—Review—

Depression as a Prodromal Symptom of Neurodegenerative Diseases

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Neurodegenerative diseases can manifest as psychiatric symptoms in the prodromal phase, before the onset of core symptoms such as neurological, motor, and cognitive symptoms. Positron emission tomography (PET) has made it possible to detect the pathology of some neurodegenerative diseases in vivo. Many studies have indicated that depression is a preclinical symptom of neurodegenerative diseases. Approximately 10% of non-demented participants with depression developed Alzheimer's disease (AD) during the follow-up period. The prevalence of depression/dysphoria was 42.9% in the preclinical stage of dementia with Lewy bodies. Depression was present in 33.3% of patients with preclinical behavioral-variant frontotemporal lobar degeneration. Approximately 10% of patients had a history of depression at the time of diagnosis with Parkinson's disease. PET studies have revealed the pathology of neurodegenerative diseases in some cases of geriatric depression. Increased brain amyloid-beta deposition in late-onset depression is a possible reflection of prodromal AD. The severity of depression was significantly associated with greater inferior temporal tau and marginally associated with greater entorhinal cortex tau, and depression was associated with significantly greater mean cortical tau deposition. Thus, the presence of depression as a preclinical/prodromal symptom of neurodegenerative diseases has been demonstrated by epidemiological, pathological, and biomarker studies. A growing body of evidence from PET studies indicates that some cases of geriatric depression have pathologies of degenerative neurological disease. In the future, it is expected that PET will be utilized as an imaging biomarker for diagnosis of psychiatric disorders and development of new therapeutic agents.
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Key words: neurodegenerative disease, depression, prodromal symptom, positron emission tomography

Introduction

The debate over the causes of depression remains unresolved. In the past, depression was diagnosed based on a pathophysiological hypothesis, as it was thought that the etiology of depression could be classified as exogenous (e.g., from physical disease or trauma), psychogenic (e.g., from stress), and endogenous (due to some common biological basis other than physical disease or trauma). Today, depression is diagnosed using diagnostic criteria (e.g., whether certain symptoms are present or whether symptoms persist over a certain period of time) because the pathogenesis of endogenous depression, which was regarded as the original depression, has not yet been clarified. It is now widely understood that conditions that meet the diagnostic criteria for depression frequently occur in patients with a variety of physical illnesses and that antidepressant treatment is effective[1,2]. These factors suggest that depression can develop in association with the pathology of a variety of physical illnesses and that the effectiveness of pharmacotherapy is comparable for depression that is and is not associated with physical disease.

Among the physical diseases in which depression frequently occurs, as neurodegenerative diseases have their pathogenesis in the brain and are thus important in clarifying the pathogenesis of depression. Among the physi-

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Table 1 Pathology of neurodegenerative disease in psychiatric disease

Authors	Subjects	Diagnosis	Results
Nagao S. et al., 2014[10]	N=23	Psychosis, age over 40	LBD 26.1%, AGD 21.7%, CBD 4.3%
Shioya A. et al., 2015[9]	N=11	Bipolar disorder	LBD 9.1%, AGD 27.3%, CBD 9.1%
Nishida N. et al., 2015[11]	N=24	Post-stroke depression	AGD 33.3%, PSP 8.3%
Sweet RA. et al., 2006[7]	N=10	Late-onset depression	LBD 40.0%, Braak stage (III 30.0%, IV 10.0%, V 10.0%)

LBD: Lewy body disease, AGD: argyrophilic grain disease, CBD: corticobasal degeneration, PSP: progressive supranuclear palsy

cal diseases with a high incidence of depression, neurodegenerative diseases have the brain as their site of onset and are important for clarifying the pathogenesis of depression. Clinically, patients with neurodegenerative diseases may present with psychiatric symptoms in the prodromal phase, before the onset of core symptoms such as neurological, motor, and cognitive symptoms. While early diagnosis of neurodegenerative diseases affects prognosis, it is often overlooked that depression manifesting before the onset of disease is a prodromal symptom because it is not accompanied by core symptoms. A useful procedure for revealing the prodromal stages of neurodegenerative disease is autopsy. Nogami et al. investigated 324 consecutive autopsies from a general geriatric hospital and detected pure progressive supranuclear palsy (PSP)-type tauopathy in 2.5% of the consecutive autopsy cases[3]. The incidence was 1.6 times greater than that of neuropathologically definite PSP[3]. However, while autopsy is a method of delineating the pathophysiology of neurodegenerative diseases, it has not been able to reveal the pathophysiology of neurodegenerative diseases in the prodromal phase of the disease in vivo. Recent advances in functional brain imaging research, such as by positron emission tomography (PET), have made it possible to detect the pathology of some neurodegenerative diseases in vivo. For this reason, it is expected that PET will serve as a brain imaging biomarker for depression, a preclinical/prodromal symptom of neurodegenerative disease.

This article reviews depression in the preclinical/prodromal stages of neurodegenerative disease and, using findings from brain imaging studies, discusses the utility of PET as a brain imaging biomarker for depression due to neurodegenerative disease.

Evidence of Neurodegeneration in Mood Disorders

Cohort and epidemiological studies have reported that depression sometimes precedes the onset of neurodegenerative disease[4–6]. In addition, autopsy studies of patients with psychiatric disease, and especially mood disorders, have reported the presence of neurodegenerative disease pathology[7–11] (**Table 1**). In 10 consecutive autopsy cases of geriatric depression with an onset age of 65 or older, 3 had only Alzheimer's disease pathology and 3 had mixed pathology of Alzheimer's disease and Lewy body disease[7]. The mixed pathology of Alzheimer's disease and Lewy bodies is often reported[8]. The amygdala is said to play a major role in the development of depression, as 2 neuronal circuits centered in the amygdala are known to be associated with depression: the affective transmission circuit and the reward system circuit. Among those with mixed pathology of Alzheimer's disease and Lewy body disease, 12.8% (19 of 149) had Lewy body pathology only in the amygdala[8]. Among 11 patients with bipolar disease, 6 had neurodegenerative changes (dementia with argyrophilic disease 4, corticobasal degeneration 1, Lewy body disease 1)[9]. The results of these autopsy studies also revealed that some patients with depression and other mood disorders have a neurodegenerative pathology despite not having been diagnosed with neurodegenerative disease.

The problem with autopsy studies, as noted above, cannot reveal when pathological change occurred. To elucidate the impact of neurodegenerative disease pathology on neurodegenerative disease and depression, it is necessary to investigate whether neurodegenerative disease pathology was already present at the onset of depression.

What Are the Preclinical/Prodromal Stages of Neurodegenerative Disorders?

The preclinical stage may be defined as the period before the diagnosis of disease onset based on clinical symptoms, while at the same time the pathology leading to onset is already present and is progressing. In neurodegenerative disorders, the first signs of protein misfolding may appear early in the disease, although there is neither neuronal dysfunction nor neurodegeneration. The disease process is initiated by neurotoxic misfolded proteins, and the first identifiable feature of the preclinical stage may be abnormal accumulation of pathogenic protein aggre-

Table 2 Frequency of depression in neurodegenerative disease

Disease		N	% of depression	diagnostic criteria
Alzheimer's disease	Mirza SS 2014[4]	4,393	13.2%	CES-D score ≥16
Lewy body disease	McKeith 2005[18]	Review	40%	N/A
	Takahashi 2009[19]	167	14%	DSM-IV-TR
Frontotemporal dementia	Cheran 2018[26]	58	32.8%	DSM-IV
Parkinson's disease	Leentjens 2003[6]	105,416	9.2%	ICPC

CES-D: the Center for Epidemiology. Depression Scale, N/A: not available, DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, ICPC: the International Classification of Primary Care

gates within cells. Thus, the preclinical stage of neurodegenerative disorders may be characterized by the start of protein accumulation and misfolding. Accumulation of toxic proteins, affecting multiple cellular mechanisms, leads to neuronal dysfunction, resulting in neuronal loss and neurodegeneration. Both minor neuronal dysfunction and loss occur before clinical symptoms appear.

The late preclinical stage is also known as the prodromal stage. In the prodromal stage, subtle changes in cognition and behavior emerge. Evidence from large genetic cohorts suggests that the cognitive prodromal period begins with gradually progressive deterioration in executive dysfunction, which may occur alone or in association with other cognitive changes, such as social cognitive impairment or language disturbances[12]. The concept of mild cognitive impairment (MCI), which was developed to define the prodromal stages for AD, is an example[12].

For the prodromal stage of dementia with Lewy bodies (DLB), 3 prodromal DLB subtypes are considered, such as mild cognitive impairment (DLB-MCI), delirium onset DLB (DLB-del), and psychiatric onset DLB (DLB-psych). DLB-MCI is the most obvious of these, including a non-amnestic form, a multidomain form, and a form thought to be associated with early visual perception and attention impairment[13]. Conversion to DLB in such patients may occur even more frequently than conversion to AD in patients with amnestic MCI. DLB-del, with induced or spontaneous delirium, has also been reported, often occurring months to years before the onset of dementia, and was found in up to 25% of DLB patients, as compared with only 7% of AD patients[14]. DLB-psych has late-onset affective disorder or psychosis as its primary symptom, is typically treatment-resistant, and has hypersensitivity to neuroleptic and other psychotropic agents[13].

Depression in Preclinical and Prodromal Stages of Neurodegenerative Disorders

The frequencies of depression in neurodegenerative diseases are summarized in **Table 2**.

1. Alzheimer's Disease

Since AD is the most common form of dementia, numerous studies have been conducted on its relationship to depression. Depression is reportedly a common complication after the onset of AD. For example, the Cache County Study, a large cohort study, reported that 40% of patients with AD had depression[15]. In recent years, there has been growing interest in depression in the prodromal phase of AD. Experts now agree that depression in elderly should be considered a prodromal symptom of dementia and not a stand-alone clinical entity[16]. The symptoms of depression in AD differ according to the stage of dementia and can be differentiated from apathy by the presence of sadness, depressive thoughts and early-morning awakening[16]. It has been reported that 13.2% of non-demented participants developed dementia during a 13.7-year follow-up period[4]. Depressive symptoms increased the risk of dementia during the overall follow-up period, with the risk being highest in the short and intermediate follow-up periods[4]. These results suggest that some late-life depressive symptoms are part of a dementia prodrome rather than an independent risk factor of dementia.

Several hypotheses have been proposed for the pathogenesis of depression in the prodromal phase of AD. Pathophysiological events such as increased vascular load and neurodegenerative processes can cause structural and functional damage to the brain, compromising cognitive function and emotional domains[16]. Another hypothesis is that hippocampal atrophy may be caused by neuroendocrine changes due to depression, or ischemic changes due to worsening cerebrovascular lesions caused by depression in the prodromal stage may contribute to

onset of AD[17]. Yet another hypothesis is that dexamethasone administration increases amyloid production and tau aggregation in neuronal cell bodies and dendrites, and it is thought to be involved in amyloid plaques and neurofibrillary changes in the hippocampus and in glial cell involvement and development of AD[17].

2. Lewy Body Disease

Depression is one of the supportive signs in the clinical diagnostic criteria for DLB. In the Amsterdam Dementia Cohort, neuropsychiatric symptoms, particularly apathy, depression, and hallucinations, were more common in a prodromal DLB group than in a prodromal AD group[18]. Five years prior to the diagnosis of DLB, the prevalence of depression/dysphoria was 42.9%[18]. There is also a report on the frequency of DLB in patients diagnosed with depression, with 14% of patients older than 50 years hospitalized for depression also being diagnosed with DLB in the prodromal phase or dementia[19].

In 2020, the DLB Diagnostic Study group proposed research criteria for prodromal DLB, which largely follow the core clinical features outlined in the 2017 DLB criteria. The prodromal phase of DLB includes (1) DLB-MCI, (2) DLB-del, and (3) DLB-psych[20]. Eighteen of 35 patients with a first onset of major depressive disorder at age 50 or older and with bradykinesia developed a clinical diagnosis of DLB after 6 years of follow-up[5]. Unfortunately, it is not yet clear how to identify patients with prominent late-onset psychiatric symptoms who may have underlying Lewy body disease pathology and will subsequently progress to DLB. Thus, although we cannot have formal criteria for the psychiatric onset of DLB at present, clinicians in mental health and other settings need to be aware that this possibility exists, because of the risk of severe antipsychotic sensitivity reactions with increased morbidity and mortality.

Several hypotheses have been proposed for the pathogenesis of depression in the prodromal phase of DLB. There is evidence of mesocortical dopaminergic pathways in neuropsychiatric symptoms in DLB. Depression, fatigue, and early anosmia characterize an olfactory-to-limbic pattern of pathology, and early cognitive deficits and apathy are features of a neocortical route of spread[21]. A previous study reported that delusions, depression, and apathy were inversely correlated to decreased caudate dopamine transporter levels[22]. Although dopaminergic neurons are lost over time in DLB, it has been reported that abnormalities in the serotonergic system as well as the dopaminergic system may be involved in the development of depression. In a study comparing 10 DLB patients and 17 Parkinson's disease dementia patients with 9 healthy controls, serotonin 1A receptors in Brodmann's area 36 were higher in patients with depression[23].

How α-synuclein relates to the pathogenesis of depression is not yet fully understood, but several reports have been published. The accumulation of α-synuclein was identified in raphe nuclei in the early stages of PD, and previous study reported an almost 50% reduction of 5-HT neurons in the raphe nuclei of depressed PD patients with Lewy bodies pathology[24]. Miquel-Rio reported that mice overexpressing wild-type human α-Syn (h-α-Syn) in hippocampal 5-HT neurons showed aggregation of h-α-Syn protein in the 5-HT system[25]. This mouse model also showed axonal impairment in the raphe nucleus, impaired expression of brain-derived neurotrophic factor and 5-HT neurotransmission, resulting in a depression-like phenotype[25]. Alpha-Synuclein impairment in 5-HT neurons negatively affects brain circuits that control mood and emotion, and is associated with the onset of PD. The authors concluded that α-synuclein impairment in 5-HT neurons negatively affects brain circuits that control mood and emotion, similar to the neuropsychiatric manifestations that occur during PD[25].

3. Frontotemporal Lobar Degeneration (FTLD)

Compared to AD and DLB, there have been fewewer studies have investigated depression as a prodromal symptom of FTLD. A previous study reported that depression in preclinical behavioral-variant FTD was 33.3%[26]. The study of FTD gene variation carriers, anxiety and depression were most common in granulin carriers (23.8-100%) and microtubule-associated protein tau carriers (26.1-77.8%)[27]. It now appears that bvFTD patients with the C9orf72 mutation have a high rate of psychiatric symptoms[28,29]. In particular, anxiety and depression, hallucinations and delusions may be present in people with FTD, the latter being more highly expressed in C9orf72 expansion carriers than in other FTD subtypes[30].

4. Parkinson's Disease (PD)

The relationship between depression and subsequent PD appears to be strongest in the immediate "premotor" years before PD diagnosis. A retrospective case-control analysis of a population-based study from Rotterdam suggested that both anxiety and depression become significantly more common in patients only about 1-2 years before PD diagnosis[31]. However, depressive symptoms of PD precede motor symptoms, appear at all stages, and affect quality of life. Clinically significant depressive disorders occur in more than 40% of patients with PD[32–34].

The onset of depressive syndromes and their natural history do not parallel the course of the motor symptoms[35]. Depression is more common in patients with PD than in the general population[36]. A higher incidence of depression in patients who were later diagnosed with PD has been reported. A study of 105,416 patients found that, at the time of diagnosis with PD, 9.2% of the patients had a history of depression, compared with 4.0% of the control population[6].

It is difficult on the basis of clinical symptoms to distinguish depression from depression as prodromal symptoms of PD during this period. Several theories have been proposed for the pathogenesis of depression as a precursor of PD. By the time motor symptoms appear, about 50% of substantia nigra neurons have been lost[37]. Depression in PD has been related to multiple neurotransmitter dysfunctions, including dopamine (SNpc), serotonin (raphe nuclei), and noradrenaline (locus coeruleus). The involvement of both raphe nuclei and locus coeruleus at Braak stage 2 might indicate depression as a prodromal symptom of PD[38]. If a method for evaluating the dopaminergic nervous system and alpha-synuclein in the brain in vivo could be established, it would help to elucidate the pathogenesis of depression, a prodromal symptom of PD.

Imaging Biomarkers of Depression in the Preclinical/Prodromal Stage of Neurodegenerative Disease

In psychiatric disorders, where the pathogenesis of the disease or the point of action of therapeutic agents is in the brain, it is necessary to establish a method for evaluating lesions in the brains of living organisms, to consider diagnosis and treatment. Advances in molecular imaging techniques, such as PET, which evaluates the dynamics of substances in the body as described so far, have made this possible. In PET, a test drug labeled with a positron-emitting nuclide is administered to a subject, and the distribution of radioactivity within organs is captured on a tomographic image by a detector. To take one example, [^{18}F]FDG is covered by insurance for tumors, but it is also used in health checkups. To perform PET studies, it is necessary to synthesize test agents with a cyclotron and to have a PET scanner. Although some test agents are available for delivery, the variety is small, and the number of facilities conducting PET research is limited, even in Japan. If a disease-causing substance is identified, PET can be an imaging biomarker by developing a test drug that binds to that substance. Unfortunately, no common pathology for all depression has been identified. Nevertheless, degenerative neurological studies have revealed many pathologies, and we can therefore discuss the potential of PET as an imaging biomarker for the diagnosis of depression due to neurodegenerative disorders.

Amyloid beta (Aβ) and tau protein are believed to be involved in the onset and progression of AD. Definitive diagnosis of AD is made by pathological autopsy, which verifies the presence of certain amounts of senile plaques (accumulation of Aβ) and neurofibrils (phosphorylation of tau protein) in the brain. Amyloid imaging and tau imaging, which emerged in the 2000s, have good sensitivity and specificity for the diagnosis of AD and have become the testing agents for evaluating accumulation of Aβ and tau protein in vivo. In the following section, the findings from PET-based studies in depression that capture neurodegenerative disease pathology will be discussed.

1. Amyloid Imaging

Aβ PET drugs, mainly benzothiazole and benzoxazole derivatives, detect the β-sheet structures[39]. Although not listed in the National Health Insurance drug price list in Japan, [^{18}F]florbetapir and [^{18}F]flutemetamol were approved for use as amyloid imaging drugs, in 2014 and 2015, respectively. The number of medical institutions and health screening facilities that perform amyloid imaging is increasing along with development of test drug delivery systems. While most studies using amyloid PET have focused on dementia, there is growing interest in psychiatric disorders as a research target. Amyloid imaging is thought to be useful in differential diagnosis of pseudodementia due to depression and AD[40].

In our studies of depression we used [^{18}F]florbetapir PET to examine patients with mild cognitive impairment with a history of geriatric depression, to evaluate the role of amyloid pathology in geriatric depression[39]. We found that the frequency of Aβ-positive was almost 40% and the onset age of geriatric depression was significantly associated with SUVR of amyloid PET[41]. We also reported that patients with both geriatric depression (GD) and Aβ were significantly older at onset of GD than patients with GD without Aβ[41]. Our results that the rate of Aβ positivity was higher in late-onset GD and that onset-age was associated with SUVR support the hypothesis that the later the onset of GD, the more Aβ pathology affected its onset[41]. A recent review also summarized that late-onset depression could be a risk factor for a prodromal phase of AD. Global and region-specific increases in Aβ deposition, detected by amyloid PET, were sometimes as-

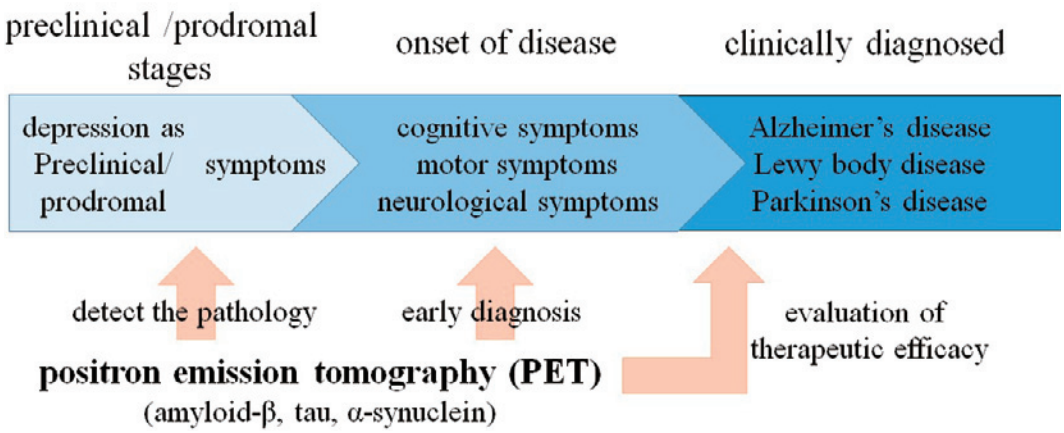

Fig. 1 Clinical usefulness of positron emission tomography (PET) for depression due to neurodegenerative disease. If disease-modifying drugs for neurodegenerative disease pathology are developed, PET will be an imaging biomarker of therapeutic efficacy.

sociated with late-onset depression, and Aβ42 reductions in plasma and CSF possibly reflect increased brain amyloid deposition and prodromal AD[42].

2. Tau Imaging

A recent study found that tau protein accumulates in different forms in different diseases, as the ratio of 3-repeat to 4-repeat tau accumulates at a 1:1 ratio in AD, 3-repeat tau in Pick disease, and 4-repeat tau in corticobasal degeneration, progressive supranuclear palsy, and FTLD[43]. Tau PET drugs are characterized by their selectivity for a variety of tau proteins, as [^{11}C]PBB3 binds to a wide range of both 3-repeat tau and 4-repeat tau, but [^{18}F]THK-5351 binds only to 4-repeat tau, and [^{18}F] flortaucipir has strong affinity for paired helical filaments in AD. A previous study of 111 cognitively normal older adults using the Geriatric Depression Scale (GDS) and in vivo cerebral tau using T807 PET reported that higher GDS was significantly associated with greater inferior temporal tau and marginally associated with greater entorhinal cortex tau[44]. It was suggested a link between depressive symptoms and tau-mediated neurodegeneration in a region vulnerable to AD[44]. Another study that used PET with tau radioligand [^{11}C]PBB3 showed that, compared to healthy subjects, MDD showed significantly higher mean cortical [^{11}C]PBB3 SUVRs and that these values were higher in MDD patients with psychotic symptoms than in those without[45]. They concluded that tau depositions may underlie MDD, especially in patients with psychotic symptoms[45]. Unlike amyloid-β, tau protein has 6 different isoforms. It is hoped that more detailed knowledge of the relationship between PET test drugs and pathological findings will be gained in the near future to clarify the characteristics of tauopathy in depression.

3. Other Imaging Findings

Dopamine transporter imaging has been used for PET imaging for Parkinson's disease and dementia with Lewy bodies[46]. More important as a potential therapeutic target is α-synuclein, since misfolded α-synuclein appears at Braak state 1 and the loss of dopaminergic neurons in substantia nigra occurs at Braak stage 4[47]. There are some drugs for imaging of α-synuclein, such as BF-227, [^{11}C]PBB3, and [^{18}F]C05-01[48,49]. The usefulness of 18F-SPAL-T-06, a new PET tracer that quantifies α-synuclein, has recently been reported, and future results are expected[50].

Conclusion

In summary, the presence of depression as a prodromal symptom in the preclinical/prodromal stages of neurodegenerative diseases has been reported in epidemiological, pathological, and biomarker studies. PET studies are providing a growing body of evidence that depression in old age is a precursor to depression due to neurodegenerative disease. In the future, this will make it possible to quantify and evaluate the pathology of neurodegenerative diseases in preclinical/prodromal stages by the application of these kinds of PET drugs (**Fig. 1**). Once pathological diagnostic methods using molecular imaging are established, PET is expected to be utilized as an imaging biomarker for the diagnosis of psychiatric disorders and development of new therapeutic agents.

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