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ABOUT COVER

Peer Reviewer of *World Journal of Clinical Cases*, Eugen Javor, PharmD, Chief Pharmacist, Lecturer, Pharmacy Department, General Hospital Bjelovar, Bjelovar 43000, Croatia. eugen.javor@gmail.com

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CASE REPORT

Human immunodeficiency virus-associated dementia complex with positive 14-3-3 protein in cerebrospinal fluid: A case report

Yun-Sen He, Xiao-Hong Qin, Min Feng, Qin-Jiang Huang, Meng-Jun Zhang, Li-Li Guo, Ming-Bin Bao, Ye Tao, Hong-Yuan Dai, Bo Wu

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Yun-Sen He, Department of Neurosurgery, Sichuan Lansheng Brain Hospital & Shanghai Lansheng Brain Hospital Investment Co., Ltd., Chengdu 610036, Sichuan Province, China

Xiao-Hong Qin, Meng-Jun Zhang, Department of Psychiatry, Sichuan Provincial Center for Mental Health, Chengdu 610072, Sichuan Province, China

Min Feng, Department of Geriatrics, Municipal People's Hospital in Luzhou, Luzhou 646000, Sichuan Province, China

Qin-Jiang Huang, Department of Neurosurgery, Wenjiang District People's Hospital of Chengdu, Chengdu 611100, Sichuan Province, China

Li-Li Guo, Ming-Bin Bao, Ye Tao, Bo Wu, Department of Neurosurgery, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China Chengdu, Chengdu 610072, Sichuan Province, China

Hong-Yuan Dai, Department of Neurology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu 610072, Sichuan Province, China

Corresponding author: Hong-Yuan Dai, MD, Chief Physician, Doctor, Department of Neurology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, No. 32 West Section 2, First Ring Road, Chengdu 610072, Sichuan Province, China. dhydaihongyuan@sina.com

Abstract

BACKGROUND

Human immunodeficiency virus (HIV)-associated dementia (HAD) is a subcortical form of dementia characterized by memory deficits and psychomotor slowing. However, HAD often presents with symptoms similar to those of Creutzfeldt-Jakob disease (CJD), particularly in patients with acquired immune deficiency syndrome (AIDS).

CASE SUMMARY

We report the case of a 54-year-old male who exhibited cognitive dysfunction and secondary behavioral changes following HIV infection and suspected prion exposure. The patient was diagnosed with HIV during hospitalization and his cerebrospinal fluid tested positive for 14-3-3 proteins. His electroencephalogram showed a borderline-abnormal periodic triphasic wave pattern. Contrast-enhan-

ced magnetic resonance imaging revealed moderate encephalatrophy and demyelination. Initially, symptomatic treatment and administration of amantadine were pursued for presumed CJD, but the patient's condition continued to deteriorate. By contrast, the patient's condition improved following anti-HIV therapy. This individual is also the only patient with this prognosis to have survived over 4 years. Thus, the diagnosis was revised to HAD.

CONCLUSION
In the diagnostic process of rapidly progressive dementia, it is crucial to rule out as many potential causes as possible and to consider an autopsy to diminish diagnostic uncertainty. The 14-3-3 protein should not be regarded as the definitive marker for CJD. Comprehensive laboratory screening for infectious diseases is essential to enhance diagnostic precision, especially in AIDS patients with potential CJD. Ultimately, a trial of diagnostic treatment may be considered when additional testing is not feasible.

Key Words: HIV-associated dementia; Cognitive dysfunction; Creutzfeld-Jakob disease; Rapidly progressive dementia; Case report

Core Tip: In the present case report, we excluded an extremely rare patient with human immunodeficiency virus (HIV) and cerebrospinal fluid 14-3-3 protein-positive. Unlike the previously reported 7 cases, our patient had sustained improvement with anti-HIV therapy and was also the only patient in this entity to survive. Consequently, our report provided a completely different reference for managing rapidly progressive dementia in particular cases.

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INTRODUCTION

Human immunodeficiency virus (HIV)-associated dementia (HAD) is subcortical dementia characterized by memory deficits and psychomotor slowing, which occurs after the brain is infected with the HIV[1]. Cognitive dysfunction is a common symptom in patients with acquired immune deficiency syndrome (AIDS) and non-opportunistic infections caused by other viruses. Creutzfeldt-Jakob disease (CJD), also known as Cortico-striatum-myeloid degenerative disease, is characterized by mental disorders, dementia, Parkinson-like manifestations, ataxia, myoclonus, and muscle atrophy. CJD is a chronic and progressive disease caused by a rare infection with the prion protein[2]. Additionally, the cerebrospinal fluid (CSF) 14-3-3 protein is an essential marker for diagnosing CJD.

Here, a rare case is presented of a patient with AIDS and a positive 14-3-3 protein[2]. Although similar cases have been reported[3-7], this case provides new insights and is an important learning point for managing patients with rapidly progressive dementia due to its distinct diagnosis, treatment, and efficacy.

CASE PRESENTATION

Chief complaints

A 54-year-old male (Han ethnicity) presented to the neurology clinic of our institution with a 6 mo history of slurred speech that had worsened over the past 3 months.

History of present illness

The patient had suffered from memory disturbances for more than 1 year, with symptoms primarily including progressive memory loss and episodic anterograde amnesia. Additionally, he had developed an unstable gait. Initially diagnosed with brain atrophy, his symptoms had intensified after treatment at another facility, from which no case report was provided. One year prior, the patient had exhibited unclear speech, pain at the base of the tongue, and general malaise.

Additionally, dizziness, and left ear tinnitus were occasionally noted but he did not present physical signs of dysphagia or choking. The patient rejected therapy until 3 months ago when the above conditions were aggravated and the patient became unable to take care of himself. During the first consultation in our clinic on July 13, 2018, the patient demonstrated advanced manifestations of unsteady gait with one reported fall (details unavailable); severe cognitive dysfunction; hypopsychosis, which gradually became silent; and significantly decreased speech. Functionally, the patient

was unemployed and lost self-care ability.

History of past illness

The patient's past medical history was unremarkable.

Personal and family history

The patient had no history of exposure to toxic substances or family history of specific genetic diseases.

Physical examination

The patient was alert and entered the ward with a normal gait. He exhibited slurred speech, uncontrolled frowning, and pursing of the lips. Neurological deficits were noted, including impairments in memory, orientation, reasoning, and emotional expression. Meningeal signs were absent. The pharyngeal reflex was diminished, limb muscle tone was heightened, the Babinski sign was positive, and there was evident dysmetria on the finger-to-nose test (more pronounced on the left side) and the heel-to-knee test. Additionally, the patient tested positive for the Romberg sign, but there were no signs of tongue deviation or other pathological indicators.

Laboratory testing

Upon his admission, the family reported abnormality on the Mini-Mental State Examination and Montreal Cognitive Assessment tests during a previous assessment at another hospital, although the medical records from that visit were not available to us. Following his admission, an initial HIV antibody screening returned positive results, prompting us to perform a confirmatory HIV antibody test on the patient's blood (the final results were pending at that time). Laboratory tests indicated leukocytopenia with a white blood cell count of 3.2×10^9/L and lymphocytes at 0.96×10^9/L. Analysis of T cell subsets showed a T helper (TH)/T suppressor (TS) ratio of 0.1, with TH/inducer (cluster of differentiation 4 [CD4]) cells at 78/μL and TS/killer (CD8) cells at 1218/μL. In addition, the patient's CSF protein concentration was elevated at 0.73 g/L. The CSF cell count was normal, and extensive CSF testing for biochemical markers, routine cultures (including bacteria, fungi, *Mycobacterium tuberculosis*, and *Cryptococcus*), and antibodies associated with autoimmune and paraneoplastic encephalitis all returned negative results. Liver and kidney functions were normal, as were tests for anti-thyroid peroxidase antibody, anti-thyroglobulin antibody, ceruloplasmin, anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, folic acid, and vitamin B12 levels. The CSF tested positive for the 14-3-3 protein, and genotyping confirmed 129 M/M and 219 E/E variants (Figure 1). An electroencephalogram (EEG) showed borderline abnormalities with periodic triphasic waves, which were not indicative of a typical disorder.

Imaging examination

Cranial computed tomography (CT) revealed cerebral atrophy and demyelination abnormalities in the white matter (Figure 2), given the multiple pinpoint hypodensities within the white matter exhibited in the bilateral basal ganglia with non-enhancement in all lesions and was initially diagnosed with lacunar infarction (Figure 2A). Medium encephalatrophy imaging accompanying white matter demyelination around the bilateral cerebral ventricle on T2-weighted images with pre-contrast c-magnetic resonance imaging (MRI) (Figure 2B). Meanwhile, 3–5 punctate hypodense lesions were identified in the bilateral basal ganglia on post-contrast MRI scans, with no evidence of enhancement (Figure 2C). Furthermore, the diffusion-weighted imaging (DWI) sequences on MRI did not display the characteristic "satin-like" high signal (Figure 2D).

FINAL DIAGNOSIS

HIV-associated dementia.

TREATMENT

The patient's condition worsened while awaiting a conclusive AIDS diagnosis. We treated the patient with symptomatic treatment and amantadine (Amantadine Hydrochloride Tablets, USP) for CJD, which was the initial diagnosis considered. Despite these measures, the patient's health continued to decline. During this period, confirmatory tests for HIV antibodies returned positive results.

The patient was subsequently transferred to a specialized local center for infectious disease control to receive targeted treatment. Over the course of 4 years, the anti-HIV regimen provided by the center consisted of efavirenz (600 mg daily), tenofovir disoproxil (300 mg daily), lamivudine (100 mg daily), and compound sulfamethoxazole tablets (480 mg twice a day). The patient experienced rapid amelioration of symptoms following the commencement of antiretroviral therapy during his hospital stay.

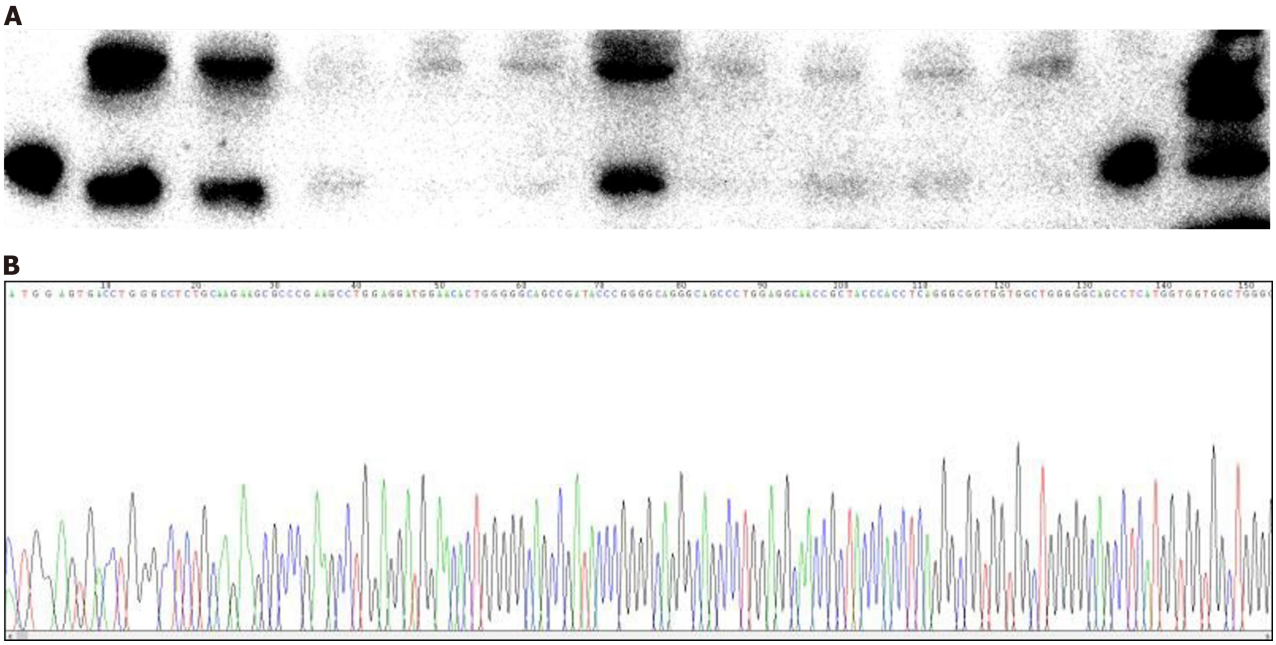

Figure 1 The 14–3–3 protein was found in cerebrospinal fluid, and 129 M/M and 219 E/E genotype was further verified. The 14-3-3 protein was positive, and the protein gene test showed M/M type.

OUTCOME AND FOLLOW-UP

Four years later, during a comprehensive outpatient follow-up assessment the patient exhibited clear consciousness and coherent speech; while recent memory and emotional expressiveness were mildly diminished, they were only marginally below the normal range; and the orientation and logical thinking functions were unremarkable. The limb muscle tension slightly increased, and the muscle strength was normal. The neurological signs and other symptoms were normal. The neuroradiological re-examination of the c-MRI (Figure 2E) revealed that the mild cerebral atrophy accompanying obvious demyelination in the white matter around the bilateral cerebral ventricle had improved than previous imaging. Additionally, several punctate hypointense lesions were spotted in the bilateral basal ganglia, exhibiting no enhancement (Figure 2F). The comparative scales and additional assessments conducted before and after treatment are summarized in Table 1.

DISCUSSION

CJD is a degenerative central nervous system disease caused by prion proteins, mainly manifested as advancing dementia, myoclonus, cerebellar ataxia, and akinetic mutism[8]. The average survival from onset to death is only a few months[3-7]. According to its etiology, CJD is mainly divided into four types: Sporadic (accounting for approximately 85%), hereditary/family (5%-15%), iatrogenic, and variant (0%-10%)[2]. Sporadic (sCJD) hinges on rapidly progressive cognitive decline, verified through neuropathological examination or supportive immunochemical or biochemical markers. For a tentative diagnosis of sCJD, clinical symptoms must be corroborated by additional tests, such as an EEG showing periodic sharp wave complexes, DWI exhibiting the ribbon sign, elevated 14-3-3 protein levels in the CSF, and a positive real-time quaking-induced conversion (RT-QuIC) test[9].

In their comprehensive review of the literature from 1995 to 2011, Muayqil *et al*[10] analyzed 38 studies involving 1849 suspected cases of sCJD with 14-3-3 protein assays conducted. Their findings indicated that the 14-3-3 protein is a valuable diagnostic marker for sCJD with a sensitivity of 92% and specificity of 80%. Furthermore, the detection of prions through RT-QuIC has demonstrated enhanced diagnostic accuracy, boasting a sensitivity of 96% and specificity reaching 100%[11,12].

MRI sensitivity is 80% in CJD[9,11,13,14], Some studies put the sensitivity as high as 92% to 98%[15-17]. At the same time, its specificity is 74%–98%[9,13].

Periodic sharp-wave complexes (PSWCs) at a frequency of 1 Hz are a hallmark EEG pattern for CJD, demonstrating a sensitivity of 64% and a specificity of 91% in diagnosis[18]. The molecular classification of sporadic CJD hinges on polymorphisms at codon 129 (M and V) and the PrP^Sc glycotype (1 and 2), leading to distinct molecular subtypes such as MM1 and MV1[9]. Crucially, a single somatic mutation in the prion protein (PRNP) gene, specifically at M129V and E2-19K, is implicated in CJD pathogenesis[19]. The frequency of this gene mutation varies across ethnicities, with the Han population showing a higher propensity for the 129 M/M genotype, which correlates with an earlier disease onset. Notably, typical PSWCs generally manifest in the later stages of the disease and are less common in MV2, VV2, and MM2 subtypes[9].

Table 1 Comparison of conditions between before and after treatment with anti-human immunodeficiency virus

Test items	Before	After
MoCA	16	25
ADL	25	70
Muscle strength	V	V
Hypertonia	(+)	Improvement
Pathological reflex	(-)	(-)
Neuroradiology	(+)	Improvement

ADL: Activities of daily living; MoCA: Montreal Cognitive Assessment.

In such cases, the diagnosis of probable CJD should meet the criteria for symptomatology, ancillary tests, and exclusion. Symptomatically: First: Rapidly progressive cognitive impairment. (1) Myoclonus; (2) Visual or cerebellar disturbance; (3) Pyramidal or extrapyramidal signs; and (4) Akinetic mutism. Ancillary criteria include: (1) Typical EEG; (2) Typical brain MRI; and (3) Positive CSF 14-3-3. Simultaneously, other possible diseases must also be excluded. Possible diagnostic criteria for CJD must meet the first and second symptoms (at least two), a positive criterion on a combined auxiliary test. Of course, other possible diseases must be ruled out to be diagnosed as probable CJD. A probable diagnosis of CJD is sufficient, in addition to meeting the criteria for the first and second symptoms (at least two), with a duration of less than 2 years. The PRNP test demonstrated M/M type, which increased the suspicion of CJD. Despite the strong consideration of HAD in this patient, the likelihood of probable CJD should still be taken into account during their hospital stay.

HAD is a common neurological complication after HIV infection and is mainly associated with memory impairment, motor coordination difficulties, cognitive deficits, difficulty performing complex tasks, and behavioral changes, including apathy and atypical reactions[1,20].

Most patients initially present with only short-term memory disorders in the early stages of AIDS; however, as the disease progresses, HIV-related chronic inflammation and immune activation may affect multiple brain regions. This can lead to dysfunctions in memory, cognition, language expression, and comprehension. With the widespread application of highly active antiretroviral therapy, the life expectancy of patients with HIV has significantly increased. Despite this, the incidence of moderate neurocognitive impairments remains high. A possible reason is that most anti-HIV drugs do not efficiently cross the blood-brain barrier to enter the central nervous system (CNS), resulting in insufficient drug concentrations in the CNS. Combined with the environmental factors within the CNS, HIV is prone to mutation, and the chronic accumulation of neurotoxicity leads to moderate neurocognitive dysfunction[20].

In this case, the diagnosis was considered infectious dementia combined with the medical history of the patient and auxiliary examination. The prime suspect was HIV, based on the following. Both HIV antibody screening test and HIV antibody confirmatory tests were positive. The apparent symptoms, including memory disorders, slowed mental processing, and behavioral disorders, were the primary symptoms of HAD, and there was a significant decrease in the patient's ability to perform daily activities. Regarding neuroradiology, CT and c-MRI revealed brain atrophy, demyelination, and white matter changes without enhancement. Consequently, the information above was consistent with HIV infection.

Four years after initiating anti-HIV treatment, we noted improved cognitive function and self-care abilities. However, memory remained worse than before; therefore, it is possible that prions may also play a role in the patient's rapid progressive dementia (RPD), Additionally, we speculate that HIV and CJD are not entirely coincidental as previously suggested[4,6].

Patients with co-infection of HIV and prions are very rare. To the best of our knowledge, only 5 cases have been diagnosed to date, and 3 others including our patient are highly suspected (Table 2). Unlike previously reported cases, our patient demonstrated sustained improvement following anti-HIV therapy and is the only known survivor. Our report provides a completely different reference for managing such cases.

The first patient was published by Babi *et al*[4] in 2016. The patient had well-controlled chronic AIDS. The elderly man passed away 3 months after a positive 14-3-3 protein test in the CSF, and a diagnosis of sCJD was confirmed histopathologically by autopsy. Subsequent reports indicate that all patients with similar conditions died within 2 months to 13 months[3,5-7,21]. In 3 of these cases, the diagnosis of sCJD was also confirmed by autopsy[3,7,21], and variant CJD in 1 case[21]. In the remaining 2 cases, autopsies were unavailable, but CJD was highly suspected[5,6]. The majority of these authors concur that there is no direct evidence linking HIV infection and prion diseases; however, further investigation is needed[4,6,7,21]. Abu-Rumeileh *et al*[3] concluded that RT-QuIC should be utilized as a specific screening tool for progressive dementia, while Dahy *et al*[5] contend that screening for sCJD should be mandatory in young patients with dementia who are living with HIV.

In our case, the patient's symptoms improved following anti-AIDS treatment, reducing the likelihood to be diagnosed with CJD (Table 1). Although 7 patients documented in previous reports shared similarities with the current case, presenting with AIDS and positive 14-3-3 protein, they were ultimately confirmed to have CJD *via* autopsy (Table 2).

In patients without routine HIV screening tests, RPD and positive 14-3-3 protein in CSF may easily lead to a misdiagnosis of CJD. Neurologists should exert every effort to determine the cause of RPD during diagnosis. Positive 14-3-3

Table 2 Difference between a previous case report about rapidly progressive dementia with human immunodeficiency virus and current report

Ref.	Pt	Sex	Age	Race/Region	Symptoms	Examination	Diagnosis	Management	Outcomes
Babi *et al*[4]	2016	Male	66	United States	Conceptual apraxia, apathy, memory impairment, and gait disturbance, ataxia with gait disturbance, chronic peripheral neuropathy	CSF: 14-3-3(+); T-Tau(+); RT-Qu IC(+); MRI: signal abnormalities in the bilateral caudate, putamen, and thalami, as well as gyriform cortical; EEG: (-); PRNP: N/A; Autopsy: CJD	Sporadic CJD	Palliative care	Passed away (3 months)
Eimer *et al*[7]	2018	Male	59	Caucasian	Mildly disoriented being insecure about the situation and location	CSF: 14-3-3(+); MRI: signal abnormalities in the caudate nuclei, frontal cortex, and parietal cortex bilaterally; EEG: periodic triphasic spike and wave complexes; PRNP: M129V; Autopsy: CJD	Sporadic CJD	Palliative care	Passed away (2 months)
Abu-Rumeileh *et al*[3]	2018	Male	62	Italy	Drowsy, with reduced verbal fluency, miotic reagent pupils, and a mask face. Axial and limb plastic hypertonia and dystonia of both hands	CSF: 14-3-3(+); MRI: cortical atrophy and multiple white matter lesions. EEG: pseudo-periodic slow spike discharges; PRNP: N/A; Autopsy: CJD	Sporadic CJD	Palliative care	Passed away (4 months)
De Carvalho Neto *et al*[6]	2019	Male	52	Caucasian	Progressive imbalance, motor and cognitive deterioration and hypersomnia	CSF: 14-3-3(+); MRI: cortical gyri_x005f form restriction on both hemispheres; EEG: triphasic PSWC; PRNP: N/A; Autopsy: N/A	Probable sporadic CJD	Palliative care	Passed away (greater than 2 months)
van de Ven *et al*[21]	2019	Male	63	Black Zimbabwean	Progressive difficulties with decision-making, obsessive compulsive disorder and visual hallucinations	CSF: 14-3-3 (weakly+); MRI: bilateral abnormal signal within the posterolateral thalami compatible with pulvinar sign; EEG: Diffuse excess of slow activity; PRNP: M129V; Autopsy: CJD	Variant CJD	Palliative care	Passed away (10 months)
Dahy *et al*[5]	2021	Male	52	Brazil	Global cerebellar syndrome, bilateral Babinski, 4-limb paratonia and release of face axial reflexes. The memory, attention and executive function deficits	CSF: 14-3-3(+); MRI: bilateral hyper intensity of images in caudal nuclei; EEG: (-); PRNP: M129V; Autopsy: N/A	Probable sporadic CJD	N/A	Passed away (13 months)
Dahy *et al*[5]	2021	Male	61	Brazil	Asthenia, lack of appetite, difficulty sleeping and occasional memory lapses, uncoordinated steps, visual delusions and bladder incontinence	CSF: 14-3-3(+); MRI: bilateral cortical ribboning in the cerebral cortex; PRNP: N/A; EEG: N/A; Autopsy: N/A	Probable sporadic CJD	N/A	Passed away (5 months)
Current report	2022	Male	54	Han/China	Progressive hypomnesis, paroxysmal anterograde amnesia, unsteady gait	CSF: 14-3-3 (weakly+); MRI: Bilateral abnormal signal within the posterolateral thalami compatible; EEG: Borderline abnormality of the periodic triphasic wave; PRNP: 129 M/M; Autopsy: N/A	Probable ADC	Anti-HIV	Improved and following-up

ADC: AIDS dementia complex; CJD: Creutzfeldt-Jakob disease; CSF: Cerebrospinal fluid; EEG: Electroencephalogram; HIV: Human immunodeficiency virus; N/A: Not available; PRNP: Prion protein gene; PSWC: Periodic sharp and slow wave complex; Pt: Publish time.

protein expression is of great value in CJD diagnosis, but it also has some limitations and presents interference. Re-evaluation of the CSF 14-3-3 protein or an RT-QuIC test should be considered to enhance diagnostic accuracy when additional examinations are not available for such rare cases.

CONCLUSION

HAD and CJD are easily misdiagnosed. In the etiological diagnosis of RPD, it is vital to exclude as many causes as possible and, if necessary, perform an autopsy to minimize diagnostic bias. The 14-3-3 protein should not be regarded as the only marker for CJD. Comprehensive laboratory screening for infection markers is essential to enhance diagnostic pre-

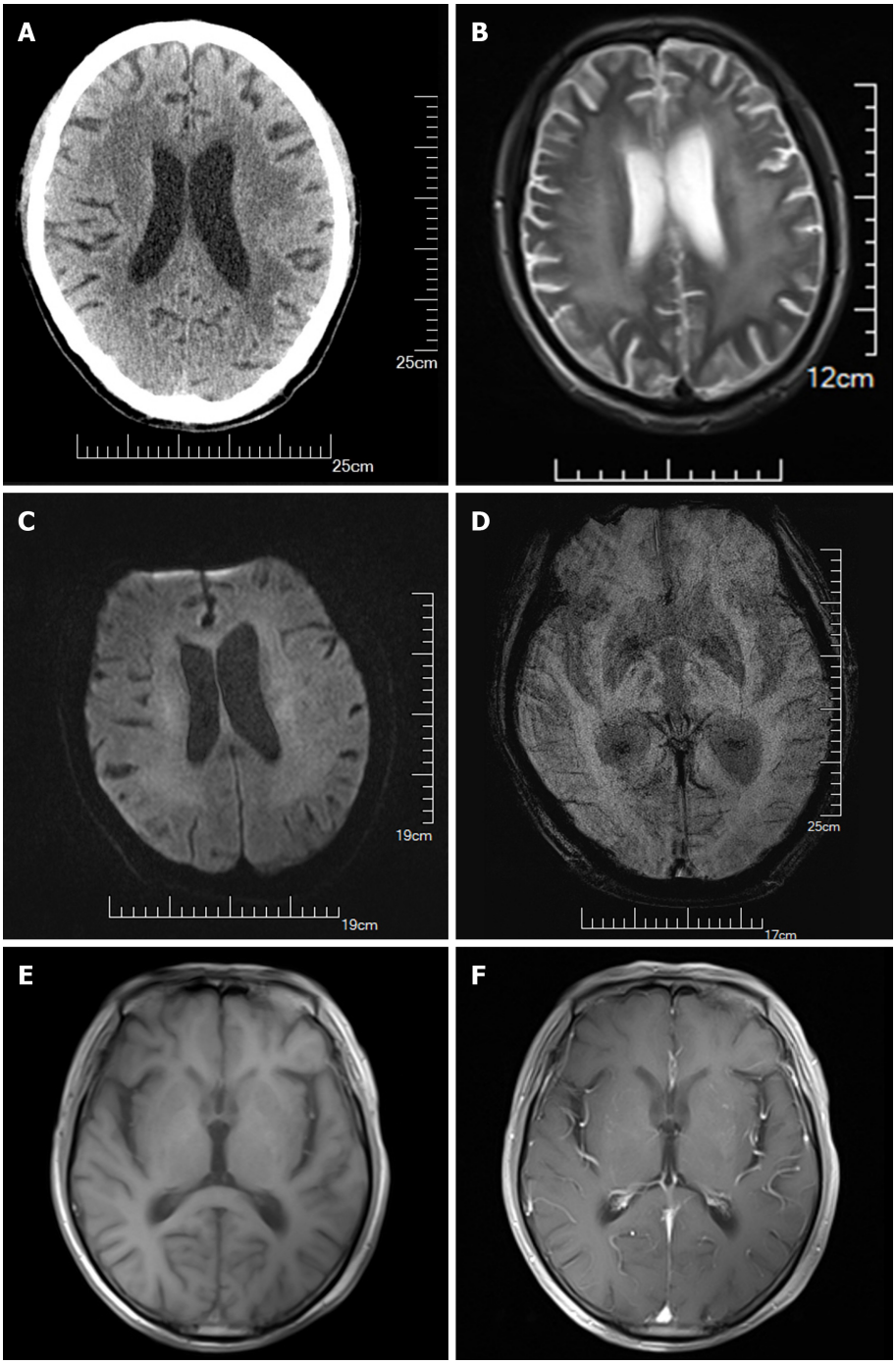

Figure 2 Pre- and post-treatment cranial imaging examinations of the patient. A-D: Neuroradiological presentation of this patient before treatment; The brain computed tomography reveals encephalatrophy and demyelination in the white matter (A); Axial T1-weighted brain magnetic resonance imaging (MRI) with pre-contrast shows mild encephalatrophy and demyelination around the bilateral cerebral ventricles (B); Axial T1-weighted brain MRI with post-contrast displays no enhancement of any lesions (C and D); E and F: Neuroradiological presentation of this patient after treatment; Axial T1-weighted brain MRI with pre-contrast illustrates slight encephalatrophy and the significantly improved demyelination in the white matter around the bilateral cerebral ventricles (E); Axial T1-weighted brain MRI with post-contrast demonstrates no enhancement in any of the lesions (F).

cision, particularly in cases where AIDS coexists with CJD. Furthermore, a trial of diagnostic treatment may be beneficial when additional diagnostic tests are not accessible.

FOOTNOTES

Co-first authors: Yun-Sen He and Xiao-Hong Qin.

Co-corresponding authors: Hong-Yuan Dai and Bo Wu.

Author contributions: Min F contributed to investigation, writing – original draft, review and editing; Huang QJ, Zhang MJ, Bao MB, Tao Y, Wu B, and Dai HY contributed to writing – review and editing; He YS, Qin XH, Min F, Huang QJ, Zhang MJ, Bao MB, Tao Y, and Wu B contributed to data curation; He YS, Qin XH, Min F, and Wu B contributed to methodology; He YS, Qin XH, Huang QJ, Zhang MJ, Bao MB, Tao Y, and Dai HY contributed to the resources; Tao Y contributed to funding acquisition; Dai HY contributed to conceptualization. He YS and Qin XH contributed equally to writing the original draft and to formal analysis, and merit co-first authorship. Dai HY and Wu B have each made distinct contributions to this case report, encompassing clinical treatment and the writing of the case report, respectively, and merit co-corresponding authorship; Dai HY was involved in the clinical treatment and the extended follow-up of this case, as well as verifying the authenticity of clinical data and patient outpatient consultations; Wu B participated in the search for relevant literature, guided the writing of this case report, and was involved in editing, proofreading, and submitting the manuscript. All authors have read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report.

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ORCID number: Hong-Yuan Dai 0000-0002-7249-4113; Bo Wu 0000-0003-3448-267X.

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