation in the temporal cortex is supported by the fact that pimavanserin, an inverse serotoninergic receptor agonist, is efficacious against psychosis in PD [34,35]. Quetiapine, which has partial antagonistic activity against 5-HT2A, also provides beneficial effects against PD hallucinations [36,37].

Intrinsic and Extrinsic Factors

Psychosis often occurs suddenly, even in patients who have never experienced psychosis. In these patients psychosis is caused, not by intrinsic factors, but rather by extrinsic factors [38]. Extrinsic factors include systemic inflammation and use of trigger medications.

Trigger Medications

We previously examined potential trigger medications in a retrospective case-crossover study [38] by comparing drugs used in the period of psychosis development (hazard period) and those used in the periods without psychosis (control periods), and estimating the odds ratio (relative risk) of drugs for psychosis. Central anticholinergic drugs had the highest-risk (relative risk of 17.9) and the risk was dramatically increased in elderly patients. Dopaminergic agonists also had a high risk for psychosis, with an estimated odds ratio of 1.65 in patients aged ≥ 70 years.

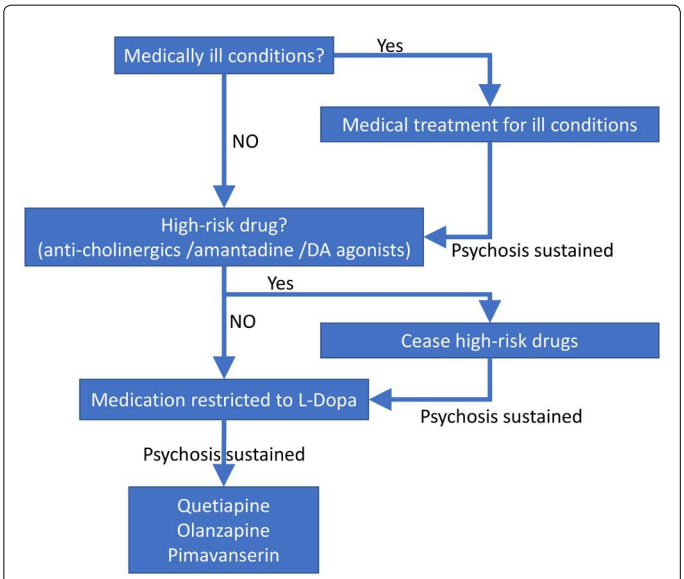

Figure 1: Therapeutic strategy for psychosis in Parkinson disease.

Amantadine is well known to elicit psychosis, especially in patients with impaired renal function, and often causes encephalopathy presenting with myoclonus when the plasma concentration is elevated [39].

Systemic Inflammation

We previously reported that serious infections can exacerbate motor signs and symptoms of PD, with often irreversible effects [40,41]. Marked inflammation such as serious infection or surgical intervention can cause psychotic symptoms even in healthy people. In PD patients, even when infection is not identified clinically, a small elevation of C-reactive protein, a peripheral marker of systemic inflammation, is associated with development of psychosis [6]. Brain microglias are also activated in patients with PD and activated microglias are associated with the neurodegenerative process [42]. Using neuroimaging, Ouchi and colleagues reported that microglia is activated in the early stage of PD [43]. Microglia activation was also reported in early patients with dementia with Lewy bodies [44]. In Alzheimer disease, systemic infection can cause behavioral changes termed 'sickness behavior'. In this context, a cross-talk between systemic inflammation and neuroinflammation may be an important clue to development of psychosis.

Concluding Remarks

Psychosis is a multifactorial complication in PD. The causes of psychosis include intrinsic (or patient-related) factors and extrinsic trigger factors. Intrinsic factors include severity of Lewy body pathology, genetic risk factors (including apolipoprotein ε4, cholecystokinin, and glucocerebrosidase), older age, cognitive decline, and longer disease duration. Identifying patient at high risk of psychosis by these factors, trigger factors should be checked and fixed. Our recommendation is shown in Figure 1. If systemic ill conditions including elevated

C-reactive protein are identified, the conditions should be treated. In cases psychosis sustains, risky drugs including anti-cholinergics, amantadine and dopamine agonists should be ceased and medication should be restricted to L-dopa if required. Finally, use of anti-psychotic drugs should be considered.

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