Pseudodementia Revisita: Case Report and Narrative Review

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บทคัดย่อ

ในปัจจุบันที่สังคมกำลังก้าวเข้าสู่สังคมผู้สูงอายุ ภาวะรู้คิดบกพร่อง (cognitive impairment) มักพบได้บ่อยและมีการแย่ลงอย่างต่อเนื่องโดยช้าหรือเร็วขึ้นกับเหตุปัจจัยของแต่ละบุคคล ในการประเมินคนไข้ที่มีภาวะรู้คิดบกพร่องนั้นจำเป็นต้องมีการสืบค้นหาสาเหตุที่สามารถแก้ไขได้ก่อนที่จะสรุปว่าคนไข้นั้นมีสาเหตุจากโรคความเสื่อมของระบบประสาท ซึ่งภาวะซึมเศร้าหรือเดิมทีเรียกว่าภาวะสมองเสื่อมลวง (pseudodementia) ก็ถือเป็นหนึ่งในสาเหตุที่หากแก้ไขก็สามารถทำให้ภาวะรู้คิดบกพร่องกลับมาเป็นปกติได้ ในปัจจุบันเราทราบดีว่าภาวะซึมเศร้านอกจากจะเป็นหนึ่งในสาเหตุที่หากแก้ไขแล้วอาการดีขึ้น ยังอาจเป็นอาการนำอย่างหนึ่งก่อนที่จะมีภาวะสมองเสื่อมหรืออาจเป็นส่วนหนึ่งของอาการพฤติกรรมจิตประสาทของโรคสมองเสื่อม (BPSD) ก็ยังได้ เราจึงได้รายงานกรณีศึกษา เพศชายอายุ 67 ปี มาด้วยอาการภาวะรู้คิดถดถอยลงอย่างต่อเนื่องช้าๆ มา 5 ปี ผู้ป่วยได้รับการประเมินและตรวจสืบค้นต่างๆ ก่อนที่จะส่งมาปรึกษาคลินิคความจำซึ่งได้รับการวินิจฉัยในภายหลังว่าเป็นภาวะซึมเศร้า ภาวะรู้คิดถดถอยของคนไข้ดีขึ้นอย่างมากหลังจากได้รับการรักษาภาวะซึมเศร้าซึ่งเป็นตัวยืนยันที่ดีของการวินิจฉัยภาวะสมองเสื่อมลวง

คำสำคัญ : การตรวจตัวบ่งชี้ทางชีวภาพในน้ำไขสันหลัง, ภาวะซึมเศร้า, FDG เพทสแกน, ภาวะสมองเสื่อมลวง

Abstract

In the geriatric population, cognitive impairment frequently manifests with a progressive decline that varies in severity and rate, contingent upon individual etiological factors. Clinical protocols recommend identifying and addressing reversible factors contributing to cognitive decline prior to ascribing symptoms to irreversible neurodegenerative conditions. Depression, once termed pseudodementia, is recognized as a reversible contributor to cognitive

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dysfunction in older adults. Current perspectives reveal that the interplay between depression and dementia encompasses more than reversible cognitive deficits; it may precede dementia or appear as part of the behavioral and psychological symptoms of dementia. We detail the case of a 67-year-old male with a 5-year history of gradual cognitive decline. Extensive assessments were conducted before his referral to our memory clinic, where a depressive disorder was diagnosed. Remarkable cognitive improvement followed the treatment of his depression, affirming a diagnosis of pseudodementia.

Keywords: CSF biomarkers; Depression; FDG-PET; Pseudodementia

Introduction

Cognitive impairment has emerged as a prevalent symptom among adults of advanced age, imposing significant impacts on individual health, caregiver burden, and public health infrastructure[1]. In the diagnostic assessment of cognitive impairment, clinicians are urged to consider and exclude various reversible causes before concluding a neurodegenerative origin[2]. Depression, historically referred to as "pseudodementia," stands out among these reversible factors[3]. The decline in the use of the term pseudodementia over the past two decades is attributable to multiple factors, notably, the recognition that depression may not always lead to reversible dementia and may instead serve as a risk factor or a prodromal sign of dementia[4–7]. Another contributing factor to the diminished use of this term is the persistent cognitive impairment observed in at least 24% of patients following remission from depression, despite treatment[8–10]. Additionally, the ineffectiveness of acetylcholinesterase inhibitors and cognitive enhancers in addressing depression-related cognitive impairment, coupled with their adverse effects in nondemented patients, further complicates this issue[11,12]. Although the term pseudodementia has fallen out of favor in contemporary clinical practice, our case report aims to highlight the clinical importance of this condition by demonstrating its presentation and management outcomes.

Case Presentation

We describe a 67-year-old male who consulted a general neurologist due to a slowly progressive cognitive decline observed over a period of 5 years. His educational background included 4 years of formal education, and his professional history involved working as an electrical repairman from the age of 30 to retirement at 60. He was right-handed. His medical history revealed well-controlled essential hypertension that was managed with medications and bilateral sensorineural hearing loss, for which he had been utilizing hearing aids for the last decade.

Approximately 5 years ago, at age 62, the patient began exhibiting pronounced forgetfulness, notably misplacing personal items, neglecting to extinguish lights before retiring, and struggling to remember the next steps while repairing electrical appliances—a task within his expertise for more than 20 years. He reported a perceptible slowdown in cognitive processes, necessitating increased time to formulate and recall intentions. Initially, he was adept at managing his medication regimen. However, over the subsequent 4 years, his condition deteriorated, culminating in the inability to administer medications or perform household appliance repairs—activities previously within his competence. Despite these cognitive setbacks, his basic activi-

ties of daily living remained unaffected. Additionally, the patient experienced sleep disturbances and a diminished appetite, further complicating his clinical picture. His daughter, observing a substantial deterioration in his memory, sought medical evaluation.

During his evaluation, both physical and neurological parameters were found to be within normal ranges. The Thai Mental Status Examination resulted in a score of 22 out of 30, which falls below the normal threshold of 24. Similarly, the Montreal Cognitive Assessment produced a score of 15 out of 30, which is indicative of cognitive impairment, as scores above 25 are typically considered within the normal range. Comprehensive investigations, including blood tests and magnetic resonance imaging with a dementia-specific protocol, were conducted to identify any reversible causes of cognitive decline. These investigations confirmed normal hematological parameters and revealed generalized brain atrophy consistent with the patient's age, without evidence of focal or asymmetrical lobar atrophy. In light of his premature cognitive decline, which occurred before the age of 65, further diagnostic procedures were pursued, including a lumbar puncture for cerebrospinal fluid (CSF) analysis and a fluorodeoxyglucose–positron emission tomography (FDG-PET) scan. CSF analysis revealed that the amyloid beta, total tau, and phosphorylated tau protein levels were within normal limits, and FDG-PET showed no regions of hypometabolism, ruling out many common neurodegenerative conditions.

At our memory clinic, referring patients for an exhaustive neuropsychological evaluation is a cornerstone of our diagnostic approach. This patient's assessment revealed inconsistencies: although he demonstrated adeptness in visual memory tasks (both immediate and delayed recall), he failed to score in auditory memory tasks. Notably, during instances of testing failure, the patient exhibited considerable stress, often digressing into recounting distressing life events, which occasionally necessitated the premature cessation of testing. This significant variance within the cognitive domain of memory, combined with his pronounced stress response, suggested underlying depressive disorder. Application of the Geriatric Depression Scale yielded a score of 13 out of 30, suggesting mild depression.

A deeper investigation of the patient's stress-related history revealed pivotal events. Five years prior, concurrent with the onset of his cognitive decline, he experienced the loss of a cherished pet, leading to significant grief. This period was further complicated by financial pressures stemming from his wife's debts, compelling him to deplete a substantial portion of his savings. These events precipitated a marked deterioration in his marital relationship, characterized by increased conflict. Clinically, he reported insomnia, a diminished appetite, episodes of isolated weeping, and a general lack of motivation. Although there was a slight improvement in his mood over time, his cognitive deficits persisted.

The therapeutic strategy included the initiation of an antidepressant regimen alongside supportive psychotherapy. At the patient's 3-month follow-up, a discernible improvement was observed in both his mood and cognitive functions. Notably, at the 6-month evaluation, his performance on the Thai Mental Status Examination and the Montreal Cognitive Assessment improved to scores of 25 and 23, respectively, indicating substantial cognitive

recovery. Concurrently, an enhancement in his mood was substantiated by both clinical observation and a decrease in the Geriatric Depression Scale score to 5. Impressively, the patient was able to resume his previous competencies, including the repair of items and the self-management of his medication regimen, mirroring his pretreatment capabilities.

Discussion

In assessing patients with cognitive decline, two fundamental questions arise. The first concerns the etiology of the cognitive impairment, necessitating a comprehensive evaluation for reversible causes. This approach is crucial, as the amelioration of such causes can potentially improve cognitive function, unlike the inevitable progression associated with irreversible, neurodegenerative diseases[2]. The second question distinguishes between dementia and mild cognitive impairment, given that treatment regimens and the resulting caregiver burden and patient prognosis differ markedly between these conditions[13].

Historically, depression was considered a reversible factor, with the expectation that cognitive function would normalize following appropriate treatment, leading to the use of the term “pseudodementia.” This term has also been applied to cognitive declines associated with other psychiatric disorders such as mania, schizophrenia, and conversion disorder[3,14]. However, current research has shown that depression may precede dementia as a prodromal symptom or co-occur with it, challenging the notion of its reversibility[7]. Although the treatment of depression does not guarantee a full reversal of cognitive deficits, it is advocated due to the potential for untreated mood disorders to exacerbate cognitive decline[15], as illustrated in our case study. This evolving understanding underscores the complexity of diagnosing and treating cognitive impairment within the context of psychiatric comorbidities

Identifying depression in our patient proved challenging due to time constraints inherent in clinical assessments and the patient’s inherent temperament. His daughter revealed that he often concealed his emotional struggles, a tendency attributed to his perceived role and obligations within the family structure. This necessitated multiple consultations to construct a comprehensive clinical picture, with particular emphasis on conducting assessments in a setting isolated from familial influences to encourage candid disclosure of symptoms. Following a detailed explanation of his condition, with an emphasis on the concept of pseudodementia, the patient recognized the extent of his stress and its previously underestimated effect on his cognitive capacities and daily functioning.

Cognitive impairments associated with depression notably affect psychomotor speed, sustained attention, memory, and executive functions[16–18]. The debate regarding the reversibility of these impairments after depression treatment persists within the scientific community. The literature on this topic presents conflicting evidence; certain studies indicate complete cognitive restoration posttreatment [18–20], while others highlight enduring deficits, especially in attention, memory, and executive functions[9,21]. Recent advancements in our understanding suggest that depression not only constitutes a risk factor for dementia[22] but also may present as a prodromal symptom during the preclinical stages or even within the dementia

phase itself[7]. This duality in depression's relationship with cognitive function may explain the observed disparities in cognitive recovery outcomes following the improvement of depressive symptoms. The diagnosis of depression in patients with Alzheimer's disease, the predominant neurodegenerative dementia type, presents significant challenges due to symptom divergence from that in nondemented individuals of advanced age and the insensitivity of conventional diagnostic criteria and scales. In Alzheimer's disease patients, depression is more frequently marked by motivational disturbances, including psychomotor retardation, apathy, and fatigue. These characteristics contrast with the mood-centric symptoms (depressed mood, anxiety, and disturbances in appetite and sleep) observed in nondemented older adults[23,24]. Standard diagnostic instruments—such as the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), the Hamilton Depression Rating Scale, the Cornell Scale for Depression, and the Geriatric Depression Scale—were primarily devised for nondemented individuals, lose validity in dementia patients due to their impaired self-awareness of mood conditions[25–27]. In response to these diagnostic dilemmas, the National Institute of Mental Health introduced the Provisional Diagnostic Criteria for Depression of Alzheimer's Disease (NIMH-dAD) in 2002 (Table 1)[28]. This set of criteria has demonstrated high concordance with DSM-IV diagnoses, exhibiting 94% sensitivity and 85% specificity, thereby offering a reliable tool for identifying depression in Alzheimer's disease patients[29].

Table 1. National Institute of Mental Health Provisional Diagnostic Criteria for Depression of Alzheimer's Disease [Adapted from Reference 28]

A. Three (or more) of the following symptoms must be present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms must either be 1) depressed mood or 2) decreased positive affect or pleasure 1. Clinically significant depressed mood 2. Decreased positive affect or pleasure in response to social contacts and usual activities 3. Social isolation or withdrawal 4. Disruption in appetite 5. Disruption in sleep 6. Psychomotor changes 7. Irritability 8. Fatigue or loss of energy 9. Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt 10. Recurrent thoughts of death, suicidal ideation, plan or attempt
B. All criteria are met for Dementia of the Alzheimer Type (DSM-IV)
C. The symptoms cause clinically significant distress or disruption in functioning
D. The symptoms do not occur exclusively in the course of delirium
E. The symptoms are not due to the direct physiological effects of a substance
F. The symptoms are not better accounted for by other conditions such as major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of Alzheimer disease, anxiety disorders, or substance-related disorders

Given its ease of use in clinical settings, the Geriatric Depression Scale was employed to assess the severity of depression and to monitor therapeutic response in our patient. Application of the NIMH-dAD revealed that the patient's symptoms, including depressed mood, alterations in appetite and sleep patterns, psychomotor retardation, and diminished energy levels, were indicative of depression. This diagnosis could be established irrespective of the presence of Alzheimer's disease. Notably, these symptoms could also meet the criteria for a depression diagnosis using other standards designed for nondemented patients, such as the DSM-IV. The case underscores the critical nature of comprehensive history-taking: an absence of detailed inquiry into the patient's sleep and dietary habits could have led to an oversight of the underlying mood disorder. Therefore, meticulous history-taking is essential, often providing key insights that may not be as readily apparent through cognitive testing alone.

The diagnosis of depression lacks specific or standardized biomarkers, necessitating reliance on clinical history and anomalous test findings. The pathophysiology of depression is multifaceted, with theories ranging from monoamine depletion[30] and hypothalamic–pituitary–adrenal axis hyperactivity[31] to glutamatergic system imbalances[32] and neuroinflammation[33]. CSF, which is closely associated with brain chemistry, offers a potential avenue for depression diagnosis through analysis, akin to its use in other neurological disorders. Despite the exploration of numerous CSF biomarkers within research settings, the heterogeneity of the underlying mechanisms of depression has led to a proliferation of potential biomarkers. These molecular markers have been studied primarily in small cohorts, complicating the identification of definitive biomarkers for clinical use. A recent meta-analysis of CSF biomarkers in depression reviewed 97 studies that involved 165 biomarkers[34]. Only 42 biomarkers were investigated in more than one study, and of these, only 9 biomarkers (from 48 of the studies) showed significant differences between depressed patients and healthy controls. The small sample sizes associated with these 9 biomarkers currently preclude their utility in enhancing the clinical diagnosis of depression.

In addition to CSF biomarkers, FDG-PET scans and functional magnetic resonance imaging have been instrumental in detecting specific regions of hypometabolism indicative of depression. FDG-PET scans have identified variations ranging from normal to diminished metabolic activity in critical areas, including the frontal, temporal, anterior cingulate, and parietal lobes[35,36]. This imaging technique has also been applied to explore depression within the realms of mild cognitive impairment and Alzheimer's disease, and this approach has consistently detected hypometabolism within the frontal cortex [37,38]. The presence of abnormal hypometabolism in FDG-PET scans, particularly in the context of depression or other neuropsychiatric conditions, is associated with a heightened risk of progressing to mild cognitive impairment[39]. The challenge arises in distinguishing between depression and Alzheimer's disease due to shared hypometabolic regions, such as the parietal and temporal lobes, leading to mixed outcomes in studies attempting differentiation via FDG-PET scans[40]. However, case reports have noted the normalization of hypometabolic areas following depression treatment through antidepressants, electroconvulsive therapy, or a combination thereof, suggesting the potential reversibility of these neuroimaging findings[41–44].

In our reported case, the FDG-PET scan did not reveal any hypometabolic regions typically associated with Alzheimer's disease, presenting a diagnostic conundrum. This absence of hypometabolism might suggest that the patient's depressive symptoms were an early, prodromal indication of Alzheimer's disease, during which FDG-PET scans can still appear normal, or alternatively, that the patient was experiencing late-onset depression accompanied by mild cognitive impairments linked to mood disturbances. Differentiating between these potential diagnoses poses a significant challenge, often necessitating an assessment of a patient's clinical response to mood disorder treatments for a more definitive diagnosis[45]. The marked improvement in mood and cognitive capabilities in our patient following treatment with antidepressants and psychotherapy supports the diagnosis of pseudodementia. Nonetheless, it remains imperative to closely monitor the patient's cognitive functions over time, as there remains a risk for future cognitive decline, possibly due to a resurgence of depressive symptoms or the emergence of a neurodegenerative disorder.

Conclusions

The term pseudodementia has become less prevalent in modern medical discourse, primarily due to its potential to cause diagnostic confusion and its limited contribution to clarifying the complex interplay between dementia and depression. This term historically denoted a reversible form of cognitive decline, often linked to depression or mood disorders, necessitating precise diagnostic labeling rather than the broad use of "pseudodementia." While treatment may not completely reverse cognitive deficits in all cases, it is imperative to rigorously investigate the presence of such reversible conditions. A thorough assessment for treatable causes of cognitive decline is essential before definitively diagnosing a patient with irreversible, neurodegenerative dementia, thereby highlighting the critical need for accurate diagnosis and management in such cases.

Ethics Approval and Consent to Participate

This study received ethical approval from the Siriraj Institutional Review Board at the Faculty of Medicine Siriraj Hospital, Mahidol University in Bangkok, Thailand (reference number: Si 119/2024). Owing to the retrospective design of our study, which inherently preserved the anonymity of the patient, the acquisition of written informed consent from the patient was deemed unnecessary. This exemption was formally granted by the Siriraj Institutional Review Board. The authors affirm that all aspects of this research were performed in strict accordance with the ethical guidelines outlined in the Declaration of Helsinki.

Consent for Publication

Not applicable.

Conflict of Interest Statement

The authors affirm that there are no personal or professional interests that could be construed as conflicts of interest in relation to this study.

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Author Contributions

CD take part in reviewing case and lab test, and manuscript writing. CR take part in review neuropsychological test. LW take part in analysis of

CSF. SC and AR take part in doing neuropsychological test. VS take part in suggestion of case report and manuscript revision.

Data Availability Statement

The datasets generated and analyzed during the course of this study are fully incorporated within the text of this article.

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