Research Article

Identifying reversible psychiatric dementia mimics in new memory clinic outpatients

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Abstract

Background: Timely identification of reversible conditions that mimic dementia is critical in memory clinic practice. However, psychiatric conditions as potential dementia mimics have not been studied as thoroughly as neurological ones, and detailed data on their reversibility remain limited.

Objective: To identify reversible psychiatric dementia mimics.

Methods: A retrospective chart review was conducted on 749 new outpatients to investigate etiologies, progression rates, a neuropsychological assessment, cognitive and functional levels, and potential reversibility, categorized by psychiatric and neurological conditions. Cases showing cognitive reversibility following treatment were also identified. Comparisons were made based on the presence or absence of potential reversibility, as well as actual reversibility.

Results: Among the 749 individuals, 121 (16.2%) had potentially reversible conditions: 75 psychiatric and 46 neurological. Psychiatric conditions included depression, schizophrenia and delusional disorders, developmental disorders, alcohol use disorder, and dissociative and anxiety disorders. Compared to individuals without potentially reversible conditions, individuals with psychiatric conditions were younger, had a faster progression rate, and demonstrated higher cognitive function. Of the individuals who had mild cognitive impairment or dementia mimic, 6 (0.9%) showed complete cognitive resolution (3 cases) or partial cognitive improvement (3 cases). These 6 cases included two individuals with psychiatric conditions manifesting psychotic features.

Conclusions: While rare, reversible psychiatric dementia mimics highlight the importance of comprehensive evaluations in memory clinics, particularly for younger individuals experiencing rapid cognitive decline. The infrequency of reversibility may reflect a strong association between these potentially reversible conditions and dementia risk factors, or their role as prodromes of dementia itself.

Keywords

Alzheimer's disease, dementia, differential diagnosis, memory clinic, psychiatric conditions, reversibility

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Introduction

Differentiating potentially reversible dementia mimics is crucial for first-time visitors to dementia clinics or related facilities. Recently, this issue has primarily been addressed in hospital-based studies on rapidly progressive dementia, particularly in distinguishing Creutzfeldt-Jakob disease from other etiologies.[1–3] The etiologies of rapidly progressive dementias, based on the time from onset to dementia, include neurovascular diseases, toxic-metabolic encephalopathies, inflammatory central nervous system diseases, central nervous system neoplasms, prion diseases, and other neurodegenerative dementias.[3] However, the proportion of reversibility in individuals with rapidly progressive dementias remains unclear. Existing studies in this field have primarily focused on pathological or autopsy findings,[1–9] often excluding psychiatric conditions. In hospital-based studies of rapidly progressive dementias, cases that are difficult to differentiate are typically referred to specialized hospitals, leading to selection bias and challenges in investigating the etiologies and reversibility of these conditions, especially in individuals with psychiatric disorders.

In contrast to hospital-based studies, community-based outpatient dementia clinics offer the advantage of reduced selection bias when investigating reversibility, though such studies have not been extensively conducted in recent years.[10–16] Some studies from these clinics have provided data on the proportion of potentially reversible conditions and their actual reversibility rates.[10,11,14,16–20] A review by Clarfield (2003)[13] found that the proportion of potentially reversible conditions in these settings was 9.0%, with an actual reversibility rate of 0.6%. The etiologies of these potentially reversible conditions, listed by frequency, include metabolic diseases, normal pressure hydrocephalus, central nervous system neoplasms, depression, subdural hematoma, infectious diseases, and medication-induced dementia.[13]

However, there is significant variation in the frequency of depression across studies. For instance, Bayer et al. (1987),[21] Freter et al. (1998),[11] and Djukic et al. (2015)[22] identified depression as the most common condition (notably, the findings by Djukic et al. were based on diagnoses at admission to a geriatric unit, rather than a memory clinic). In contrast, Roberts et al. (1990)[23] and Walstra et al. (1997)[10] did not mention depression in their studies. Additionally, many studies either listed only depression and/or alcohol use disorder[11,13,24] or used non-specific terms such as 'psychiatric diseases'[1,2] or 'psychosis'[24] to describe psychiatric conditions. Detailed investigations into psychiatric conditions beyond depression and alcohol use disorder remain limited. This may be due to the fact that many memory clinics are predominantly staffed by neurologists rather than psychiatrists. However, in these clinical settings, outpatients often present with a range of psychiatric disorders beyond depression and alcohol use disorder, including delusional disorders,[25,26] schizophrenia,[27,28] bipolar disorder,[27] anxiety disorders,[29–31] and neurodevelopmental disorders such as attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder.[28,32,33] These conditions are often described using broader or non-specific terms, despite their specific treatment. In fact, psychiatric morbidity—encompassing both conditions with and without concomitant dementia—affects up to 23% of all patients in a neurology-based memory clinic.[34] Identifying specific psychiatric conditions in these settings is crucial, as interventions may offer cognitive and/or behavioral recovery, particularly in cases of depression and schizophrenia.[35,36] Furthermore, accurate diagnosis of psychiatric conditions is essential for distinguishing behavioral variant frontotemporal dementia from other psychiatric disorders, as this poses a significant diagnostic challenge.[37,38] According to Krudop et al. (2017),[38] nearly half of initial diagnoses of behavioral variant frontotemporal dementia are later revised to psychiatric diagnoses upon follow-up. Conversely, approximately 50% of patients with behavioral variant frontotemporal dementia initially receive a psychiatric diagnosis.[37] This confusion is particularly common among general practitioners.[39]

While potentially reversible neurological conditions have been extensively studied, there has been limited attention to potentially reversible psychiatric conditions, other than depression and alcohol use disorder. To address these gaps, we conducted a retrospective investigation into the breakdown of potentially reversible conditions, focusing on psychiatric disorders and their actual reversibility in a community-based memory clinic. This study benefits from the clinic's dual staffing of neurologists and psychiatrists.

Methods

Participants

The ethical aspects of this study were reviewed and approved by the Human Research Ethics Committee at Ashikaga Red Cross Hospital in Ashikaga, Japan. Informed consent was obtained from participants and/or their primary caregivers via an opt-out method, with details provided on the hospital website. This retrospective cohort study included all 749 new outpatients who visited the memory clinic affiliated with Ashikaga Red Cross Hospital, a tertiary referral center, for the first time between October 2014 and May 2024. Patients were referred by general practitioners within an approximately 30-km (20-mile) radius of the hospital. Referrals were based on suspected dementia or mild cognitive impairment (MCI), following initial assessments conducted by these practitioners in the community.

Examination

The clinic is staffed by neurologists, psychiatrists, and a nurse certified in dementia diagnosis and care. All

medical doctors, except for one psychiatrist working under the supervision of their colleagues, are board-certified specialists in neurology or psychiatry. Additionally, one neurologist and one psychiatrist hold certifications in dementia diagnosis and care. At the time of the assessments, each professional had over six years of experience in diagnosing and managing dementia. During the initial outpatient visits, triage is conducted by the certified nurse. Individuals presenting with significant psychiatric symptoms, such as a depressed mood or verbal hallucinations—a type of auditory hallucination that are often associated with psychosis[40]—are referred to a psychiatrist. Conversely, those with prominent neurological symptoms, such as paralysis, are referred to a neurologist. If a patient with substantial psychiatric symptoms is initially evaluated by a neurologist, they are subsequently referred to a psychiatrist. Similarly, outpatients suspected of having neurological conditions, such as encephalitis, who are first examined by a psychiatrist are then referred to a neurologist.

To assess cognitive and functional abilities and determine potential etiologies, outpatients undergo a comprehensive initial interview. This evaluation includes their current medical history related to cognitive decline, such as the duration of symptoms (time from onset to examination), past medical history, current medications, functional abilities (activities of daily living and instrumental activities of daily living), and any psychiatric conditions. Functional abilities are assessed through interviews with the primary caregiver, focusing on tasks like problem-solving (e.g., managing finances), housework (e.g., cooking and maintaining hygiene), medication management, and community engagement (e.g., participating in social functions and paying bills).

The initial interview is conducted jointly by a nurse and a medical doctor. This is followed by a neurological examination and a neuropsychological assessment using the Japanese version of the Mini-Mental State Examination (MMSE-J).[41] Additional evaluations typically include brain imaging (e.g., computed tomography, magnetic resonance imaging, dopamine transporter scintigraphy, or metaiodobenzylguanidine myocardial scintigraphy) and blood tests, which often include assessments for syphilis, liver function, and thyroid function. However, brain imaging and blood tests may be omitted in cases where evident psychiatric conditions rather than dementia are identified or when patients choose to decline these tests.

Diagnosis

The cognitive and functional levels of new outpatients were provisionally classified into three categories—normal cognitive function, MCI, and dementia level—prior to determining the final diagnosis. MCI was assessed using the criteria of the National Institute on Aging-Alzheimer's Association,[42] while dementia level was diagnosed using the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) criteria.[43]

These three cognitive and functional categories—normal cognitive function, MCI, and dementia level—represent preliminary assessments made during the initial visit of new outpatients and are not definitive. A diagnosis of MCI or dementia is typically reserved for cases deemed irreversible. However, as our study focuses on identifying potential reversibility or improvement, these categories are used provisionally, including for patients with psychiatric conditions. In such cases, the categories are adapted as follows: normal cognitive range, MCI, and dementia mimic. Additionally, some individuals classified within the normal cognitive function range may exhibit subtle cognitive changes that fall short of the criteria for MCI.

When diagnosing these three levels, the MMSE-J score was considered a valuable reference, but the determination of MCI and dementia levels was based on a comprehensive evaluation. This included input from both the patient and their primary caregiver, as well as assessments of functional abilities. Typically, an MMSE-J score of 24–27 suggests MCI, while a score of 23 or lower indicates dementia level.[44] However, the MMSE is known to have a false-positive rate of up to 10% and a false-negative rate of 15% at this cutoff for detecting dementia.[45] To reduce false positives, adjustments were made based on educational background, as reported in previous studies.[46,47] For instance, a cutoff of 20 or lower, rather than 23 or lower, was applied for individuals with nine or fewer years of education. In patients with primary progressive aphasia,[48,49] less emphasis was placed on the MMSE score due to the condition's predominantly verbal deficits. Instead, greater weight was given to their social and personal functioning. On the contrary, higher education also increases the risk of false negatives.[50] Similarly, the MMSE may be particularly inaccurate in cases of atypical dementia,[51] including those associated with psychiatric symptoms in this study, due to overlapping behavioral features. Consequently, while the MMSE-J served as a useful diagnostic reference, it was not the primary determining factor. Subjective complaints and caregiver input were critical, especially in identifying genuine memory dysfunction.

For diagnosing specific etiologies, each type of dementia was identified using internationally accepted criteria.[52–58] The diagnosis of degenerative conditions was categorized as either possible or probable, but not definitive, due to the absence of specific biomarkers. For potentially reversible conditions, we included all neurological or psychiatric conditions (ICD-10 codes F04 to F09), excluding dementia (ICD-10 codes F01 to F03), as classified under the International Classification of Diseases, 10th Revision (ICD-10).[59] This also encompasses conditions with the potential for cognitive recovery through interventions, particularly in cases of severe depression and schizophrenia

that fall within the range of dementia mimics.[35,36] Importantly, this category also includes neurodevelopmental disorders, such as autism spectrum disorder, which often co-occurs with ADHD and may show some cognitive improvement with specific ADHD medications.[60] We also included potentially reversible neurologic conditions, using internationally accepted criteria for defining each condition. These include normal pressure hydrocephalus, chronic subdural hematoma, hepatic encephalopathy, neurosyphilis, epilepsy, vitamin B12 deficiency, hypothyroidism, and autoimmune encephalitis.[61–68] Differentiating potentially reversible cerebrovascular diseases from vascular dementia depends on whether the stroke is a first-time event, as some recovery occurs after an initial stroke,[69] whereas recurrent strokes are the primary cause of cognitive decline in stroke survivors.[70] Additionally, cerebral small vessel disease was not considered a reversible cerebrovascular disease.[71]

When multiple etiologies were present, the case was classified as potentially reversible if at least one of the etiologies was deemed reversible. This typically applied to cases with comorbid depression in degenerative diseases[72–74] or the presence of Alzheimer's disease in normal pressure hydrocephalus.[75]

Resolution and partial improvement

For individuals with potentially reversible conditions, the follow-up period was six months, with MMSE re-examinations typically conducted six months after the initial visit. To account for practice effects,[76,77] 0.6 points were subtracted from the MMSE-J re-examination score. This adjustment reflects the maximum mean increase from baseline observed in a study of mild to moderately severe Alzheimer's disease patients, where the MMSE was administered at three-week intervals over 12 weeks.[76] For the diagnosis of MCI and dementia level, the MMSE score was considered important, but the determination was made comprehensively, incorporating input from the patient and primary caregiver, as well as assessments of functional abilities.

This analysis included cases of complete or partial improvement, categorized as either resolution, with normal cognitive function restored from MCI or dementia mimic, or partial improvement, with dementia mimic improving to MCI.

Statistical methods

We first compared demographic information, including age, sex distribution, and time from onset to examination, along with neuropsychological assessment (MMSE-J), across three cognitive and functional levels: normal cognitive function, MCI, and dementia level. For numerical data, the Kruskal-Wallis test was used for overall comparisons, followed by post-hoc analyses with Mann-Whitney U tests and Bonferroni correction for multiple comparisons, as the data did not follow a normal distribution. For categorical data, such as sex distribution, a chi-square test was applied.

Next, we compared demographic information and neuropsychological assessment between the potentially reversible and non-reversible groups, and further between psychiatric conditions and potentially reversible neurological conditions. The same statistical methods were applied as described above. These two types of potentially reversible conditions—psychiatric and neurological—were then categorized into three cognitive and functional levels, with specific diagnoses outlined within each level.

For cases with complete resolution or partial improvement, we compared demographic information and neuropsychological assessments with those of individuals with MCI and dementia level who did not experience reversibility. Mann-Whitney U tests and Fisher's exact test were used for this comparison.

Results

All 749 outpatients underwent detailed interviews. Neuropsychological examinations were conducted on 727 individuals (97.1%), brain imaging on 686 individuals (91.6%), and blood tests on 584 individuals (78.0%). Lumbar punctures were performed on 8 individuals (1.1%). The exact onset time of the disease was unclear for 138 individuals (18.4%), primarily due to factors such as the nature of certain conditions (e.g., developmental disorders, where determining the exact onset is difficult), the challenge of pinpointing onset in individuals with normal cognitive function, and a combination of patients' unawareness of their cognitive decline and insufficient caregiver observation.

Table 1 presents the characteristics of the entire study group (leftmost column), as well as the normal cognitive function range group, the MCI group, and the dementia level group, from left to right. These results reflect the participants' status at their first visit, before treatment of potentially reversible conditions. As expected, age, time from onset to examination, and MMSE-J score differed significantly across the three groups ($p < 0.001$ for all). No significant difference in sex distribution was found across the groups ($p = 0.44$). In post-hoc analyses, age was youngest in the normal cognitive function range group, followed by the MCI group, and oldest in the dementia level group ($p < 0.001$ for all). The time from onset to examination was shortest in the normal cognitive function range group, followed by the MCI group, and longest in the dementia level group ($p < 0.001$ for all). The MMSE-J score was highest in the normal cognitive function range group, followed by the MCI group, and lowest in the dementia level group ($p < 0.001$ for all). The most common

Table 1. Cohort characteristics stratified by cognitive and functional levels at initial visit.

	All individuals (N = 749)	Normal cognitive function range (n = 101)	Mild cognitive impairment (n = 243)	Dementia level (n = 405)
Age	76.9 ± 9.1	66.8 ± 13.2	77.1 ± 7.6	79.4 ± 6.6
Sex (female %)	57.0%	56.4%	53.9%	59.0%
Time from onset to examination (y)	1.9 ± 2.0	1.2 ± 1.8	1.6 ± 1.6	2.3 ± 2.2
MMSE-J	22.2 ± 5.6	28.1 ± 2.2	25.3 ± 2.8	18.9 ± 5.2
Alzheimer's disease	420 (64.8%)	–	155 (63.8%)	265 (65.4%)
Vascular dementia	54 (8.3%)	–	9 (3.7%)	45 (11.1%)
Dementia with Lewy Bodies	37 (5.7%)	–	13 (5.3%)	24 (5.9%)
Frontotemporal dementia	4 (0.6%)	–	2 (0.8%)	2 (0.5%)
Mixed dementia	37 (5.7%)	–	-	37 (9.1%)

MMSE-J: Japanese version of Mini-Mental State Examination.

Table 2. Potentially reversible conditions and non-reversible conditions.

Item	Potentially reversible conditions (psychiatric and potentially reversible neurologic conditions combined) (n = 121)	Psychiatric conditions (n = 75)	Potentially reversible neurologic conditions (n = 46)	Non-reversible conditions (n = 628)
Age	71.2 ± 12.7†	69.5 ± 13.9‡	74.2 ± 9.9§	78.0 ± 7.8
Sex (female, %)	54.1%	52.6%	56.5%	57.2%
Time from onset to examination	1.2 ± 1.7†	1.5 ± 1.9‡	0.6 ± 1.0‡	2.0 ± 2.1
MMSE-J	25.1 ± 5.8†	25.3 ± 4.2‡	22.3 ± 7.2	21.8 ± 5.5

MMSE-J: Japanese version of Mini-Mental State Examination; †$p < 0.001$ in comparison between combined potentially reversible conditions and non-reversible conditions; ‡$p < 0.001$ in comparison between psychiatric conditions or potentially reversible neurologic conditions and non-reversible conditions; §$p < 0.05$ in comparison between potentially reversible neurologic conditions and non-reversible conditions; ¶$p < 0.001$ in comparison between potentially reversible neurologic conditions and psychiatric conditions.

etiologies of dementia were Alzheimer's disease, followed by vascular dementia and dementia with Lewy bodies.

Difference between potentially reversible and non-reversible conditions

Table 2 demonstrated the difference between potentially reversible and non-reversible conditions. Potentially reversible conditions were identified in 121 out of 749 outpatients (16.2%). The ages of individuals in the potentially reversible group were significantly younger than those in the non-reversible group ($p < 0.001$). In sub-analyses, the ages for both psychiatric conditions and potentially reversible neurologic conditions were significantly younger than those in the non-reversible group ($p < 0.001$ and $p = 0.014$, respectively). The time from onset to examination was shorter in the potentially reversible group compared to the non-reversible group ($p < 0.001$). In sub-analyses, this difference was particularly significant for potentially reversible neurologic conditions, which had a shorter duration even compared to psychiatric conditions ($p < 0.001$). Both potentially reversible neurologic and psychiatric conditions had a shorter duration compared to the non-reversible group ($p < 0.001$ for both). The MMSE scores were significantly higher in the potentially reversible group than in the non-reversible group ($p < 0.001$). In the sub-analyses, the MMSE score in the psychiatric conditions was significantly higher than in the non-reversible group ($p < 0.001$). There was no significant sex difference between the potentially reversible and non-reversible groups ($p = 0.88$).

Potentially reversible conditions stratified by cognitive and functional levels

Figure 1 illustrates the percentage of psychiatric and potentially reversible neurologic conditions stratified by cognitive and functional levels. As shown in Figure 1, in the normal cognitive range group, psychiatric conditions were more common than potentially reversible neurologic conditions ($p = 0.015$). In contrast, no significant differences were observed between the two groups in the MCI or dementia level groups ($p > 0.38$ for both). When comparing within each condition, the proportion of psychiatric conditions varied significantly across the three cognitive and

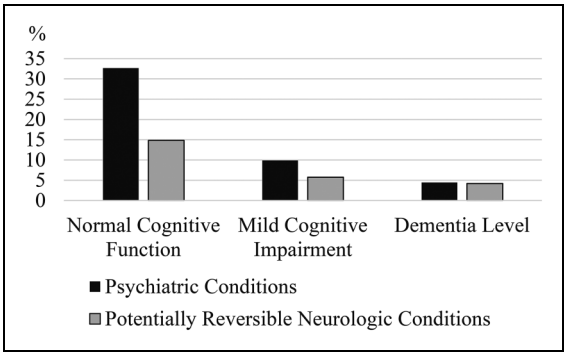

Figure 1. Percentage of psychiatric and potentially reversible neurologic conditions stratified by cognitive and functional levels.

functional levels ($p < 0.001$). Post-hoc analyses showed that psychiatric conditions were most common in the normal cognitive range group, followed by the MCI, and then dementia level groups ($p < 0.001$ for the comparison between the normal function range and MCI or dementia level groups, and $p = 0.032$ for the comparison between the MCI and dementia level groups). Similarly, the proportion of potentially reversible neurologic conditions differed across cognitive and functional levels ($p < 0.001$). Post-hoc analyses revealed that potentially reversible neurologic conditions were more common in the normal cognitive function range group compared to the MCI group ($p = 0.032$) and dementia level group ($p < 0.001$). No significant difference in the proportion of potentially reversible neurological conditions was found between the MCI and dementia level groups ($p = 1.0$).

Specific etiologies for potentially reversible conditions

Table 3 details the etiologies of psychiatric conditions ($n = 75$) and potentially reversible neurologic conditions ($n = 46$), stratified by cognitive and functional levels. Among the 75 psychiatric conditions, mood disorders were the most common (30 individuals: 26 depression, 4 bipolar disorder), followed by schizophrenia and delusional disorders (15 individuals: 9 delusional disorder, 5 schizophrenia, 1 acute and transient psychotic disorder). Neurotic, stress-related, and somatoform disorders were identified in 11 individuals (4 functional amnesia, 4 anxiety disorder, 2 acute stress reaction, 1 panic disorder). Developmental disorders affected 10 individuals (6 ADHD, 4 autism spectrum disorder), and alcohol use disorder was noted in 9 individuals. Among the 46 potentially reversible neurologic conditions, cerebrovascular disease was the most frequent (11 individuals: 8 cerebral infarction, 3 subarachnoid hemorrhage), followed by transient global amnesia (5), subdural hematoma (5), normal pressure hydrocephalus (4), epilepsy (4), delirium (4), traumatic brain injury (4), hepatic encephalopathy (3), drug-related dysfunction (3), infection-related dysfunction (2), and autoimmune encephalitis (1).

Among 73 individuals with potential reversibility in the MCI and dementia level groups, 14 (19.2%) had concurrent degenerative disorders—2 out of 38 (5.3%) in the MCI group and 12 out of 35 (34.3%) in the dementia level group. Of these 14 individuals, Alzheimer's disease was identified in 13 cases and dementia with Lewy bodies in 1 case. Regarding the potentially reversible conditions in these 14 individuals, 6 involved neurologic conditions, while 8 involved psychiatric conditions.

Actual reversibility

Among 73 individuals with potential reversibility in the mild cognitive impairment and dementia level groups, 18 (24.7%) were not followed up in our memory clinic—9 out of 38 (23.7%) in the MCI group and 9 out of 35 (25.7%) in the dementia level group. Among these 18 outpatients who did not receive follow-up, 17 had psychiatric conditions. This was primarily because they continued follow-up at their original clinics from which they were referred, rather than at our memory clinic. These 18 individuals were excluded from the following analyses. Thus, the results below were derived from the remaining 55 individuals.

During the six-month follow-up, six outpatients (10.9%) experienced cognitive resolution or improvement in their dementia symptoms, including 2 with psychiatric conditions and 4 with potentially reversible neurologic conditions (Table 4). This represented 8.0% of the 25 individuals with psychiatric conditions and 13.3% of the 30 individuals with potentially reversible neurologic conditions, all within the MCI or dementia level groups. In contrast, one individual with amnesic MCI and depression (1.8%) progressed to dementia due to Alzheimer's disease, despite near-complete improvement in her depression. Another individual (1.8%) died from incidental lung cancer. The remaining 48 individuals (87.3%) remained cognitively stabile throughout the follow-up period.

As shown in Table 4, both individuals with psychiatric conditions who experienced reversibility exhibited psychotic features. One with acute and transient psychotic disorder achieved complete improvement following antipsychotic medication, while the other, with a severe depressive episode and psychotic symptoms, showed partial improvement after electroconvulsive therapy. Among the neurologic cases, dementia symptoms in a patient with hydrocephalus fully resolved after ventriculoperitoneal shunt placement. Two patients with hepatic encephalopathy showed complete or partial improvement after Aminoleban infusion therapy, which delivered branched-chain amino acids to lower ammonia levels. Another patient with a first-time cerebral infarction experienced natural cognitive improvement.

These 6 individuals with reversibility represent 0.9% of the 630 individuals with MCI or dementia level (excluding the 18 mentioned above). As shown in Table 5, the time

Table 3. Detailed etiologies of psychiatric and potentially reversible neurologic conditions stratified by cognitive and functional levels.

			Potentially reversible conditions depending on cognitive and functional levels		
		Potentially reversible conditions combined (N = 121)	Normal Cognitive Function Range (n = 48)	Mild Cognitive Impairment (n = 38)	Dementia Mimic (n = 35)
Psychiatric Conditions (n = 75)	Mood disorders	30	11	9	10
	Schizophrenia and delusional disorders	15	4	9	2
	Neurotic, stress-related, and somatoform disorders	11	8	2	1
	Developmental disorders	10	10	–	–
	Alcohol use disorder	9	–	4	5
Potentially Reversible Neurologic Conditions (n = 46)	Cerebrovascular diseases	11	3	6	2
	Transient global amnesia	5	5	–	–
	Subdural hematoma	5	–	1	4
	Normal pressure hydrocephalus	4	–	–	4
	Epilepsy	4	1	1	2
	Traumatic brain injury	4	–	2	2
	Delirium	4	1	2	1
	Hepatic encephalopathy	3	–	1	2
	Drug-related cognitive dysfunction	3	3	–	–
	Infection-related cognitive dysfunction	2	2	–	–
	Autoimmune encephalitis	1	–	1	–

from symptom onset to examination was shorter in these six outpatients compared to those with MCI or dementia without actual reversibility ($p < 0.001$). Although the ages of these six outpatients did not differ significantly from those with MCI or dementia without actual reversibility, they tended to be younger ($p = 0.057$).

Importantly, these results do not encompass all the benefits individuals received at this memory clinic. For example, slight improvements were excluded from the reversibility section unless they met the specific criteria for cognitive reversibility outlined in this manuscript, such as transitioning from dementia level to MCI. Additionally, while psychiatric symptoms frequently improved with psychotropic drugs and/or psychosocial interventions, these improvements did not involve cognitive function and were therefore excluded from the criteria. Similar undocumented benefits were observed in potentially reversible neurological conditions. For instance, seizure frequency in epilepsy often decreased with antiepileptic drugs, and neurological functions like gait frequently improved in individuals with subdural hematoma or normal pressure hydrocephalus following hematoma removal surgery or ventriculoperitoneal shunt placement.

Discussion

Our study revealed that individuals with psychiatric conditions having potential for reversibility were younger, exhibited faster progression, and demonstrated higher cognitive function compared to those without potentially reversible conditions. These psychiatric conditions encompassed not only depression and alcohol use disorder but also schizophrenia, delusional disorders, ADHD, and dissociative amnesia. Notably, progression rates in potentially reversible neurological conditions were faster than those observed in psychiatric conditions. These findings align with previous studies indicating that younger age and faster progression are markers of potentially reversible conditions.[3,13] Furthermore, our study highlights that potentially reversible neurological conditions progress more rapidly, whereas individuals with psychiatric conditions tend to be younger and maintain relatively better cognitive function. In this study, 0.9% of individuals with MCI or dementia level were found to have truly reversible cases, consistent with previous studies that reported an actual reversibility rate of 0.6% in similar clinical settings.[13] The relatively small percentage of actual reversibility may stem from the strong association of these psychiatric and neurological conditions with dementia risk factors or their role as prodromes of dementia itself, such as depression,[72,73] neurogenerative normal pressure hydrocephalus,[78,79] or epilepsy.[80] Nevertheless, it is crucial to identify and treat potentially reversible conditions, as this can sometimes transform a person's entire life.[81] Both individuals with psychiatric conditions who

Table 4. Cases with complete resolution or partial improvement in cognitive function.

Extent of Improvement	Age/ Sex	Etiology	Improvement Details	Time from Onset to Examination
Complete Resolution	75/M	Acute and transient psychotic disorder	MCI to normal	1.5 months
	82/F	Hydrocephalus	Dementia level to normal	2 months
	70/F	Hepatic encephalopathy	MCI to normal	1 year
Partial Improvement	71/F	Depression (Severe depressive episode with psychotic symptoms)	Dementia level to MCI	2 months
	75/F	Hepatic encephalopathy	Dementia level to MCI	2 weeks
	75/F	First-time cerebral infarction	Dementia level to MCI	3 days

MCI: mild cognitive impairment.

Table 5. Actual reversibility and non-reversible conditions.

Item	Actual Reversibility (n = 6)†	Non-Reversible Conditions (n = 630)‡	p
Age	74.7 ± 4.2	78.7 ± 7.1	0.057
Sex (female, %)	83.3%	52.6%	0.41
Time from onset to examination	0.3 ± 0.4	2.0 ± 2.1	<0.001
MMSE-J	19.8 ± 4.4†	21.3 ± 5.4‡	0.32

MMSE-J: Japanese version of Mini-Mental State Examination; †psychiatric and neurologic conditions combined; ‡Includes individuals with mild cognitive impairment and dementia without actual reversibility, excluding 18 who were not followed up.

exhibited cognitive reversibility manifested psychotic features at their first visit. These findings suggest that clinicians should be particularly attentive to psychiatric conditions when examining younger individuals or those with relatively preserved cognitive function, especially if they manifest psychotic features.

Psychiatric conditions

Psychiatric conditions in our cohort included a variety of disorders that can negatively impact cognitive function.[35,36,82,83] The relationship between psychiatric disorders and memory function has been extensively studied using neuropsychological assessment tools.[84] In this regard, schizophrenia has been shown to affect working memory, processing speed, verbal learning, and visual learning. Mood disorders are associated with dysfunction in episodic memory, particularly impaired recall of positive events, as well as deficits in working memory. Anxiety disorders have also been linked to working memory dysfunction.[84] Potential neurophysiological mechanisms underlying cognitive dysfunction in psychiatric disorders mainly include: (i) Dysregulation of neurotransmitter systems (glutamatergic, dopaminergic, GABAergic, and serotonergic); (ii) Inflammatory and neurotrophic factors (IL-6, TNF-α, IL-1β, CRP, BDNF, NGF); (iii) Chronic stress, which can lead to dendritic atrophy in the hippocampus and layer 5 pyramidal cells, as well as reduced dendritic spines in the medial prefrontal cortex.[85–87] These mechanisms may overlap, contributing to the cognitive dysfunction observed in psychiatric patients at memory clinics. Schizophrenia was originally termed "dementia praecox (early-onset dementia)" by the German psychiatrist Emil Kraepelin in the late 19th and early 20th centuries to describe a group of disorders characterized by early onset and progressive cognitive decline.[88] The term "schizophrenia" was later introduced by Swiss psychiatrist Eugen Bleuler in 1911 to better reflect the disorder's primary symptoms of split or disordered thinking, rather than focusing solely on cognitive decline.[88] Consistent with this historical terminology, schizophrenia has been linked to cognitive decline.[82] Delusional disorders have traditionally been considered a psychotic syndrome that do not evolve into cognitive deterioration. However, recent studies show that patients with delusional disorder perform significantly worse on cognitive tests, revealing deficits in both executive functions and memory, suggesting that delusional disorders are also associated with cognitive impairments.[83,89,90] Delusional disorders can also manifest as prodromes of dementia.[83] In line with these perspectives, schizophrenia and delusional disorders were also identified in our memory clinic. Interestingly, previous studies have not identified clear differences in cognitive dysfunction between schizophrenia and depression,[35,36] challenging earlier assumptions. It is therefore unsurprising that many individuals with depression were categorized within the MCI and dementia level groups in our study. This was particularly true for those with depression accompanied by psychotic features, which is associated with greater cognitive impairment than depression without psychotic features.[91] In our cohort, individuals with depression involving psychotic features were exclusively placed in the MCI or dementia level groups, with none in the

normal cognitive function group. Notably, one individual with depression and psychotic features experienced cognitive improvement after electroconvulsive therapy, while another with brief and transient psychosis in the schizophrenia and delusional disorder category showed complete cognitive resolution with psychotropic medications. These cases suggest that individuals with psychotic features may achieve cognitive benefits from targeted treatments.

Alcohol use disorder was observed in the MCI and dementia level groups in our study. While alcohol-related dementia lacks distinctive pathological features, it can persist even after prolonged abstinence.[92,93] Identifying alcohol-related dementia is essential, as successful abstinence can prevent its progression.[92,93] In contrast, cognitive dysfunction in neurotic stress-related and somatoform disorders, such as dissociative and anxiety disorders, is generally milder. In our study, these conditions were often found within the normal cognitive function range. Dissociative disorders, particularly dissociative amnesia, are significant causes of functional amnesia, primarily affecting retrograde memory while sparing other cognitive functions. These preserved functions include anterograde memory, which was assessed in our neuropsychological testing, specifically through subtests of the MMSE.[94,95] This explains why all four patients with functional amnesia were categorized as having normal cognitive function. Although anxiety generally has a weaker impact on cognitive function than depression,[96] moderate to severe anxiety has been associated with reduced cognitive performance, particularly in executive function, as shown in a population-based mega-cohort study.[97] These findings may account for the milder cognitive dysfunction observed in neurotic stress-related and somatoform disorders compared to other psychiatric conditions in this study.

Psychiatric conditions in our cohort included developmental disorders, particularly ADHD and autism spectrum disorder. Several factors may explain why individuals with developmental disorders initially visit memory clinics. Persistent ADHD symptoms, such as working memory deficits, are often mistaken for MCI in older adults.[33,97,98] The underdiagnosis of ADHD in adults—especially the predominantly inattentive type rather than the hyperactive type[99,100]—combined with the cognitive demands of managerial roles, where limited working memory capacity may be exceeded, and potential age-related cognitive decline, can also drive such visits.[101] Autism spectrum disorder may be misdiagnosed as dementia due to overlapping behaviors with the behavioral and psychological symptoms of dementia.[102] Some adults develop increased autistic traits as they age,[103] further complicating differential diagnosis. Additionally, dementia and autism spectrum disorder can coexist, with the latter potentially exacerbating the behavioral and psychological symptoms of dementia.[104] Therefore, diagnosing developmental disorders remains valuable, even in individuals with existing dementia. Obtaining a developmental history from childhood is crucial for distinguishing developmental disorders from dementia, such as behavioral variant frontotemporal dementia, as symptoms of the former must manifest early in life.[28] In our cohort, individuals with developmental disorders were within the normal cognitive function range. This may be due to the relatively small difference in cognitive dysfunction between those with developmental disorders and healthy controls. For example, while working memory dysfunction is a hallmark of adults with ADHD,[98] it differs from that of healthy controls by only 0.5 standard deviations, a relatively minor difference. Thus, it is understandable that these individuals fell within the normal cognitive function range in our cohort.

Actual reversibility

To our knowledge, eight previous studies have addressed specific etiologies with actual reversibility in memory or dementia outpatient clinics.[10,11,14,16–20] In these studies, depression was the most common condition associated with either complete cognitive reversal or partial improvement, though it may later overlap with a degenerative disease.[13] Neurologic conditions with reversibility included those requiring surgical intervention (e.g., hydrocephalus, subdural hematoma), infections (e.g., neurosyphilis), toxic-metabolic conditions (e.g., vitamin B12 deficiency, drug-related cognitive dysfunction), epilepsy, endocrine disorders (e.g., hypothyroidism), and neoplasms. The etiologies in our study align with those in the previous studies, including cases of depression, hydrocephalus, and metabolic conditions. Although the proportion of reversibility is low, at 0.9% in our study and at 0.6% in the review,[13] meticulous attention should always be given to these reversible conditions.

Most of the etiologies mentioned align with potentially reversible conditions commonly observed in rapidly progressive dementias, which are primarily used to differentiate prion diseases from other dementias in specialized hospitals.[1–3] The key distinction between rapidly progressive dementias in hospitals and potentially reversible conditions in community-based memory clinics is that the latter includes a higher prevalence of hydrocephalus, subdural hematoma, epilepsy, and depression. This may be due to the fact that memory clinics can more easily detect hydrocephalus and subdural hematomas using computed tomography, while epilepsy and depression are often managed or treated within these clinics or other community-based settings, allowing for their exclusion before referral to specialized hospitals focused on prion diseases.

Limitations

Several issues must be considered before generalizing our results. While we provisionally diagnosed MCI or dementia level, diagnosing dementia requires excluding other psychiatric or neurologic conditions, which can only be confirmed

after comprehensive evaluations over time. A hasty or overly broad preliminary diagnosis may inflate reversibility rates, while a more conservative approach may lower them. Additionally, reversibility is influenced by the response to treatment of underlying conditions, such as depression or hypothyroidism. This complexity raises questions about the clinical utility of defining reversibility. Nevertheless, the primary role of memory clinics is to identify potentially reversible conditions, whether psychiatric or neurologic. In other words, our study provides examples of common potentially treatable psychiatric dementia mimics typically seen in memory clinics, which we believe are not yet widely recognized by all memory clinic practitioners. Second, although we differentiated our outpatients through detailed interviews, clinical examinations, neuropsychological testing, blood tests, and brain scans in most cases, misdiagnoses may still occur. Third, dementia diagnosis was based on clinical assessment rather than pathological proof, which could lead to discrepancies between the actual etiologies and our diagnoses. Fourth, improvements that did not meet our criteria for reversibility were excluded from this study. Setting criteria for resolution or improvement can be challenging, as previous studies have not established standardized guidelines.[10,11,14,16] We should not dismiss the potential benefits of treatment, even if it does not lead to complete resolution or substantial improvement. Additionally, improvements in psychiatric or neurological aspects other than cognitive function were not considered in this study. Fifth, there were individuals with potentially reversible conditions, particularly psychiatric ones, whom we were unable to follow up, potentially leading to an underestimation of reversibility, especially for psychiatric conditions. Lastly, while early treatment of depression during the course of dementia may lead to cognitive improvements, these initial gains can be misinterpreted as permanent reversibility, particularly if adequate follow-up is not conducted.[13] This issue may also apply to other psychiatric disorders, such as delusional disorders that can emerge during degenerative conditions,[25,26] or neurological conditions like the combination of normal pressure hydrocephalus and Alzheimer's disease, where shunt replacement can result in temporary cognitive improvement.[75] A six-month follow-up may not be sufficient in this regard. However, previous reports on this reversibility in memory clinics have not specified follow-up period, reversibility criteria, or standardized cognitive assessment methods.[10,11,14,16–20] We believe that by employing these measures, we can more easily avoid the overdiagnosis of reversibility, as improvements in depressive mode should not be conflated with improvements in cognitive function. Additionally, even if these improvements are not sustained, the temporary benefits of treatment remain valuable. Therefore, identifying reversibility, even if short-lived, remains a crucial task in clinical settings.

Conclusions

Although rare, reversible dementia mimics should be identified in memory clinics, particularly in younger individuals with rapid cognitive decline, including those with psychiatric conditions. Psychiatric conditions with psychotic features, in particular, may exhibit cognitive reversibility. The rarity of reversibility likely reflects the strong association between some of these potentially reversible conditions and dementia risk factors or their role as prodromes of dementia itself.

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Statements and declarations

Ethics approval

Ethical aspects of this study were reviewed and approved by the Human Research Ethics Committee of Ashikaga Red Cross Hospital.

Consent to participate

This retrospective observation study was conducted after informing patients about the study using an opt-out method.

Author contributions

Michitaka Funayama Conceptualization; Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Validation; Visualization; Writing – original draft; Writing – review & editing
Shin Kurose Data curation; Writing – original draft
Taketo Takata Data curation
Hiroyo Sato Data curation
Naoki Izawa Data curation; Investigation; Methodology
Kazuo Isozumi Conceptualization; Data curation; Investigation; Methodology; Project administration; Supervision
Yumi Abe Conceptualization; Data curation; Investigation; Project administration; Supervision

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Data availability

Data are available upon request. For further details, please contact the corresponding author, M.F.

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