

Case Report of an Unusual Stroke-like Creutzfeldt - Jakob disease with Medulla Oblongata Motor Nuclei Lesion

Cheng-fang Huang¹, Xi Chen², Dan Jiang¹, Hua-li Wang³, Hong-hua JIN⁴, Wei Yang⁴, Jun Peng¹, Jie Liu^{5*} and Hong Zhang^{6*}

¹Department of Neurology, Affiliated Tianyou Hospital, Wuhan University of Science and Technology, China

²Department of Clinical Medicine, Zhejiang University, China

³Peking University Institute of Mental Health, Beijing, China

⁴Magnetic Resonance Imaging Room, Affiliated Tianyou Hospital, Wuhan University of Science and Technology, China

⁵Translational Center for Stem Cell Research, Tongji Hospital, Tongji University School of Medicine, Shanghai, China

⁶Clinical Pharmacology Departments, Tongji Hospital, Tongji University School of Medicine, Shanghai, China

*Corresponding authors: Jie Liu, Translational Center for Stem Cell Research, Tongji Hospital, Stem Cell Research Center, Tongji University School of Medicine, Shanghai, 200065, China, Tel: 86-21-66111590; Fax: 86-21-66111430; E-mail: liujie3131@tongji.edu.cn

Hong Zhang, Clinical Pharmacology Department, Tongji Hospital of Tongji University School of Medicine, Shanghai, 200065, China, Tel: 86-21-66111245; Fax: 86-21-66111245; E-mail: hongzh97@sina.com

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Abstract

Background: The reports of long-term imaging traces for sporadic Creutzfeldt–Jakob disease (sCJD) have been rare to date, although diffusion-weighted imaging (DWI) has high sensitivity and specificity in the diagnosis of sCJD in the early stage of disease. And sCJD-associated neuropathologic brainstem abnormalities on DWI are considered uncommon. Here, we provided a sequential neuroimaging of a late-onset sCJD with medulla oblongata motor nuclei lesion.

Case presentation: We report the case of a 77-year-old woman who presented a typical late-onset sCJD clinical manifestation including rapidly progressive dementia, ataxia, and myoclonus, except vision loss. 14-3-3 protein of CSF was found to be positive, blood gene test detected that the polymorphism at codon 129 was M/M subtypes, genotyping the human prion protein gene (PRNP) did not reveal mutations related to hereditary CJD. The hyperintensity was found only in the bilateral cerebral cortices on initial DWI. One month later, increased basal ganglia signal in addition to cortical hyperintensity was found on the follow-up image, which was not consistent with the more frequently MRI profile of sCJD patients over 75 years old. PET/CT imaging detected extra regions with abnormalities as the left thalamus in addition to the hyperintense areas shown on DWI. MRS did not show abnormal metabolism in some areas of DWI abnormalities, but abnormal areas in MRS were accompanied by DWI abnormally high signal. In the late stage, disappearance of abnormal hyperintense lesions on DWI was observed. And very rare clinic characteristic is the subacute and focal involvement of right IX, X and XII nuclei, with abnormalities in the right of medulla oblongata on magnetic resonance imaging (MRI) and DWI from early to late stage, clinical manifestation showing weak pharyngeal reflex, tongue to left, and uvula to left at early stage, suggesting a medulla ischemic event. Sequential electroencephalography recordings showed no characteristic PSWCs in the whole course of the disease.

Conclusion: The rapidly progressive clinical course with dementia, ataxia, and myoclonus plus corroborative neuroimaging and spinal fluid findings confirmed a clinicoradiographic diagnosis of Creutzfeldt-Jacob disease. This is an unusual report of an initial clinical presentation involvement of right IX, X and XII nuclei lesions of sCJD, expanding the known clinical spectrum of prion disease presentations.

Keywords: Sporadic Creutzfeldt-Jakob disease; DWI; PET-CT; Medulla oblongata lesion; IX Nuclei neuronal loss; IX Nuclei neuronal loss; XII Nuclei neuronal loss

Abbreviations

sCJD: Sporadic Creutzfeldt–Jakob Disease; DWI: Diffusion-Weighted Imaging; MRI: Magnetic Resonance Imaging; MRS: Magnetic Resonance Spectroscopy; MRA: Magnetic Resonance Angiography; EEG: Electroencephalography; PRNP: Human Prion Protein Gene

Background

Sporadic Creutzfeldt–Jakob Disease (sCJD) is a rare and fatal neurodegenerative disease characterized by rapidly progressive dementia. Early diagnosis is important to avert dissemination. While a definite diagnosis of sCJD is restricted to neuropathological examination, *in vivo* diagnosis of sCJD is based on clinical symptoms, Cerebro Spinal Fluid (CSF) markers, Magnetic Resonance Imaging (MRI) and Electroencephalography (EEG) profiles [1].

Clinical symptoms of sCJD sometimes are not typical, and in some patients, the characteristic waves of EEG are never found during

disease progression, therefore, early clinical diagnosis could be difficult.

As a result, neuroimaging is expected to play an important role in early diagnosis of sCJD, especially in cases with unusual clinical presentation. Diffusion-weighted MR imaging (DWI) has been frequently reported to be highly sensitive in the diagnosis of sCJD in the early stage [2-4]. Nevertheless, the reports of long-term imaging traces for DWI have been rare so far. A few studies found that PET-CT had important value of early diagnosis [5,6].

It has also been reported that patients with late-onset sCJD (over 75 years old) differ from younger sCJD patients in terms of clinical symptoms and MRI profiles presentation [7]. However, literature data with late onset sCJD are very rare.

sCJD-associated neuropathologic brainstem abnormalities are considered uncommon until the late disease stage [8]. Moreover, the reports of brainstem lesions in sCJD patients are very rare.

Here, we provide a long term case investigation of a late-onset sCJD patient, with involvement of right IX, X and XII nuclei lesions, suggesting a medulla oblongata lesion event. And we described the clinical features, laboratory tests and sequential neuroimaging of this late-onset sCJD patient.

Case Presentation

A 77-year-old woman who was admitted to the neurological department of Affiliated Tianyou Hospital, Wuhan University of Science and Technology, on March 6th, 2012, because of dull reaction, hypomnesia, and coming up with a word difficulty for half a month.

She had a past history of hypertension, cerebral infarction, exodontias and denture implantation for several times, despite the lack of trauma, surgery, or other contributory personal and family medical histories.

Neurological examination at admission only revealed dull reaction, hypomnesia, especially on transient memory, word-finding difficulty, weak pharyngeal reflex and tongue to left, uvula to left. The patient was oriented and there were no other neurological findings. She was diagnosed as stroke-like Creutzfeldt-Jakob Disease with medulla oblongata motor.

After the subject hospitalized, a thorough EEG detected mildly abnormal change without aberrant sharp-slow wave or thorn-slow wave. MRI revealed thrombosis in the right of the medulla oblongata, lacunar infarction in the left of the basal ganglia and the right of the pons-cerebellum arm.

Some other neurologic symptoms were also detected, such as cerebral atrophy, slightly ischemic change of cerebra, eukoencephalopathy (Figure 1A). Abnormal hyperintensity was detected in the right lateral medulla oblongata on T2 FLAIR (Figure 1B). However, there is no hyperintensity in the cerebral cortical on FLAIR (Figure 1A).

DWI showed mildly abnormal hyperintensity in the bilateral cerebral cortices of the frontal, parietaloccipital, temporal, and insular lobes and hippocampus, especially in the left temporal lobe (Figures 1C-1F). Head Magnetic Resonance Angiography (MRA) was in accordance with mild atherosclerosis change; cervical MRA revealed no obvious abnormality.

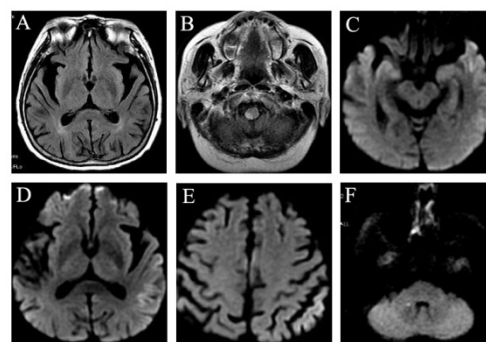


Figure 1: MRI and DWI images for the patient. A) There is no hyperintensity in the cerebral cortical on FLAIR on admission. B) Abnormal hyperintensity was detected in the right lateral medulla oblongata on T2 FLAIR. C-E) Slight hyperintensity was only found in the bilateral cerebral cortices and hippocampus, especially in the left temporal lobe on DWI. F) Abnormally hyperintensities was not found in both side of the cerebellum.

We initially suspected the patient had ischemic cerebrovascular disease combined with cognitive dysfunction, so we treated her with some drugs to anti-platelet and ameliorate cerebral circulation hyperbaric oxygen therapy to protect brain function. However, after 16 days of hospitalization, she exhibited disorientation, anomia aphasia, alexia, worsened speech deficiency and weaker retelling ability. On 23 day of hospitalization, she exhibited comprehensive ability disorder. Her retelling ability deteriorated, and other symptoms emerged, such as agraphia, dysphoria with forced crying and laughter, and slightly bradykinesia. On day 35 of hospitalization, mutism emerged combined with general cognitive disorder, she could not recognize her family members, and was inclined to the right side while walking. She was also troubled with facial and limb's muscle spasm, fumbling and forced grasp of right upper limb. Sucking and mandibular reflex could be led out. Muscle strength of general limb was at level 4. Muscle tone of right limb, especially in the upper limb strengthened. Pathologic reflex could not be led out.

As the illness exacerbated, we suspected that the patient might be having undergone neurodegenerative dementia; therefore head MRI, DWI, PET-CT, MRS and EEG were performed. DWI abnormal signal was changing during the course of the disease. DWI showed not only widespread hyperintense lesions in the cortices bilaterally, but also the bilateral putamen and caudate nucleus appeared high signal, and symmetrical abnormally hyperintensities was found in both side of the cerebellum cortex (Figures 2A-2D). However, MRI results were the same as the obtained on admission. PET-CT showed that glucose metabolic rate declined in each lobular cortex of the left hemiserebrum, left basal ganglia region caudate nucleus and the left thalamus; metabolic rate declined in the right cerebellar-hemisphere (Figures 2E and 2F), which coincided with crossed cerebellar diaschisis, compared with that of medulla oblongata. Metabolic rate did not exhibit obviously unusual change in each lobular cortex of the right cerebellar-hemisphere, basal ganglia region and thalamus and the left cerebellar, besides, cerebral atrophy was found (Figures 2C, 2D). MRS performed at the medial parietal cortices showed NAA lower, high peak value of cho, a reduced NAA/Cr ratio below the cutoff value (Figures 2G and 2H). However, besides moderate abnormal change with increased slow wave, EEG examination did not find obvious

specific waves, including in the characteristic of DWI hyperintensities region.

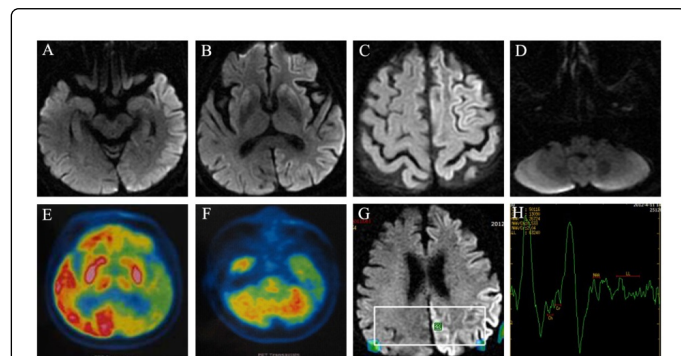


Figure 2: DWI (A-D), PET-CT(E, F) and MRS (G, H) images for the patient on the day 35 of hospitalization. A-C) DWI shows widespread hyperintense lesions in the cortices bilaterally and with increased signal in the heads of the caudate nuclei and the putamina bilaterally. D) Symmetrical abnormally hyperintensities was found in both side of the cerebellum cortex. E, F) Glucose metabolic rate declined in each lobular cortex of the left hemiserebrum, left basal ganglia region caudate nucleus and the left thalamus declined in the right cerebellar-hemisphere. G, H) MRS performed at the medial parietal cortices showed a reduced NAA/Cr ratio (1.29) below the cutoff value. A rectangular box indicates the volume of interest for spectroscopy.

Further course was characterized by rapidly progressive tetraparesis, dysphagia and dysarthria, frequent spasm on her angulus oris and right limbs. Her eyes gazed to the left. On day 60, she had gatism and coma. She subsequently underwent endotracheal intubation and was put on a ventilator. On day 66, EEG detected high-voltage slow wave in both hemiserebrum, typically in the left anterior region and right posterior region, no sharp wave was detected.

Six months after onset, 14-3-3 protein of CSF was found to be positive, blood gene test detected that the polymorphism at codon 129 was M/M subtypes, genotyping the human prion protein gene (PRNP) did not reveal mutations related to hereditary CJD. Based on combination of laboratory test with clinical characteristic, the patient was diagnosed as sCJD.

On 222 days after hospitalization, the symptoms of damaged cerebral cortex, eencephalon, extrapyramidal system and tractus pyramidalis appeared one after another during this period. MRI and DWI showed cortex disappearance, severe brain atrophy, and serious degeneration of brain white matter (Figures 3A and 3B), the hyperintensities increased and expended in the right medulla oblongata.

But the high signal was not apparent or gradually disappear along with the brain cortex largely and hippocampus, and in the bilateral putamen and caudate nucleus on DWI at the late stages (Figures 3C-3E).

Consequently, she suffered from repeated pulmonary infection and eventually died of multiple system organ failure on June 1st 2013. She had lived 451 days after the disease onset. As the patient's family refused the autopsy, advanced proof of prion could not be obtained.

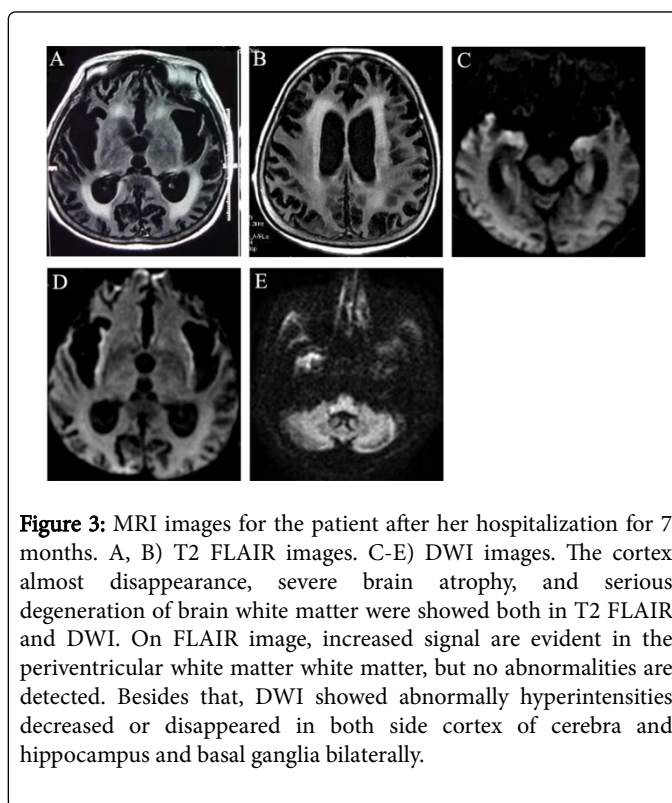


Figure 3: MRI images for the patient after her hospitalization for 7 months. A, B) T2 FLAIR images. C-E) DWI images. The cortex almost disappearance, severe brain atrophy, and serious degeneration of brain white matter were showed both in T2 FLAIR and DWI. On FLAIR image, increased signal are evident in the periventricular white matter white matter, but no abnormalities are detected. Besides that, DWI showed abnormally hyperintensities decreased or disappeared in both side cortex of cerebra and hippocampus and basal ganglia bilaterally.

Discussion

CJD was deadly spongiform encephalopathy caused by mutation of prion gene. CJD was divided into 4 types, among which the sCJD ranked first in the clinical classification. The main clinical manifestations of sCJD were cortex impairment, cerebellar dysfunction, pyramidal tract and extrapyramidal impairment. It's characterized by rapidly progressive dementia accompanied by symptoms and signs such as ataxia and myoclonus. The onset of the disease could be rapid or slow, although most cases progressed rapidly. In China, patients with sCJD were characterized by a relatively early age of onset, acute or subacute onset, obvious dementia, myoclonus and extrapyramidal motor symptoms, visual impairment and cerebellar signs appeared comparatively early, besides mild and later pyramidal tract damage, dementia is obvious, but signs of encephalopathy were relatively less obvious. Historical studies found that older patients than 75 years showed a faster disease progression represented by an earlier point of diagnosis and a shorter survival time, they suffered slightly more often with dementia or dysarthria in the early stage of disease [9], When expanding this analysis to the entire duration of disease, patients over 75 years old had a higher risk of the pyramidal signs' presence. The above case was comparable to typical late onset sCJD profiles, and was consistent with the Chinese sCJD disease except vision loss. The patient had subacute onset of the disease and possessed obvious clinical manifestation such as dementia, dysarthria, dementia is obvious, but signs of encephalopathy were relatively less obvious, in the early stage. The clinical picture deteriorated dramatically in the following 35 days progressing to severe ataxia of trunk and limbs, cognitive impairment and dysarthria. Next the patient developed frequent spontaneous and startle myoclonic jerks of the four limbs, akinetic mutism. The patient died, about 451 days after the disease onset.

EEG changes have been proved to be valuable in the diagnosis of sCJD, however the specific PSWCs on EEG are observed in only 60% of CJD patients and usually appear after the middle stage of the disease [10]. In our case, sequential EEG recordings showed progressive slowing of background activity, but no PSWCs in the whole course of the disease. It is likely that PSWCs was paroxysmal, thus not caught by the ordinary EEG. Alternatively, the change of the EEG was not typical or never showed periodic discharges in the entire duration of disease [11]. For those highly suspected as sCJD, repeated EEG and dynamic EEG might help to find specific EEG signals for sCJD diagnosis.

Recent studies have found that DWI could sensitively reflect the abnormally high signals at the first time. The high signals were most commonly found in the cerebral cortex, the lesion might also involve the dorsomedial thalamus, corpus striatum, ependymal and hippocampus. DWI showed sensitivity and specificity of 100% in patients with rapidly progressive dementia in autopsy-proven CJD [2], and the sensitivity of DWI is superior to that of conventional MRI (T1, T2, FLAIR) in detecting specific basal ganglia and cortical abnormalities early in the course of CJD [12]. The earliest high signals in DWI was visible long before ECG characteristic of PSWCs and CSF changes as well as the expression of 14-3-3 protein [13]. DWI signals might even be earlier and more sensitive than clinical symptoms such as dementia and myoclonus. In our case, DWI on admission showed cortical hyperintensity (Figures 1C-1E), while there were no typical clinical symptoms, no evident changes in T2WI and FLAIR at the same time and in the same locality (Figure 1A). This is consistent with previous findings that DWI is useful for early diagnosis of CJD [3,5,14].

Pathogenic viruses may result in the cerebral cortex PrPSc deposition, cortex neuron degeneration and dysfunction. DWI high signals are most closely related with PrPSc deposition, consequently, closely related with the clinical symptoms. Our study indicates that DWI abnormal signal was changing during the course of the disease. At early stage of our case, DWI showed that high signal changes in cerebral cortex could be seen mainly in the left part (Figures 1C-1E), consistent with the symptoms like walking towards the right side, fumble, strong grip syndrome in the right upper limb, and the following myoclonic symptoms mainly in the right limbs.

With the progressive exacerbation of disease, the high signal of the cortical in DWI became higher and gradually distributed to wider region (Figures 2A-2D), and appeared high signal in the bilateral putamen and caudate nucleus (Figure 2B), and symmetrical abnormally hyperintensities was found in both side of the cerebellum cortex (Figure 2D). Dementia became the main expressions. Aphasia, agnosia, conduct disorder appeared and developed the characteristic of myoclonus. The symptoms of damaged cerebral cortex, ependymal, extrapyramidal system and tractus pyramidalis appeared one after another during this period. But the high signal was not apparent or gradually disappears along with the cortex largely and in the bilateral putamen and caudate nucleus at the late stages (Figure 2C-2E). The change of high signal in DWI could be regarded as the reflection of the various stage of CJD. At the climax of the prion accumulation, DWI displayed high signal with brain cell necrosis, while sponge kind material disappear, DWI imaging high signal can also gradually disappear. Extensive neurons depigmentation and cerebral gliosis result in the disappearance of spongiform substance. The abnormal signal changes might result from microvacuolation of neurotic processes in spongiform degeneration. When the abnormal vacuoles reduced, then abnormal signal disappeared [11].

MRI profiles of patients over 75 years old were significantly less frequently accordant with established MRI criteria for sCJD than MRI profiles of the younger group. Researchers found that atypical MRI profiles that showed lesions localized in one hemisphere or cortex only were found more frequently in patients over 75 years old, whereas typical cortical and basal ganglia hyperintensities were more common in the younger group [9]. The MRI profile of our current case was not in accord with sCJD patients over 75 years old, with hyperintensity only in the bilateral cerebral cortices on initial DWI and increased basal ganglia signal in addition to cortical hyperintensity on the follow-up image 1 month later.

The correlation between PET/CT and DWI & CJD has been rarely reported, although a previous study showed that PET/CT imaging detected extra regions with abnormalities in addition to the hyperintense areas shown with DWI. However, DWI did not identify corresponding hyperintense changes in the thalamic nuclei [6]. In our case, PET/CT imaging detected extra regions with abnormalities in addition to the hyperintense areas shown on DWI as the left thalamus (Figures 2E and 2F), but failed to detect abnormalities hyperintense areas shown on DWI as right basal ganglia region and the left cerebellar-hemisphere. We speculate that DWI was more sensitive in the diagnosis of cerebral cortex and basal ganglia region change, but was less sensitive in that of thalamus. PET could be less sensitive in the thalamus. In the absence of neuropathological findings, PET/CT could improve the accuracy of sCJD diagnosis when combined with DWI, therefore, PET/CT could have significant value for early and differential diagnosis of sCJD [15].

H-MRS of the medial parietal cortices revealed a reduced N-acetylaspartate (NAA)/ creatine (Cr) ratio below the cutoff value, a sign of tissue loss (Figures 2G and 2H). MRS did not show abnormal metabolism in some areas of DWI abnormalities, but abnormal areas in MRS were accompanied by DWI abnormally high signal in our case. Hence, the sensitivity of DWI is superior to that of MRS.

The three major features of the sCJD were long incubation period, short clinical course after the onset, and 100% mortality. Currently there is no effective treatment, 85% of patients die 1 year after the onset, and some patients die within 3 weeks after the start of disease. Nonetheless, there have been a few rare cases where in patients lived for more than 8 years. Meissner etc. [16] found that the patients with the cortical plus basal ganglia hyperintensity on DWI in the early stages had a shorter interval from symptom onset to akinetic mutism than those with only cortical ribbon hyperintensity, which may be indicative of shortened the duration. In our case with rapid clinical progression, the extended active hospitalization also contributed to the long survival time.

The brainstem remains relatively resistant to the pathologic process of sCJD, sCJD-associated neuropathologic brainstem abnormalities are considered uncommon until the late disease stage, and there have been a few reports of sCJD brainstem lesions in sCJD. Neuronal loss was relatively prominent in the pontine nucleus and less so in the motor nuclei of the brainstem tegmentum. However, an interesting issue with our case is the subacute and focal involvement of right IX, X and XII nuclei lesions suggesting a medulla oblongata ischaemic event. Our case had weak pharyngeal reflex, tongue to left, uvula to left at early stage, but there were no other pyramidal system findings, and head MRI was in accordance with mild atherosclerosis change, MRI revealed thrombosis in the right of the medulla oblongata from early to late. These showed that the case sCJD had vascular deformation and narrow. Although accumulation of PrP in the brainstem appears to be an early pathologic event in sCJD, may remain into the late disease stage. On 222 days after hospitalization, MRI and DWI showed the

hyperintensities increased and expended in the right medulla oblongata.

In conclusion, DWI examinations from the early stages of the disease accompanied by detailed descriptions of symptoms could help our understanding of the relationship between DWI signal changes and the clinical evolution of the disease. In cases of clinically possible CJD, the follow-up DWI would be useful, not only for ruling out other disorders, but also for evaluating progression of the disease. DWI is one of the most sensitive indicators while differentiated with other dementia syndrome identification in the early disease. The sensitivity of DWI is superior to that of conventional MRI, MRS, PET. DWI combined with PET and MRS technology could improve the accuracy of diagnosis in the early stage of CJD.

Conclusion

This report provides a narrative of our patient's experience of sCJD from onset to death in just 451 days.

Consent

Written informed consent was obtained from the caregiver of our patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Authors' Contributions

CH, JL and HZ drafted the manuscript; JL and HZ revised the manuscript; CH, JL, HZ, XC, DJ and JP treated and followed up the patient, WY performed radiological diagnostics and image interpretation; JL, HW and HZ made a contribution to laboratory work. All authors read and approved the final manuscript.

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References

1. Zerr I, Kallenberg K, Summers DM, Romero C, Taratuto A, et al. (2009) Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. *Brain: A Journal of Neurology* 132: 2659-2668.
2. Demaerel P, Sciot R, Robberecht W, Dom R, Vandermeulen D (2003) Accuracy of diffusion-weighted MR imaging in the diagnosis of sporadic Creutzfeldt-Jakob disease. *Journal of Neurology* 250: 222-225.
3. Shiga Y, Miyazawa K, Sato S, Fukushima R, Shibuya S, et al. (2004) Diffusion-weighted MRI abnormalities as an early diagnostic marker for Creutzfeldt-Jakob disease. *Neurology* 63: 443-449.
4. Wang LH, Bucelli RC, Patrick E, Rajderkar D, Alvarez III, et al. (2013) Role of magnetic resonance imaging, cerebrospinal fluid, and electroencephalogram in diagnosis of sporadic Creutzfeldt-Jakob disease. *Journal of Neurology* 260: 498-506.
5. Renard D, Vandenberghe R, Collombier L, Kotzki PO, Pouget JP, et al. (2013) Glucose metabolism in nine patients with probable sporadic Creutzfeldt-Jakob disease: FDG-PET study using SPM and individual patient analysis. *Journal of Neurology* 260: 3055-3064.
6. Xing XW, Zhang JT, Zhu F, Ma L, Yin DY, et al. (2012) Comparison of diffusion-weighted MRI with 18F-fluorodeoxyglucose-positron emission tomography/CT and electroencephalography in sporadic Creutzfeldt-Jakob disease. *Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia* 19: 1354-1357.
7. Holman RC, Belay ED, Christensen KY, Maddox RA, Minino AM, et al. (2010) Human prion diseases in the United States. *PLoS One* 5: e8521.
8. Iwasaki Y, Hashizume Y, Yoshida M, Kitamoto T, Sobue G (2005) Neuropathologic characteristics of brainstem lesions in sporadic Creutzfeldt-Jakob disease. *Acta Neuropathologica* 109: 557-566.
9. Karch A, Raddatz LM, Ponto C, Hermann P, Summers D, et al. (2014) Diagnostic profiles of patients with late-onset Creutzfeldt-Jakob disease differ from those of younger Creutzfeldt-Jakob patients: a historical cohort study using data from the German National Reference Center. *Journal of Neurology* 261: 877-883.
10. Zerr I, Schulz-Schaeffer WJ, Giese A, Bodemer M, Schroter A, et al. (2000) Current clinical diagnosis in Creutzfeldt-Jakob disease: identification of uncommon variants. *Annals of Neurology* 48: 323-329.
11. Matoba M, Tonami H, Miyaji H, Yokota H, Yamamoto I (2001) Creutzfeldt-Jakob disease: serial changes on diffusion-weighted MRI. *Journal of Computer Assisted Tomography* 25: 274-277.
12. Murata T, Shiga Y, Higano S, Takahashi S, Mugikura S (2002) Conspicuity and evolution of lesions in Creutzfeldt-Jakob disease at diffusion-weighted imaging. *AJNR American Journal of Neuroradiology* 23: 1164-1172.
13. Vitali P, Maccagnano E, Caverzasi E, Henry RG, Haman A, et al. (2011) Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. *Neurology* 76: 1711-1719.
14. Nougaret S, Brunel H, Bourbotte G, Bonafe A (2007) Diffusion-weighted MRI in sporadic Creutzfeldt-Jakob disease. *Journal of Neuroradiology* 34: 260-266.
15. Lim CC, Tan K, Verma KK, Yin H, Venketasubramanian N (2004) Combined diffusion-weighted and spectroscopic MR imaging in Creutzfeldt-Jakob disease. *Magnetic Resonance Imaging* 22: 625-629.
16. Yi SH, Park KC, Yoon SS, Kim EJ, Shin WC, et al. (2008) Relationship between clinical course and Diffusion-weighted MRI findings in sporadic Creutzfeldt-Jakob Disease. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 29: 251-255.