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Developments in auxiliary examination of Creutzfeldt-Jakob disease

Wei Zhao[1,2], Jiao-Jiao Jiang[1], Jia-Tang Zhang[1]

[1]*Department of Neurology, Chinese People's Liberation Army General Hospital, Beijing 100853, China.*
[2]*Shijingshan Teaching Hospital of Capital Medical University, Beijing Shijingshan Hospital, Beijing 100043, China.*

Correspondence to: Prof. Jia-Tang Zhang, Department of Neurology, Chinese People's Liberation Army General Hospital, No.28 Fuxing Road, Haidian District, Beijing 100853, China. E-mail: edwin-zhang@263.net

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Prof. Jia-Tang Zhang, is a Chief Physician, Department of Neurology, Chinese People's Liberation Army (PLA) General Hospital. He is the committee member of Neurology Branch of Chinese Medical Association and of other neurology academic societies. As the director, he takes charge of 5 national and PLA's research projects and has 21 SCI articles published. His main studies focus on: the infectious disease in central nervous system, precision medicine in cerebrovascular disease, neurological severe disease and neuropsychology.

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ABSTRACT

Creutzfeldt-Jakob disease (CJD), which is caused by prion scrapie protein, is a rare, chronic, transmissible and fatal disease. Clinical manifestations of CJD include rapidly progressive dementia, cerebellar ataxia, visual disturbance, as well as pyramidal and extrapyramidal tract signs. Four subtypes of CJD have been reported, including sporadic, familial or genetic, iatrogenic and variant. Given the infectiousness and high mortality of the disease, it is imperative that earlier and more accurate diagnostic methods are developed. In the past years, 14-3-3 protein testing and periodic sharp wave complexes in electroencephalogram have been widely used in CJD clinical diagnosis; and the abnormal hyper-intensity in diffusion weighted imaging has also been used. Recently, there has been a focus on the diagnostic value of 18F-fluorodeoxyglucose positron emission tomography/computed tomography. New findings of potential biomarkers in cerebrospinal fluid and decreases in diffusion tensor imaging measures have emerged as having an association with CJD. Magnetic resonance spectroscopy has also drawn attention as an emerging method for diagnosis. In this review, the progress in auxiliary examinations of CJD is discussed and the potential, future diagnostic methods are introduced.

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a rare human transmissible spongiform encephalopathy with a subacute disease course, a long incubation period and a mortality rate of 100%. CJD is associated with central

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nervous system (CNS) degeneration that manifests as rapidly progressive dementia, cerebellar ataxia, visual disturbance, and pyramidal/extrapyramidal tract signs, *etc*. Relatively rare symptoms of CJD include epilepsy, bulbar palsy, amyotrophy and stroke-like episodes. Onset of disease in most patients is at 64-66 years and death typically occurs 1-2 years thereafter. The causative agent in CJD is prion scrapie protein (PrPsc), which results from the misfolding of prion protein and is able to self-replicate.

Four subtypes of CJD have been reported, including sporadic (sCJD), familial or genetic (fCJD or gCJD), iatrogenic (iCJD) and variant (vCJD). sCJD is the most common type and accounts for 85-95% of all cases.[1] It occurs worldwide without geographic or seasonal clustering,[1,2] and may arise because of random mutation or post-translational modification of the PrP gene (PRNP). Based on the genotype and biochemical properties, sCJD is classified into six different molecular strains: MM1, MM2, MV1, MV2, VV1, and VV2.[3,4] MM1/MV1 is the most common and typical type with 60-70% of sCJD and has very high positive rate in magnetic resonance imaging (MRI), periodic sharp wave complexes (PSWCs) and 14-3-3 protein testing. VVI is negative in PSWCs and has a longer duration of illness-about 21 months.[3-6] fCJD accounts for about 10% of prion disease cases.[7] It shows autosomal dominant inheritance of mutations in PRNP with high penetrance，and over 50 different mutations in PRNP have been found.[8] The common form of fCJD results from mutation at codon 200, and the phenotype in patients is similar to that of sCJD.[9] Some other forms of fCJD with the phenotype different from sCJD have been classified as distinct types such as Gerstmann Sträussler-Scheinker disease (GSS) and fatal familial insomnia (FFI).[5] GSS even could have a much longer disease duration lasting 5 years. The first iCJD case (a person who was infected by corneal transplant from a CJD patient) was reported in 1974.[10] CJD can be transmitted by intracerebral electrodes, corneal transplantation, dura mater grafts, injections of growth hormone extracted from human pituitary glands and contaminated neurosurgical instruments. Blood transfusion or blood products of CJD patients are also infectious.[11] vCJD was first described in 1996, and was associated with ingestion of beef with bovine spongiform encephalopathy (BSE). After the spread of BSE in the UK and the transmission to humans in 1980s-1990s, the secondary spread of the disease appeared in the 2000s from asymptomatic infected individuals to others by routes such as blood transfusion or organ grafting.[12-14] vCJD has different manifestations from sCJD such as younger age at onset (28-29 years, mean), longer disease course (14 months, mean), prominence of psychiatric and sensory symptoms, and negative of PSWCs.[5]

The clinical manifestations of CJD lack specificity, thus it is difficult to distinguish from other dementia diseases such as Alzheimer disease, autoimmune encephalitis, neurologic paraneoplastic syndrome and hepatolenticular degeneration, just depending on clinical symptoms. And the detection of PrP or the genetic diagnosis has not been extensively used clinically. Therefore, auxiliary examinations are important for accurate diagnosis of CJD. 14-3-3 protein testing and electroencephalogram (EEG) are the traditional technologies that are widely used. Diffusion weighted imaging has been intensively studied, which has a high sensitivity and plays a significant role in diagnosis. Recently, scientists propose some emerging auxiliary examination methods, such as the new biomarkers in cerebrospinal fluid (CSF), diffusion tensor imaging, magnetic resonance spectroscopy and 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT). We make a review on the progress of auxiliary examinations on CJD as follows.

AUXILIARY EXAMINATION

CSF biomarkers

14-3-3 protein is the most widely used CSF biomarker for CJD diagnosis. It has the highest expression in neuron synapses and plays a role in signal transduction, neurotransmission, cell differentiation and apoptosis.[15,16] 14-3-3 protein can be detected in CSF of CJD patients and in the neurofibrillary tangles upon pathologic examination.[17] The mechanism by which 14-3-3 protein induces CJD onset is unknown, and the diagnostic value of 14-3-3 protein is controversial. Some previous studies have reported the high sensitivity (85-97%) and specificity (68-97%) of the immunoblot test for 14-3-3 protein in CJD diagnosis.[17,18] When 14-3-3 protein testing is taken among unselected patients with rapidly progressive dementia (disease duration less than 12 months), the false positive rate is about 12%. But in some other studies about pathology confirmed cases, the negative rate is very high.[19] And the contamination of CSF by 14-3-3 protein containing blood cells may lead to false-positive results. In addition, the expression of 14-3-3 protein is also found in many conditions of neuronal injury such as infectious diseases of the CNS, metabolic encephalopathy and in the acute stage of cerebral infarction, reducing the specificity of 14-3-3 protein testing.[20] One study showed that only 17 of 32 confirmed sCJD patients (biopsy- or autopsy-confirmed) had positive results of

14-3-3 protein with the sensitivity of only 53%.[21] And in another analysis of 420 CJD patients confirmed by biopsy, the specificity was only 28%.[22] The levels of 14-3-3 protein in vCJD and fCJD subtypes are different.[17] Distinct from sCJD, vCJD has about only 50% positive rate of 14-3-3 protein. Furthermore, GSS and FFI are nearly negative for 14-3-3 protein testing.[5]

With the progress of the research, some other biomarkers of CSF are found. Total tau (t-tau) and phosphorylated tau (p-tau) proteins in CSF are considered as useful biomarkers of CJD. Tau is a brain microtubule-associated protein which can assemble into filamentous structures by itself that forming neurofibrillary tangles under pathological conditions. This kind of tau neurofibrillary tangles, referred to as tauopathies, is a common feature in neurodegenerative disease such as Alzheimer's disease. Recent studies show increased T-tau levels and increased T-tau to P-tau ratios in CJD patients,[23] with the diagnostic accuracy about 79.6%.[24] Levels of tau in CSF have also been suggested as a marker for molecular subtype (codon 129 genotype) of sCJD.[25] Other CSF biomarkers, such as neuron specific enolase, brain-specific creatine kinase, S100β protein and desmoplakin, have also been investigated as potential biomarkers, but have yet to be used clinically. Perhaps the combination of more than one CSF marker could contribute to the differential diagnosis of CJD.[26-29]

EEG

EEG is a reliable non-invasive diagnostic method for CJD, especially sCJD, and was extensively used in clinic even prior to 14-3-3 protein testing.[30] The typical feature of sCJD patient in EEG is periodic sharp wave complexes (PSWCs). The duration of PSWCs is usually 100-600 ms and the intervening background among PSWCs is generalized slow waves with low amplitude. PSWCs appear relatively later than the onset of clinical symptoms. In the early stages of disease, EEG usually shows diffuse slow waves. PSWCs become apparent by 8 to 12 weeks after the disease onset in most cases and occur even later in a few cases, but disappear in the end-stages of disease. Thus, the time to take EEG examination is extremely important.[31,32] In the regular EEG examination, the sensitivity of PSWCs is 64-66%,[32,33] and the specificity is about 80%.[34] Twenty-four-hour ambulatory EEGs could increase the sensitivity to about 79.6%.[19] EEG recording can increase the accuracy of the diagnosis from "possible" to "probable" sCJD if generalized PSWCs are demonstrated. Continuous video EEG monitoring may be useful in identifying the connection between clinical symptoms and EEG signal. In fact, PSWCs had some relevance to myoclonus.[35] Different from sCJD, vCJD shows non-specific slow-wave abnormalities or normal waves in EEG, but no typical PSWCs.[5,30] In iatrogenic CJD patients, the region of PSWCs is corresponding to the site of operation. In genetic CJD patients, the positive rate of PSWCs is only about 10%. The source and the pathophysiological mechanism of PSWCs remain unclear, although cortical and subcortical mechanisms have been proposed. The PSWCs of CJD are diffused discharges and may have multiple cortical sources or alternating ways of activation in cortex, involving a subcortical pacemaker. Frontal intermittent delta activity and triphasic wave-like activity are supposed to be forerunners of PSWCs and appear when cortical and subcortical gray matter are involved. Basal ganglia, thalamus and frontal cortex have also been suggested to be involved in generating PSWCs in CJD, but, experimental studies based on animal model are needed to validate this hypothesis.[36] PSWCs are also found in toxic encephalopathy, encephalitis and metabolic encephalopathy, especially hepatic encephalopathy.[33] Sometimes unilateral PSWCs can be observed in acute unilateral cerebral injury like cerebral infarction, encephalopyosis, and brain tumor. There are few breakthroughs in PSWCs for CJD diagnosis in recent years, compared to the in-depth studies on medical imaging of CJD. Further investigations of the pathophysiological mechanism of PSWCs and the relevance to clinical manifestation are warranted.

Diffusion weighted imaging

Diffusion weighted imaging (DWI) is a form of functional MR imaging which can detect the Brownian motion of water molecules in the pathological state by the means of Echo Planar Imaging technology. It is sensitive to the cytotoxic edema and is applied in the diagnosis of cerebral infarction most frequently. DWI is also the most widely used, intensive studied and highly valued MRI sequence for accurate radiological diagnosis and differential diagnosis of CJD at present. The typical performance of DWI on CJD patients is the abnormal ribboning hyperintensities in cerebral cortex and/or the abnormal hyperintensities in basal ganglia region. DWI signal changes reflect the presence of micro-vacuolation of brain tissue causing spongiform degeneration, which is confirmed by autopsy.[37] And it correlates well with the clinical manifestation and PrPsc accumulation.[38] The sensitivity of DWI for diagnosis is about 85-96%, and the specificity is about 93%, which is superior to that of conventional MRI (T1, T2 and FLAIR).[19,39-41] In a study on the diagnostic utility of CSF biomarkers and DWI, MRI-DWI was the best predictor, with a diagnostic accuracy of 97%. T-tau had a diagnostic accuracy of 79.6%,

and that of 14-3-3 protein was 70.4%.[24] The similar DWI signal can also be observed in patients affected by mitochondrial encephalomyopathy and toxic encephalopathy such as mercury poisoning.

The majority of sCJD patients (80-90%) have cortical abnormal hyperintensities on DWI, and the percentage of basal ganglia alterations is about 50-69%.[19,42] Other studies on DWI showed a fewer detection of increased signal in the thalamus of CJD patients. Thalamus involvement is more frequent in vCJD and VV2 subtype of sCJD patients. GSS is rarely abnormal in DWI.[5] A quantitative analysis of apparent diffusion coefficient(ADC) value can display slight changes in the thalamus of sCJD patients although abnormal signal may not be found visually. The DWI scan sequence of MRI shows high sensitivity for the abnormal hyperintensities in cerebral cortex and basal ganglia, but none of the standard MRI sequences reveal abnormal signal in cerebellum or brain stem of CJD patients. DWI appears sensitive to the restricted diffusion of water in cortex and basal ganglia but not in the cerebellum and brain stem. The abnormal regions may be unilateral at the disease onset then bilateral with time. In some cases the signal intensity decreases as the disease progresses.[40,43] Hyperintensities can be observed on DWI in early stage of sCJD when 14-3-3 protein and PSWCs are still negative. Recent study proposed that the patients with abnormal DWI hyperintensities in basal ganglia lesion had shorter disease duration and higher incidence of myoclonus. The lower apparent diffusion coefficient in basal ganglia indicated the faster presence of akinetic mutism and a shorter disease course.[44] However, others have not obtained the same results. Contrary to other rapid dementias, sCJD patients manifest wider range of hyperintensity on DWI than on FLAIR sequence.[41] The area of abnormal DWI hyperintensities are in accordance with clinical manifestation and the area of PSWCs. With the thorough researches on DWI, CJD diagnostic criteria are continuously updated. The abnormal signal of DWI was described as one of the diagnosis standards officially in 2009 (Zerr *et al*.[18]); Vitali *et al*.[41] and Meissner *et al*.[45] described the DWI hyperintensities in detail and proposed the MRI diagnostic criteria of CJD in 2009 and 2011, respectively.

Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a relatively new MRI scan technique that reflects the diffusion anisotropy of water in cerebral white matter and the integrity of white matter fiber tracts.[46] The fractional anisotropy (FA) image of DTI can visually display the structure of white matter fiber. Mean diffusivity (MD) reflects the average diffusion of water molecules from all directions-the greater MD measured, the more water molecules unrestricted in the tissue. When there is fiber loss causing the increase in extracellular space, MD increases. When there is microstructural pathology like myelination defects in the fiber, FA decreases. DTI can reflect dynamic microstructural changing in brain tissue.[47] Previously, DTI was used to study pathology in neurodegenerative diseases such as Alzheimer's disease and dementia with Lewy bodies.[48,49] Recently, advances have been made in DTI for CJD diagnosis. For instance, significant decreases have been observed in MD, but not FA, in the caudate and pulvinar of sCJD patients compared to other rapidly progressive dementia patients and normal controls. Some studies hypothesized that the spongiform changes in CJD could restrict water molecule diffusion and lead to decreased MD and a relative preservation of FA.[50,51] Along with the changing of DWI hyperintensity in the disease course of CJD, MD decreases in the early stage of disease and tends to be normal or increase in the terminal stage. The increasing MD is associated with more significant loss of function. Neuronal loss increases water diffusion and augmentation of MD measurement in the late stages of CJD. In addition, the increased size of micro-vacuolation and their coalescence in end-stage of CJD might cause an increased free water flow.[52] The DTI test is highly sensitive, but not very specific. Therefore, DTI is an important tool for diagnosis, but alone is not sufficient for a CJD diagnosis.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is a noninvasive examination that can quantitatively analyze specific atomic nucleus and their chemical components based on MRI technique and chemical shift. MRS displays the metabolism and biochemistry of pathological tissue in the form of spectrum. Proton magnetic resonance spectroscopy (^{1}H-MRS) is the most widely applied MRS technique, which can detect the resonance peak of more than twelve brain metabolite and neurotransmitter like N-acetyl-aspartate (NAA), creatine (Cr), myo-inositol (mI), and choline. Currently, ^{1}H-MRS is mainly used to study metabolic disorders of the CNS, tumors, and dementia disease. There have been very few studies on CJD although MRS provides information on chemical metabolism.

In one case report of sCJD, MRS detected marked extensive decreased NAA, and displayed increased myo-inositol/creatine ratio in basal ganglia and the insular cortex, along with slightly reduced choline/creatine ratio.[53] Similarly, other case studies revealed decreased NAA in basal ganglia, thalamus

and cortex.[54,55] MRS imaging in brain tissue of CJD patients, especially striatum, display moderate reduction in NAA, suggesting neuronal loss or dysfunction. ^{1}H-MRS can detect the absence of NAA, creatine and choline peaks in late-stage CJD patients, indicating no neuronal activity.

The metabolic changes of MRS can be detected in the initial clinical course of CJD, prior to the abnormal changes detected in DWI. For instance, the reduction in NAA/Cr ratio can be found in the brain tissue of CJD patients when DWI hyperintensity is still negative.[53] In one research on the differential diagnosis of patients with rapidly progressive neurological signs similar to the clinical symptoms of sporadic prion disease, ^{1}H-MRS presented great diagnostic value. The percentage of correctly diagnosed prion cases was 86% for DWI, 86% for thalamic NAA/Cr ratio, 90% for thalamic NAA/mI ratio and 86% for CSF 14-3-3 protein. The prion disease patients had reduced NAA/Cr ratios ≤ 1.21. In this study, researchers proposed that the combination of thalamic MRS and DWI may increase the diagnostic accuracy of the MRI scan,[56] whereas, other studies indicate that these changes in metabolism are sensitive but nonspecific. NAA is a neuronal marker that decreases in many conditions of neuronal injury, including degenerative disease. And myo-inositol is a glial marker, increased in glial proliferation. The increased myo-inositol may also be found in Alzheimer's disease, herpes simplex encephalitis, neuro-cysticercosis and progressive multifocal leukoencephalopathy.[53] Although MRS can quantitatively reveal the changes of chemical components in brain tissue infected by CJD, the studies on the diagnostic value of MRS lack specificity data. Larger sample controlled clinical trials are certainly needed.

18F-FDG PET/CT

18F-FDG PET/CT is a nuclear medicine examination method that can reveal the glucose metabolism of tissue without influence on the internal environment of human body. Clinical use of PET is now well established in early diagnosis of tumor, Parkinson's disease, Alzheimer's disease and in the accurate positioning of epileptogenic focus. PET is also used to study neural receptors, neurotransmitters, and clinical pharmacology. Theoretically, there is hypometabolism in the CJD patients' brain tissue, which is probably related to vacuolation and PrPsc accumulation. PET, as one of the most sensitive techniques to detect glucose metabolism of tissue, may be of great value for early diagnosis and appropriate differential diagnosis of CJD. PET is expected to detect cortical, basal ganglia or thalamic hypometabolism in CJD patients, while the FFI patients only present a slight hypometabolism in the thalamus. Generally, hypometabolism is more frequent and more severe in cerebral lobe cortex than in basal ganglia structures, and rarely in cerebellum and brainstem.[57] The metabolic alterations on PET appear earlier than DWI hyperintensities, partly because some vacuoles in hypometabolism tissue are too small to be detected by DWI. Some abnormal lesions which cannot be seen on DWI can be detected by PET especially in the early stage of CJD duration, suggesting a higher sensitivity of PET.[42] Others proposed PET was more sensitive than DWI for cortex, and DWI was more sensitive than PET for basal ganglia.[57]

PET is highly sensitive and an effective means of identifying early-stage tumors which is important for the differential diagnosis of CJD, particularly in identified from cases of paraneoplastic neurologic syndromes which shares similar performance including rapidly progressing dementia, prominent psychiatric symptoms, seizures and dystaxia.[19] Hypometabolism can also be detected in other rapidly progressive dementia diseases by PET, however, data on the specificity of PET among a large populations are limited. In Alzheimer's disease, the parietal lobe and the temporal lobe are most likely involved in hypometabolism on PET, whereas abnormal signals are less pronounced or occur later in the frontal lobe. In dementia with Lewy bodies, hypometabolism is most frequently detected in the occipital and temporoparietal cortex together with contrary hypermetabolism in putamen and pallidum. Hypometabolism in thalamic and upper brainstem can be observed in progressive supranuclear palsy.[57] Further study should be carried out to explore the value of PET for differential diagnosis between CJD and other rapidly progressive dementia diseases.

In addition, some studies have reported that the abnormal hyperintensities on DWI and hypometabolism areas on PET are correlated with the clinical symptoms.[19,42,58] For instance, abnormal changes in basal ganglia predict extrapyramidal tract signs and the radiographic abnormality appears earlier than clinical symptoms. Additionally, there are consistencies among the regions of abnormalities on DWI, PET and the regions of PSWCs.[59,60]

DEVELOPMENTS OF AUXILIARY EXAMINATION CAUSING A REVOLUTION IN DIAGNOSTIC CRITERIA

Pathology results from autopsy and brain biopsy

are still the gold standards for CJD diagnosis. The classic pathological features of CJD are spongiform degeneration, astrocytes gliosis and nerve cell loss. But the percentage of pathological diagnosis among CJD patients is very low. Some surgical and pathology departments are not active to do autopsy or biopsy because of the infectious and incurable characteristic. And the sterilization methods for contaminated instruments have not been promoted in many countries. Furthermore, many people refuse biopsy partly due to fear of invasive examination or refuse autopsy because of traditional cultural beliefs. Less invasive biopsy of the olfactory mucosa or skeletal muscle and other novel ultrasensitive seeding assays based on the amplified detection of PrP, such as real-time quaking-induced conversion, have been developed, but have not been extensively used in clinic.[61,62] Thus the diagnosis of CJD based on clinical manifestations and non-invasive examinations (14-3-3 protein testing, EEG, DWI, PET, *etc*.) remains significant.

The clinical diagnostic criteria for CJD were first proposed in 1979, using a combination of clinical features and EEG.[63] 14-3-3 protein test was assessed in subsequent years and added to the diagnostic criteria later. The World Health Organization (WHO) formulated detailed diagnostic guidelines in 1998, including clinic symptom, PSWCs of EEG, 14-3-3 protein and exclusion diagnosis. According to the diagnostic guidelines of WHO, 14-3-3 protein can provide a possible-to-probable diagnosis.[31,64] Abnormal findings on MRI were mentioned at that time but without high attention. In the manual for surveillance of human transmissible spongiform encephalopathies 2003, WHO described the diagnostic criteria for the four CJD subtypes (sCJD, gCJD, iCJD and vCJD, separately) in more detail. And the bilateral symmetrical pulvinar high signal on MRI brain scan was incorporated into the diagnostic criteria for vCJD.[30] As research has progressed, MRI has played an increasingly significant role in CJD diagnosis.[40,60,65,66] The clinical criteria for the diagnosis of CJD have been revised to include abnormal hyperintensities on DWI based in part on key studies (Zerr *et al*.,[18] Centers for Disease Control and Prevention[67]). Vitali *et al*.[41] also proposed detailed MRI diagnostic criteria. Although DTI and PET have received much attention, they are not readily used in diagnosis. In fact, PET is more often used for the exclusion diagnosis.

CONCLUSION

CJD is infective, untreatable and fatal. The treatment method which could reverse the disease course does not exist currently. Prior reports indicate that intensive life-sustaining treatments, such as assisted breathing with ventilator and nutritional support, can prolong the patients' lives, but could not prevent death.[68] The causative agent, prions, are not completely inactivated by exposure to high temperature, ultraviolet and ionizing radiation, or chemicals that are effective against common viruses.[69] In order to prevent transmission of this devastating disease and reduce the risk to public health, earlier and accurate clinic diagnosis of CJD are critically important. Auxiliary examination plays a significant role in CJD diagnosis. EEG is most widely used as the traditional examination method in clinic and DWI has the highest sensitivity and specificity. The value of 14-3-3 protein testing remains controversial. The use of MRS for CJD diagnosis in clinic is limited. Detection of tau protein, DTI and PET have considerable potential in the differential diagnosis of different rapidly progressive dementia, especially in the situation of overlapping clinical manifestations. In addition, DWI and DTI may be useful to assess pathological changes of CJD. The abnormal results of auxiliary examination, such as the region of PSWCs, the abnormal hyperintensity area of DWI and the low metabolism area of PET, are consistent with the symptoms and the area of pathologic change. Multiple combined auxiliary examination methods may increase the accuracy of diagnosis and differential diagnosis among CJD patients. Further investigation into potential auxiliary examination methods for earlier and more accurate diagnosis of CJD are certainly needed.

Authors' contributions

Concept and design: J.T. Zhang
Data analysis, manuscript preparation and editing: W. Zhao
Literature search: J.J. Jiang

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Conflicts of interest

There are no conflicts of interest.

Patient consent

No patients were involved.

Ethics approval

Not applicable.

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