Clinical Neurology and Neurosurgery 187 (2019) 105575

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Treatable causes of adult-onset rapid cognitive impairment

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ARTICLE INFO

Keywords:
Rapid cognitive impairment
Etiology
Treatable disorders
Cognitive outcome
Chronic
Cognitive impairment

ABSTRACT

Objectives: Acute and subacute cognitive decline, defined collectively as rapid cognitive impairment (RCI), is attributed to diverse disorders and brings great challenges for differential diagnosis. In this study we investigated the RCI patients to determine the underlying causes and the cognitive outcome of the treatable RCI.

Patients and Methods: We reviewed medical records of consecutively hospitalized patients (n = 346) with significant and new cognitive dysfunction between January 2014 and December 2015. Based on the duration of their cognitive dysfunction, patients were divided into two groups with the RCI (< 12 months) and the chronic cognitive impairment (CCI, ≥ 12 months), respectively. Etiologies of the RCI and the CCI were analyzed; the cognitive outcomes of the RCI patients with the treatable disorders were assessed in the follow-up visits.

Results: Potentially treatable or reversible causes were identified in 134 (72%) of 187 RCI patients and in 34 (21%) of 159 CCI patients. The causes in the 134 (72%) RCI patients were immune/inflammation (50, 37%), infection (30, 22%), vascular diseases (29, 22%), neoplasm (16, 12%), metabolic/toxic disorders (7, 5%), and others (2, 1%). The treatable disorders found in both the RCI and the CCI patients were vascular diseases, autoimmune encephalitis, viral encephalitis, inflammatory demyelinating diseases, Hashimoto encephalopathy, neurosyphilis, hydrocephalus, and Vitamin B12 deficiency. Total 114 RCI patients with the treatable disorders were followed up for 6 ~ 39 (median 21) months. Poor cognitive outcomes were found in 24 (21%) of the 114 followed-up patients, comprising patients with infection (1, 3%), immune/inflammation (12, 25%), vascular diseases (8, 28%), and metabolic/toxic disorders (3, 43%).

Conclusions: Treatable or reversible causes are common underlying RCI. Poor outcomes with severe cognitive deficits are considerably present in the treatable RCI patients and result in permanent dementia.

1. Introduction

Cognitive impairment (CI) refers to the decline in the cognitive function that may or may not affect patients' daily life and independence. The CI can be classified into mild cognitive impairment (MCI) or dementia based on the severity of the cognitive decline. MCI patients remain independent in their daily functional activities, while the patients with dementia, a severe type of cognitive impairment, require intensive care in their daily life and can be both physically and emotionally challenging for themselves and their caregivers. Onset of dementia is usually insidious and associated with slow progression. However, acute/subacute onset of cognitive decline is frequently encountered in clinical practice. These conditions are generally regarded as rapidly progressive dementia (RPD) [1], which may be treatable or reversible to be fully recovered. For this reason, the term RCI used in this study is referred to the conditions including the acute/subacute cognitive decline as well as the RPD. So far, the literatures regarding RCI are few and are primarily focused on the RPD and the cases of the suspected Creutzfeldt-Jakob disease (CJD) [2–7]. In these studies, the untreatable disorders such as the CJD were found to be the major cause of the RPD or the CJD mimics; treatable causes were uncommon and extremely variable.

RCI represents a collection of diverse cognitive conditions that are attributed to diverse disorders including treatable and untreatable ones, and bring great challenges for differential diagnosis. Cognitive outcome of the RCI mainly depends on the underlying causes. Dementia could develop in the treatable RCI patients if delayed in early identification due to the untypical and variable symptoms. To date, etiologies and outcome of the RCI with treatable disorders have not been well addressed. In this study we investigated the RCI and the CCI patients and demonstrated their etiologies, clinical features, and cognitive outcome of the treatable RCI patients. Our findings may help early identification and differentiation of the treatable disorders causing the RCI.

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https://doi.org/10.1016/j.clineuro.2019.105575
Received 20 January 2019; Received in revised form 26 October 2019; Accepted 27 October 2019
Available online 01 November 2019
0303-8467/

2. Patients and methods

We reviewed electronic medical records of inpatients consecutively admitted between January 2014 and December 2015 in the Department of Neurology at Xuanwu Hospital of Capital Medical University, a tertiary medical facility in Beijing. Patients with significant, new cognitive dysfunction reported by patients themselves, informants or healthcare professionals were selected. Cognitive dysfunction was manifested by memory loss, slowed mental response, and/or difficulty in speech, etc. The patients' clinical history and their neurological examination and neuropsychological assessment results were futher reviewed to confirm their CIs and meet the International Society for Vascular Behavioral and Cognitive Disorders (VASCOG) diagnostic criteria for MCI and dementia [8]. The patients were excluded if they had been admitted in the stroke units or intensive care units, or had critical illness; they were also excluded if their CI was attributed to an impaired level of consciousness, delirium, or any major psychiatric disorders such as schizophrenia and depression, or if the CI onset age was younger than 18 years. The cognitive symptom onset date was determined to be the earliest time when the symptom was first noted by patients, informants or healthcare professionals.

The RCI was defined as conditions with CI lasting < 12 months based on the onset date of the patient's first notable cognitive symptom, and CCI was defined if the CI duration is ≥ 12 months. Relevant records of the selected patients were reviewed, including their demographic and clinical data, medical history, blood and CSF laboratory tests, EEG and brain imaging data, etc. The initial symptoms were defined as the first dominantly symptoms described in the patient's medical record. If more than one diagnosis were made for the patients, the one more likely to be responsible for the CI was considered as the primary diagnosis.

In our study, treatable disease was defined as the one that can be cured, prevented, or controlled by intervention. Cognitive outcomes were assessed with follow-up by interviewing the RCI patients and their reliable informants at clinic or on telephone.

Statistical analysis was conducted using the SPSS (version 22.0). Univariate analysis of variance (ANOVA) was used to measure differences in continuous variables. When differences were detected, Fisher's protected least significant difference (PLSD) test was then applied. Differences in categorical variables were assessed using a two-tailed chi-square test. Fisher's exact test was used if one of the expected frequencies was smaller than 5. Independent samples *t* test was used to evaluate differences in continuous variables between two groups. Data are present as mean ± SD. Statistical significance was set at $P < 0.05$.

This study was approved by the institutional review board of Xuanwu Hospital. Written informed consent was obtained from all patients and their family members according to the hospital guidelines.

3. Results

3.1. Demographic and clinical characteristics of RCI and CCI patients

A total 346 hospitalized patients (187 RCI and 159 CCI) with significant, new cognitive dysfunction were identified as suitable for this study. A summary of the demographic and the clinical features of the RCI and the CCI patients are shown in Table 1. The median duration of their CIs at admission was 2 months in the RCI group (range 11 h ~11 months) and 2 years in the CCI group (range 1–20 years). The difference in the gender ratio between the RCI and the CCI groups was statistically significant ($P < 0.05$) with male patients accounting for 63% in the RCI group and 52% in the CCI group, respectively. The CI onset age tended to be younger in the RCI group. More young-onset patients (onset age < 45 years) were found in the RCI group (33%) than in the CCI group (20%, $P < 0.01$). The CI frequency at the initial manifestation was 56% in the RCI group, which was lower than the value in the CCI group (82%, $P < 0.0001$). Other initial symptoms such as seizures were found in 79% of the RCI patients compared to only 40% in the CCI group ($P < 0.0001$). Abnormal signals found in brain MRI that had diagnostic values were present in 72% of the RCI patients but only in 25% of the CCI patients ($P < 0.0001$). Brain MRIs of the most CCI patients were found to be normal or only had changes like atrophy, nonspecific white matter hyperintensities, and/or white matter degeneration.

Table 1
Characteristics of patients with rapid and chronic cognitive impairment.

	RCI (n = 187)	CCI (n = 159)	*P*
Gender(male/female)	118/69	83/76	0.041
Age at onset (y)	51 ± 16	54 ± 12	0.075
mean (range)	(18 ~ 80)	(21 ~ 79)	
< 45y	61 (33%)	31 (20%)	0.006
45 ~ 64y	89 (47%)	96 (60%)	0.017
≥ 65y	37 (20%)	32 (20%)	
Duration of CI	2 m (11 h ~ 11 m)	2y (1 ~ 20y)	
median (range)			
Initial symptoms			
CI only	40 (21%)	95 (60%)	< 0.0001
CI + /other symptoms	147 (79%)	64 (40%)	
CI as Initial symptoms	104 (56%)	130 (82%)	< 0.0001
CI only	40	95	< 0.0001
CI + Seizures	16	6	0.004
CI + Psychiatric symptoms	17	12	
CI + Focal neurologic deficits	32	16	0.0005
CI + Sleep disorders	4	1	
CI + Headache	10	0	0.0002
CI + Vertigo/ dizziness	10	2	0.0052
Other initial symptoms without CI	83 (44%)	29 (18%)	< 0.0001
Fever	22	0	0.0006
Seizures	13	3	
Psychiatric symptoms	10	5	
Focal neurologic deficits	35	14	
Sleep disorders	5	2	
Headaches	13	1	0.064
Vertigo/dizziness	3	1	
Brain MRI			
Specific changes	135 (72%)	40 (25%)	< 0.0001
Cerebral atrophy	20 (11%)	72 (45%)	< 0.0001
Normal/ Unspecific changes	32 (17%)	47 (30%)	0.006

RCI = Rapid cognitive impairment; CCI = Chronic cognitive impairment; CI = cognitive impairment.

Among the 187 RCI patients, functional decline in one cognitive domain was detected in 48 cases (26%) with living independence interfered in 27 cases. Functional decline in two or more cognitive domains was found in the other 139 RCI patients (74%) with independence affected in 116 cases. There were 44 RCI patients (24%) diagnosed as MCI and 143 (76%) cases diagnosed with dementia.

3.2. Etiology of RCI and CCI

The underlying disorders causing RCI and CCI were divided into potentially treatable and untreatable ones. The specific diagnoses were categorized and listed in Table 2. In the RCI group, the most common causes were immune/inflammation (50, 27%), infection (30, 16%), and vascular diseases (29, 16%). The less common causes were CJD (18, 10%), neoplasm (16, 9%), neurodegenerative diseases (14, 7%), genetic diseases (11, 6%), others (9, 5%), and unknown diagnoses (10, 5%). The major cause in the CCI group was neurodegenerative diseases (102, 64%).

The most common diagnoses made in the RCI group were autoimmune encephalitis (AIE, 27), viral encephalitis (VE, 22), stroke (19), CJD (18), and neoplasm (16), while, in the CCI group, the most common diagnoses were Alzheimer disease (AD, 60), frontotemporal dementia (FTD, 15), vascular cognitive impairment (VCI, 11), and Lewy

Table 2
Etiology of rapid and chronic cognitive impairment.

	RCI (n = 187)	CCI (n = 159)	*P*
Total treatable	**134 (72%)**	**34 (21%)**	< 0.0001
Immune/inflammatory	*50 (27%)*	*11 (7%)*	< 0.0001
Autoimmune encephalitis	27	3	
Inflammatory demyelinating disease	9	5	
Primary angiitis of the central nervous system	5	0	
Unspecified inflammation	5	0	
Hashimoto encephalopathy	3	2	
Behcet's disease		1	
Lupus encephalopathy	1		
Infectious	*30 (16%)*	*5 (3%)*	< 0.0001
Viral encephalitis	22	1	
Neurosyphilis	3	3	
Brucellosis	2	0	
Purulent meningoencephalitis	1	0	
Tuberculous meningoencephalitis	1	0	
Cerebral cysticercosis		1	
Unspecified	1	0	
Vascular	*29 (16%)*	*11 (7%)*	0.012
Stroke	19	0	
unspecified	10	11	
Neoplastic	16 (9%)	0	< 0.0001
Primary intracranial	11	0	
Metastatic	5	0	
Metabolic/toxic	*7 (4%)*	*3 (2%)*	
Alcholo-related	3	0	
VitB12 deficiency	1	3	
Toxic (CO or dichloroethane)	2	0	
Methylmalonic aciduria	1	0	
Other	*2 (1%)*	*4 (3%)*	
Dural arteriovenous fistulas	1	0	
Hydrocephalus	1	4	
Total untreatable	**53 (28%)**	**125 (79%)**	< 0.0001
Degenerative	*14 (7%)*	*102 (64%)*	< 0.0001
Alzheimer disease	4	60	
Frontotemporal dementia	4	15	
Lewy body dementia	0	9	
Progressive supranuclear palsy	1	3	
Parkinson disease with dementia	1	1	
Huntington disease	0	3	
Corticobasal degeneration	0	2	
Motor neuron disease	1	0	
Multiple system atrophy	0	1	
Parkinson plus syndrome	2	4	
Unspecified	1	4	
Creutzfeldt-Jakob disease	*18 (10%)*	*0 (0%)*	< 0.0001
Genetic	*11 (6%)*	*10 (6%)*	
Mitochondrial encephalopathy	6	1	
Progressive myoclonic epilepsy	2	1	
Leukoencephalopathy or leukodystrophy	0	4	
CADASIL	0	2	
Hallervorden-Spatz disease	0	1	
Unspecified	3	1	
Unknown	*10 (5%)*	*13 (8%)*	
Unspecified leukoencephalopathy	7	3	
Other	3	10	

RCI = Rapid cognitive impairment; CCI = Chronic cognitive impairment; CADASIL = Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy.

body dementia (LBD, 9).

Potentially treatable causes were identified in 134 RCI patients (72%), including immune/inflammation (37%), infection (22%), vascular diseases (22%), neoplasm (12%), metabolic/toxic diseases (5%), and others (1 dural arteriovenous fistulas and 1 hydrocephalus, 1%). In contrast, only 21% of the CCI patients (34) were caused by treatable diseases including immune/inflammation (11, 32%), vascular diseases (11, 32%), infection (5, 15%), metabolic/toxic diseases (3, 9%), and hydrocephalus (4, 12%). Treatable diagnoses made in both the RCI and the CCI groups were VCI (RCI 10, CCI 11), AIE (RCI 27, CCI 3), VE (RCI 22, CCI 1), inflammatory demyelinating diseases (IDDs, RCI 9, CCI 5), Hashimoto encephalopathy (HE, RCI 3, CCI 2), syphilis (RCI 3, CCI 3), hydrocephalus (RCI 1, CCI 4), and Vitamin B12 deficiency (RCI 1, CCI 3).

Table 3
Etiology of early-onset and late-onset rapid cognitive impairment.

	Early-onset (< 65y) (n = 151)	Late-onset (≥ 65y) (n = 36)	*P*
Gender (male/female)	96/55	22/14	
CI Duration median (range)	1.5 m (11h-11 m)	2 m (3d-6 m)	
Treatable	**113 (75%)**	**21 (58%)**	0.048
Infectious	*29 (26%)*	*1 (5%)*	0.022
Viral	21	1	
Other	8	0	
Immune/ inflammatory	*43 (38%)*	*7 (33%)*	
AIE	22	5	
IDD	7	2	
PACNS	5	0	
Other	9	0	
Vascular	*22 (19%)*	*7 (33%)*	
Stroke	14	5	
Unspecified	8	2	
Neoplastic	*12 (11%)*	*4 (19%)*	
Metabolic/toxic	*6 (5%)*	*1 (5%)*	
Other	*1 (1%)*	*1 (5%)*	
Untreatable	**38 (25%)**	**15 (42%)**	0.048
Degenerative	*6 (16%)*	*8 (53%)*	0.005
AD	2	2	
FTD	3	1	
Other	1	5	
CJD	*13(34%)*	*5 (33%)*	
Genetic	*11 (29%)*	*0 (0%)*	0.016
Unknown	*8 (21%)*	*2 (13%)*	

CI = cognitive impairment; AIE = Autoimmune encephalitis; IDD = Inflammatory demyelinating disease; PACNS = Primary angiitis of the central nervous system; AD = Alzheimer disease; FTD = Frontotemporal dementia; CJD = Creutzfeldt-Jakob disease.

Distributions of the treatable and the untreatable etiological categories in the RCI group according to their CI onset ages are shown in Table 3. Treatable conditions were more common in the early-onset RCI patients (onset age < 65 years) (75%) than in the late-onset ones (58%, $P < 0.05$). The most common treatable causes identified in the early-onset RCI patients were immune/inflammation (38%), infection (26%), and vascular diseases (19%); and the most common treatable causes in the late-onset RCI patients were immune/inflammation (33%), vascular diseases (33%), and neoplasm (19%). Infection was rarely seen in the late-onset RCI patients (5%) compared to the early-onset ones ($P < 0.05$). Untreatable conditions such as neurodegenerative diseases were more common in the late-onset RCI patients, and genetic diseases like mitochondrial encephalopathy (ME) were only found in the early-onset patients.

Based on the CI duration, the RCI group was further divided into an acute (duration < 2 months) and a subacute (duration ≥ 2 months) subgroups and shown in Table 4. The median CI duration at admission was 15 days in the acute RCI group (range 11 h ~ 1.5 months) and 4 months in the subacute RCI group (range 2–11 months). Treatable conditions were more commonly present in the acute RCI patients (84%) than in the subacute RCI patients (60%, $P < 0.001$). The most common treatable causes in the acute group were infection (30%) and vascular diseases (30%) while in the subacute group they were immune/inflammation (54%). Treatable conditions were also found in 52 out of 58 hyper-acute RCI cases (duration < 1 month) including vascular (20, 34%), infectious (18, 31%), immune/ inflammation (7, 12%), neoplasm (6, 10%), and metabolic diseases (1, 2%). The most common

Table 4
Etiology of acute and subacute cognitive impairment.

	Acute (< 2 m) (n = 92)	Subacute (≥ 2 m) (n = 95)	*P*
Gender (male/female)	61/31	57/38	
Age at onset (y)	51 ± 15 (18~80)	52 ± 16 (18~78)	
Early/late-onset	76/16	74/21	
Treatable	**77 (84%)**	**57 (60%)**	< 0.0005
Infectious	*23 (30%)*	*7 (12%)*	0.015
Viral	20	2	
Neurosyphilis	0	3	
Brucellosis	0	2	
Other	3	0	
Immune/inflammatory	*19 (25%)*	*31 (54%)*	< 0.0005
AIE	12	15	
IDDs	4	5	
PACNS	2	3	
HE	0	3	
Other	1	5	
Vascular	*23 (30%)*	*6 (11%)*	0.007
Stroke	19	0	
Unspecified	4	6	
Neoplastic	*9 (12%)*	*7 (12%)*	
Metabolic/toxic	*3 (4%)*	*4 (7%)*	
Other	0 (0%)	2(4%)	
Untreatable	**15 (16%)**	**38 (40%)**	< 0.0005
CJD	*6 (40%)*	*12 (32%)*	
Genetic	*6 (40%)*	*5 (13%)*	0.029
Mitochondrial encephalopathy	4	2	
Other	2	3	
Degenerative	*0 (0%)*	*14 (37%)*	0.004
Unknown	*3 (20%)*	*7 (18%)*	

AIE = Autoimmune encephalitis; IDD = Inflammatory demyelinating disease; PACNS = Primary angiitis of the central nervous system; HE = Hashimoto encephalopathy; CJD = Creutzfeldt-Jakob disease.

diagnoses were stroke (17, 29%) and VE (16, 28%). Untreatable disorders including ME (3, 5%) and CJD (2, 3%) were also found in the hyper-acute RCI patients.

3.3. Cognitive outcome of RCI patients with treatable neurological diseases

The long-term cognitive outcomes of the RCI patients caused by treatable neurological diseases were evaluated via follow-up as shown in Table 5. Patients were considered to be fully recovered if they were asymptomatic or able to return to previous activities and work. When patients were unable to perform certain previous activities or work but were independent during daily living activities, mildly impaired cognition was considered. Cognition was considered to be severely impaired if the patient was unable to perform most previous activities or work and lost independence for daily living activities, including severe cognitive deficits and followed by death. Favorable outcome was considered if cognition was fully recovered or mildly impaired, otherwise poor cognitive outcome was considered.

A total of 114 RCI patients caused by treatable neurological diseases were followed up for 6~39 months (median 21) (20 patients were lost to follow up). At the last follow-up, 79% of the RCI patients had favorable cognitive outcomes including 40% fully recovered and 39% mildly impaired. There were 21% RCI patients with poor outcomes. Patients with poor outcomes tended to be at higher ages (mean 54 years) than those with favorable outcome (mean 48 years, $P = 0.06$). Consistent with the finding, poor outcomes were much more commonly seen in the late-onset patients (44%, 7 out of 16) than in the early-onset ones (17%, 17 out of 98, $P < 0.05$). Poor outcomes also tended to occur more in the subacute patients (28%, 13 out of 47) than in the acute patients (16%, 11 out of 67). Patients with infectious diseases were rarely seen with poor cognitive outcomes (3%). In contrast, poor cognitive outcomes were found in 25% of the patients with immune/inflammation, in 28% with vascular disease, and in 38% with other diseases.

Table 5
Cognitive outcome of patients with RCI caused by treatable diseases.

RCI patients (n)	Fully recovered	Mildly impaired	Severely Impaired
Total (114)	**46 (40%)**	**44 (39%)**	**24 (21%)**
Male/female	24/22	25/19	17/7
Age at onset (y)	47 ± 12	49 ± 15	54 ± 17
Early/late onset	43/3	38/6	17/7
Acute/subacute	24/22	32/12	11/13
Follow up median (range) (m)	12 (12~36)	24(12~39)	21 (6~36)
Immune/ inflammatory (47)	**18 (38%)**	**17 (36%)**	**12 (25%)**
AIE (27)	10	8	9
IDDs (9)	3	4	2
PACNS (4)	3	1	0
HE (2)	1	1	0
Other (5)	1	3	1
Infectious (30)	**15 (50%)**	**14 (47%)**	**1 (3%)**
Viral (22)	11	11	0
Neurosyphilis (3)	2	1	0
Brucellosis (2)	1	1	0
Other (3)	1	1	1
Vascular (29)	**10 (34%)**	**11(38%)**	**8 (28%)**
Stroke (19)	8	7	4
Unspecified (10)	2	4	4
Metabolic/toxic (7)	**2 (29%)**	**2 (29%)**	**3 (43%)**
Metabolic(4)	1	1	2
Toxic (3)	1	1	1
DAVF (1)	**1 (100%)**	**0**	**0**

RCI = Rapid cognitive impairment; AIE = Autoimmune encephalitis; IDD = Inflammatory demyelinating disease; PACNS = Primary angiitis of the central nervous system; HE = Hashimoto encephalopathy; DAVF = Dural arteriovenous fistulas.

3.4. Characteristics of common neurological diseases causing RCI

AIE, VE, and untreatable CJD are common causes underlying RCI but sometimes difficult to differentiate from one another at onset. The major clinical features of the RCI patients with these diseases were analyzed and presented in Table 6. The difference in the CI onset ages among these diseases was noticeable with highest in CJD (~59 years) and then in AIE (~50 years) and VE (~46 years) ($P < 0.05$). The median CI duration at admission was remarkably different with ~10 days in VE, ~2 months in AIE, and ~ 4months in CJD. Acute CI was much more common in VE (91%) than in AIE (44%) and CJD (33%). Frequencies of the CI, fever and seizures as initial symptoms were also distinguishable in these diseases. Brain MRI showed abnormal signals in all CJD patients except one, but only in 59% of the AIE patients and 56% of the VE patients. Abnormal CSF tests were detected in 59% of the VE patients and in few AIE and CJD patients. Neuronal antibodies like anti-NMDA receptor and anti-LG1 were detected positive in the AIE patients but negative in the VE and CJD patients. Favorable cognitive outcomes were found in all VE patients and two-thirds of the AIE patients while all the CJD patients had poor outcomes and 14 died within 3~14 months after discharge.

Among the 22 VE patients manifested with RCI, 7 cases were diagnosed as HSE (Herpes Simplex encephalitis) and 3 cases were diagnosed as zoster encephalitis when anti-viral antibodies were detected in CSF. Other 12 cases were diagnosed as VE since anti-viral treatment was effective though anti-viral antibodies or virus DNA were not detected in the patients' CSF. The VE patients were treated with acyclovir or ganciclovir for 3–6 weeks, among which 2 cases with CI duration longer than one month were treated with acyclovir for 3 months.

Table 6
Clinical Characteristics of patients with RCI caused by AIE, VE and CJD.

	AIE (n = 27)	VE (n = 22)	CJD (n = 18)	*P*
Gender (male/female)	18/9	12/10	11/7	
Age at onset(y)	50 ± 15 (19～74)	46 ± 14 (23～69)	59 ± 11 (30～80)	0.018
CI duration median (range)	2 m (10d～7 m)	10d (2d～4 m)	4 m (14d～10 m)	
Acute/subacute	12/15	20/2	6/12	0.0012
Initial symptoms				
CI	14 (51%)	6 (27%)	11 (61%)	0.077
Seizures	13 (48%)	6 (27%)	0	0.006
Psychiatric symptoms	7	5	5	
Headache	3	5	0	
Dizziness	1	0	1	
Vomiting	1	3	0	
Fever	2 (7%)	13 (59%)	0	< 0.0001
Focal neurologic deficits	2	0	0	
Speech disorder	2	0	2	
Sleep disorders	2	0	2	
Ataxia/gait	0	0	2	
Blurred vision	0	0	2	
Brain MRI with specific changes	16 (59%)	12 (56%)	17 (94%)	0.04
Abnormal CSF	9 (33%)	13 (59%)	2 (11%)	0.018
Abnormal cell count	5	13	0	
Abnormal biochemistry	8	10	2	
Neuronal antibodies	27 (100%)	0	0	< 0.0001
Poor cognitive outcome	9 (33%)	0	18 (100%)	< 0.0001

RCI = Rapid cognitive impairment; AIE = Autoimmune encephalitis; VE = Viral encephalitis; CJD = Creutzfeldt-Jakob disease; CI = cognitive impairment.

4. Discussion

In this study we found that the RCI causes were more diverse with more complicated clinical manifestations compared to the CCI ones. Potentially treatable causes, including immune/inflammation, infection, vascular diseases, and metabolic/toxic diseases etc, were identified in 72% of the RCI patients and 21% of the CCI patients. Treatable causes were more frequently seen in the early- and acute-onset RCI patients with better cognitive outcomes. About 60% of the treatable RCI patients had unfavorable cognitive outcomes with mild or severe CI and might suffer from permanent dementia. Our findings supported that most RCI patients were treatable but could develop CCI or dementia if not diagnosed early or effectively intervened.

The frequency of treatable causes in the RCI patients was found much higher in our study compared with findings from studies regarding RPD or CJD mimics. In two studies of RPD, treatable causes were identified in 27% [2] and 40% [4] of the subjects, respectively, and both studies showed that VCI was the most common treatable diagnosis and accounted for about one third of the treatable RPD patients. Another study found only 2 out of 22 (9%) young-onset RPD outpatients (< 45 years) were caused by treatable diseases [5]. In contrast, we found that 44 out of 61 young-onset RCI patients (73%) were resulted from treatable causes (data not shown). Similar to our findings, two recent studies reported that 85% [10] and 66% [11] RPCD (rapidly progressive cognitive decline or deterioration) patients were resulted from treatable causes. In these two studies, infection was reported to be the most common treatable conditions and accounted for 51% [10] and 46% [11] of the treatable RPCD cases, respectively. Studies of RPD [6] or CJD mimics [3,7]found that treatable causes were accounted for 35% [3], 37%[7] and 49% [6] of the patients with non-prion diseases, respectively. A study confirmed by brain autopsy [3] further reported that VCI was the most common treatable diagnosis and accounted for about one third of treatable non-prion patients. Whereas another study of RPD [6] showed that immune/inflammation was the most common treatable causes and accounted for 45% of treatable patients with non-prion diseases.

The varied frequencies of treatable causes across these studies are mainly due to the different clinical setting and inclusion criteria. In our study, RCI was defined as conditions that CI duration was less than one year after onset, and patients with MCI or dementia were both included since recognizing MCI could help with early recognition of RCI. MCI patients were also included in the two RPCD studies, which could explain the higher frequency of treatable causes found in RCI or RPCD, despite the different time frame of CI used in these studies. RPD was typically referred to the conditions that progress from onset to dementia in less than 1 to 2 years [1], and only demented patients were included in the related studies, which reduced the frequency of the treatable causes in these studies. Besides, acute CI, mainly caused by infection, stroke, and immune/inflammation, was excluded in the most RPD studies, which also notably decreases the frequency of the treatable disorders in RPD.

In our study, 66% of the RCI patients with vascular disease, 71% with metabolic/toxic disorders, 33% neurosyphilis, 50% HE, and 66% IDDs had unfavorable cognitive outcomes; and 80% of patients with hydrocephalus, 75% with B12 deficiency, 52% VCI, 50% neurosyphilis, 40% HE, and 36% IDDs were also found in the CCI group. Poor cognitive outcome has been described in hydrocephalus [12], neurosyphilis [13], B12 deficiency [14], HE [15], and multiple sclerosis [16], supporting that these diseases could cause long-term or irreversible damage to cognition. On the other hand, AIE (10%), VE (4%), and other treatable diseases were rarely found in the CCI patients, implying better outcomes of these diseases. However, our follow-up revealed that 63% of the AIE patients and 50% of the VE patients had unfavorable cognitive outcomes with mild or severe CI, indicating that CCI or dementia are considerably present in these patients.

In our study, immune/inflammation was the most common cause of RCI, and AIE accounted for 54% of these patients. A study of RPD showed similar findings with AIE accounting for 60% of the patients with immune/inflammation [6]. Other studies found that immune/inflammation was the second common treatable cause of RPD or RPCD [3,4,10,11], and the frequency of AIE in this category varied from 14%4] to 23% [3]. Poor outcome was found in 25% of the patients with immune/inflammation and in 33% of the patients with AIE in our study, supporting that immune/inflammation, potentially reversible after immunotherapy, can trigger and persist irreversible damage [17]. Poor outcome was also reported in 37% [18] and 36% [19] of the patients with AIE. In two more recent studies, long-term poor outcome was found in 29% of the patients with LG1 antibodies [20] and 27% of the patients with Caspr2 antibodies [21], and early initiation and maintenance of immunotherapy may improve the outcome [19].

The second common cause underlying the treatable RCI we found in our study was infection, including VE, purulent and tuberculous meningoencephalitis, neurosyphilis, and brucellosis. VE was the most common infection found in our study (73%) as well as in one RPCD study (72%) [11] and one study of CJD mimics (36%) [3]. Neurocysticercosis, found only in the CCI patients in our study, was the most common infection (83%) of the RPCD found in an Indian study [10]. Neurosyphilis [22], brucellosis [23,24], suppurative meningitis [6], and tuberculosis [25] present as RCD or RPD were also described. Though not identified in our study, fungal infections confirmed by brain autopsy were reported in a study of CJD mimics [3].

In a study of patients with Herpes simplex encephalitis, outcome with memory impairment was reported in 69% of these patients [26]. Another study reported that 12.5% of the patients with acute VE had

poor outcome with dementia [27]. In our study we found MCI present in 47% of the patients with infection and in 50% of the VE patients, and poor cognitive outcome was only found in one patient with unknown infection but not in the VE patients. It might be due to the fact that patients with severe infections and admitted in intensive care units were excluded in our study, which could have significant influence on the long-term outcome [28]. Age, symptomatic periods, and time of treatment initiation also affect herpetic meningoencephalitis (HME) outcomes [29], and rapid diagnosis and early initiation of antiviral treatment are critical to a favorable outcome of HME [29].

Vascular conditions were reported to be the most common treatable cause underlying RPD in several studies [3,4]. In our study, contribution of vascular diseases, especially stroke, was underestimated since the patients admitted in stroke units were excluded. Even so, vascular diseases were still noted as the third common treatable cause of RCI, and 66% of the vascular RCI patients were caused by stroke, which was also the leading cause of the hyper-acute CI. Cognitive outcome after stroke has been well investigated in many previous studies. Follow-up studies showed that the prevalence of post-stroke CI (PSCI) including dementia ranged from 24% to 71% at 3 months [30–34], from 44% to 73% at 6 months [35–38], and from 16% to 61% at one year or longer [31,39–42]. A cross-sectional study in china reported that the overall prevalence of PSCI was 81% including 49% dementia and 32% MCI [43]. In our study, mild and severe CI were found in 38% and 28% of the vascular RCI patients, respectively. Despite the discrepancy in the prevalence of PSCI, these studies indicated that poor cognitive outcome was considerably present after stroke. Early intervention, such as thrombolysis, is critical to cognitive recovery and better outcome after stroke [44].

Though untreatable condition CJD were only found in 9% of the RCI patients in our study, similar to the findings in several RPD and RPCD studies [4,10,11], some AIE and VE patients at early stage were difficult to differentiate from CJD, which could delay early initiation of intervention. We found that certain clinical features, including age at onset, form of CI onset, initial symptoms, brain MRI, CSF tests, neuronal antibodies, and cognitive outcome, might facilitate differentiation of these diseases. Though seronegative AIE has been reported [9,45–47], neuronal antibodies in serum and/or CSF are crucial to exclude CJD diagnosis as antibodies against neurons were not detected in definite CJD [48]. DWI and FLAIR brain MRI have high sensitivity and specificity for CJD [49], but brain biopsy or autopsy is still required for diagnosis of definite CJD at present. A recent study reported that non-invasive detection of prion in CSF might allow definite CJD to be diagnosed [50]

There are several limitations in our study and should be mentioned. Firstly, the inherent selection bias of the study setting in a tertiary care facility lowers the reliability of frequency analysis and does not represent situation in the community. Secondly, patients admitted in the stroke units were excluded from this study, which decreased the contributions of the vascular diseases, particularly stroke, to RCI. Thirdly, most diagnoses in our study were confirmed by follow-up rather than pathology, so they should be considered with caution. Fourthly, factors other than underlying causes which might affect the outcomes of the treatable RCI, were not analyzed due to the small case number in each diagnosis. Factors associated with poor outcome of the treatable RCI should be well studied in future. Nonetheless, we found that treatable disorders such as infection, immune/inflammation, and vascular diseases were common causes underlying RCI; unfavorable cognitive outcomes were substantially present in patients with these disorders. Our findings further signify the importance of early diagnosis and effective intervention in the treatable RCI patients for better cognitive outcome.

Declaration of Competing Interest

All authors report no actual or potential conflicts of interest relating to the content of this report.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (81070874).

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Glossary

AD: Alzheimer disease
AIE: autoimmune encephalitis
CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
CCI: chronic cognitive impairment
CI: cognitive impairment
CJD: Creutzfeldt-Jakob disease
CSF: cerebrospinal fluid
DAVF: Dural arteriovenous fistulas
EEG: electroencephalogram
FTD: frontotemporal dementia
HE: Hashimoto encephalopathy
HSE: Herpes Simplex encephalitis
HME: herpetic meningoencephalitis
IDDs: inflammatory demyelinating diseases
LBD: Lewy body dementia
MCI: mild cognitive impairment
ME: mitochondrial encephalopathy
MRI: magnetic resonance imaging
PACNS: Primary angiitis of the central nervous system
PSCI: post-stroke cognitive impairment
RCI: rapid cognitive impairment
RPCD: rapidly progressive cognitive decline or deterioration
RPD: rapidly progressive dementia
VCI: vascular cognitive impairment
VE: viral encephalitis