Int J Clin Exp Pathol 2016;9(2):2744-2751
www.ijcep.com /ISSN:1936-2625/IJCEP0019164

Case Report

Clinical scenarios in creutzfeldt-jakob disease (CJD): report of nine cases

Jian Shi, Qi Chen, Xiangming Chen, Jianmin Zhang

Department of Neurosurgery, Second Affiliated Hospital, Zhejiang University College of Medicine, Hangzhou, China

Received November 4, 2015; Accepted January 1, 2016; Epub February 1, 2016; Published February 15, 2016

Abstract: Creutzfeldt-Jakob disease (CJD) is a rare, always fatal brain disorder that involves quickly progressing dementia. We retrospective reviewed nine patients suffering CJD who's clinical or neuropathological diagnoses were done. From 2006-2013, the copies of patients' records and all available test results were taken. Additionally, analyses of CSF parameters, EEG, MRI following routine standard methods. Although an intracranial biopsy procedure is invasive and carries risk of cerebral infection or hematoma, generally it is a safe, well-tolerated procedure. Special precautions to prevent the spread of prions must be taken. Disposable medical supplies must be destroyed by incineration and surgical instruments need to be autoclaved in sodium hydroxide.

Keywords: CJD, case reports, clinical scenarios

Introduction

Creutzfeldt-Jakob disease (CJD) is a rare, always fatal brain disorder that involves quickly progressing dementia. Most of patients underwent severe dementia within half year, and then death follows quickly. In a current guideline released by the American Academy of Neurology, the diagnosis process of CJD was published recent [1]. There are some typical changes to support clinical diagnosis of sporadic Creutzfeldt-Jakob disease (sCJD) have been described, included in electroencephalogram (EEG) and CSF-analysis for 14-3-3 proteins, multisequence MRI signals changes also have been described [1-5]. Until today, Creutzfeldt-Jakob disease has irreversible and incurable organic brain syndrome which is hereditarily caused by mutations of the prion protein gene [3, 6]. However, aforementioned various diagnostic methods are commonly used; none matches the accuracy of a histopathologic diagnosis obtained by brain biopsy or at autopsy. The necessary of intracranial biopsy as only conclusive criterion for the diagnosis of sCJD has controversial [3, 7-10].

Only intracranial biopsy or autopsy can confirm the presence of Creutzfeldt-Jakob disease. However the iatrogenic of sporadic Creutzfeldt-Jakob disease (sCJD) is not completely controlled [6]. Approximately 85% of prion-related diseases are sporadic and have an unknown route or source of infection [11]. Acquired by prion infection are iatrogenic CJD and variant CJD from bovine spongiform encephalopathy [1-3]. Considering those iatrogenic transmissions included pituitary hormones, human dura mater grafts, corneal grafts, and neurosurgical devices, especially intracranial devices. Thus, extensive epidemiological research focusing on essentiality and safety of in vivo biopsy is essential [12-15].

We retrospective reviewed nine patients suffering CJD who's clinical or neuropathological diagnoses were done. From 2006-2013, the copies of patients' records and all available test results were taken. Additionally, analyses of CSF parameters, EEG, MRI following routine standard methods.

Clinical presentation 3

Some authors made three major categories of CJD: sporadic CJD; hereditary CJD and acquired CJD. However, it was more popular to distinguish the different characteristics from Classic CJD to Variant CJD [3, 9, 16].

As most common form of human TSE (transmissible spongiform encephalopathy TSE), sporadic CJD, has been estimated to occur endemically at a rate of 0.5-1 case per million population per year [1, 17]. Confirming the diagnosis of Creutzfeldt-Jakob disease is extremely challenging, especially at an early stage. New cases can have a wide range of symptoms such as muscle twitching and spasms, abnormal reflexes, coordination problems, psychiatric symptoms devices or visual-spatial perception [1, 3, 7, 18]. It is frequently confused with other causes of dementia. Deterioration of brain function is similar with Alzheimer's disease, but is very rapid in progression and completely in extent [12, 18-22].

With the WHO clinical diagnosis criteria as references [9, 23], we reviewed nine cases of CJD in which EEG, CSF 14-3-3 and MRI was performed. In the early phase of the disease, 6 cases accepted intracranial biopsy and 1 case underwent tonsil biopsy. As 7 cases of sCJD progresses, clinical presentation typically develop a variety of early neurologic deficits, including worsening dementia, cerebellar dysfunction, myoclonus, pyramidal and extrapyramidal signs, and akinetic mutism; 2 case of vCJD presented prominent psychiatric/behavioral symptoms, painful sensory symptoms, and delayed neurologic signs. The survival time from illness onset to death was variable as 2-19 months (**Table 1**). The detail symptoms included that gradual decline of intelligence and walk incapable, memory defect, disability of recall the recent matters, losing count and some other higher intelligence power. Some patients appeared difficulty moving and slow in reacting, and easily fell, masked faces, movement of both eyes in various directions.

Our cases show that the ambulatory electroencephalogram are significant abnormal (1-1.5 Hz triphasic wave emerged periodically). The EEG in sCJD often shows a characteristic pattern with periodic, synchronous bi- or triphasic sharp waves (**Figure 1**). Which were named as periodic sharp wave complexes (PSWC), and there are seen in 60-70% of patients with sCJD and have a positive predictive value of 95% [5, 10]. Typical PSWC consist of sharp waves (biphasic or triphasic) or complexes with spikes, polyspikes and slower waves with a typical duration of 100-600 ms, each 0.5-2 second [9, 15]. Some authors reported slow, low-voltage background activity with frontal intermittent rhythmic delta activity (FIRDA) also could be found [3, 9]. PSWC, however, may occur in some encephalopathies, Alzheimer's disease, vascular dementia and Lewy body dementia [15, 22]. In addition to the laboratory findings, the presence of typical PSWC in the first EEG further supported the diagnosis sCJD.

Current criteria for *intra vitam* diagnosis include a distinct phenotype, periodic sharp and slow-wave complexes at electroencephalography (EEG), and a positive 14-3-3-protein assay in the cerebrospinal fluid (CSF) [3, 9]. While the 14-3-3 assay and tau protein levels were the most sensitive indicators of sCJD, the highest sensitivity, specificity and positive predictive value were obtained when all the above markers were combined [1, 5, 25]. In our institution, seven sCJD cases (77.78%) were positive in 14-3-3-protein test, one vCJD presented positive.

Discussion

Tonsil biopsy (Is it necessary?)

Because variant CJD (vCJD) is the only form of CJD to involve the lymph nodes, spleen, tonsil and appendix, the tonsil biopsy is a diagnostic surgical procedure which helps to identify abnormal cells and try to show any prions [9, 19]. Criteria for the in vivo diagnosis of probable vCJD have been defined, and MR imaging now plays a pivotal role. As with any invasive procedure, there are potential risks such as infection and bleeding. A negative tonsil biopsy result, however, does not rule out a diagnosis of vCJD [3, 20]. So, we only recommend a tonsil biopsy if vCJD is being considered in the differential diagnosis, and we consider that this test is not helpful for any other form of prion disease.

14-3-3 protein test

The guideline determined that the 14-3-3 protein test can be useful when the probability of the person having Creutzfeldt-Jakob disease is between 20 percent and 90 percent. Stoeck K. reported a clinical trial in which CSF was analyzed for 14-3-3, tau, phosphorylated tau and amyloid-b1-42 according to established protocols. CSF biomarkers were considered helpful

Table 1. Clinical characteristic of classic CJD and variant CJD

NO	Diagnosis	Initial symptoms	Epidemiological investigation	CSF 14-3-3 protein texting	Abnormal imaging presence (MRI FLAIR images, PET)	Duration of illness (Age at death)/sex	Neuropathology	Intracranial Biopsy (Age at death)/sex	Electroencephalogram	Sterilization of lumbar puncture or surgical instrument
1	sCJD	Dementia	None family outbreak	Negative	Bilateral cortex hypometabolism on PET	7 months 68/F	Florid plaques	Done None	Periodic sharp waves	Autoclaving in sodium hydroxide
2	sCJD	Dementia	None	Positive	B (C, CN)	2 months 57/M	Loss of neurons, fibrillary astrocytic gliosis, spongiform change	Done None	PSWCs	Autoclaving in sodium hydroxide
3	sCJD	Loss of memory	None	Negative	B (CN), L (C, P)	10 months 71/F	Severe fibrillary astrocytic gliosis	Done None	Periodic sharp waves	Autoclaving in sodium hydroxide
4	sCJD	Dementia	None	Positive	B (C, CN, P)	14 months 68/M	Spongy change in the gray matter	Done None	Sharp and slow-wave complexes	Autoclaving in sodium hydroxide
5	sCJD	Insomnia	Absent	Positive	B (C, CN, P, T)	4 months 68/F	Absent	None None	PSWCs	Destroyed by incineration
6	sCJD	Difficulty speaking	Absent	Positive	B (C, CN)	4 months 63/M	Absent	None None	Periodic sharp waves	Destroyed by incineration
7	sCJD	Painful dyesthesiasis	Absent	Positive	B (C, CN, P)	10 months 55/F	Absent	None None	Periodic sharp waves	Destroyed by incineration
8	vCJD	Psychiatric anxiety, depression	Eating raw beef	Negative	Pulvinar sign on MRI*	14 months 68/M	Florid plaques, spongy change in cortex/Negative	Done Done	Absent	Destroyed by incineration
9	vCJD	Behavioral abnormal	Travailing to UK, Usually drinking milk	Positive	Pulvinar sign on MRI*	19 months 38/M	Florid plaques, fibrillary astrocytic gliosis, spongiform change	Done None	Negative	Autoclaving in sodium hydroxide

*An abnormal signal in the posterior thalami on T2- and diffusion-weighted images and fluid-attenuated inversion recovery sequences on brain magnetic resonance imaging (MRI); in the appropriate clinical context, this signal is highly specific for vCJD. Source: Adapted from Belay E., Schonberger L. Variant Creutzfeldt-Jakob Disease and Bovine Spongiform Encephalopathy. Clin Lab Med 2002; 22: 849-62. Note: CJD = Creutzfeldt-Jakob disease, R = right, L = left, B = bilateral, C = cerebral cortex, CN = caudate nucleus, P = putamen, T = thalamus; PSWCs = periodic sharp wave complexes in EEG.

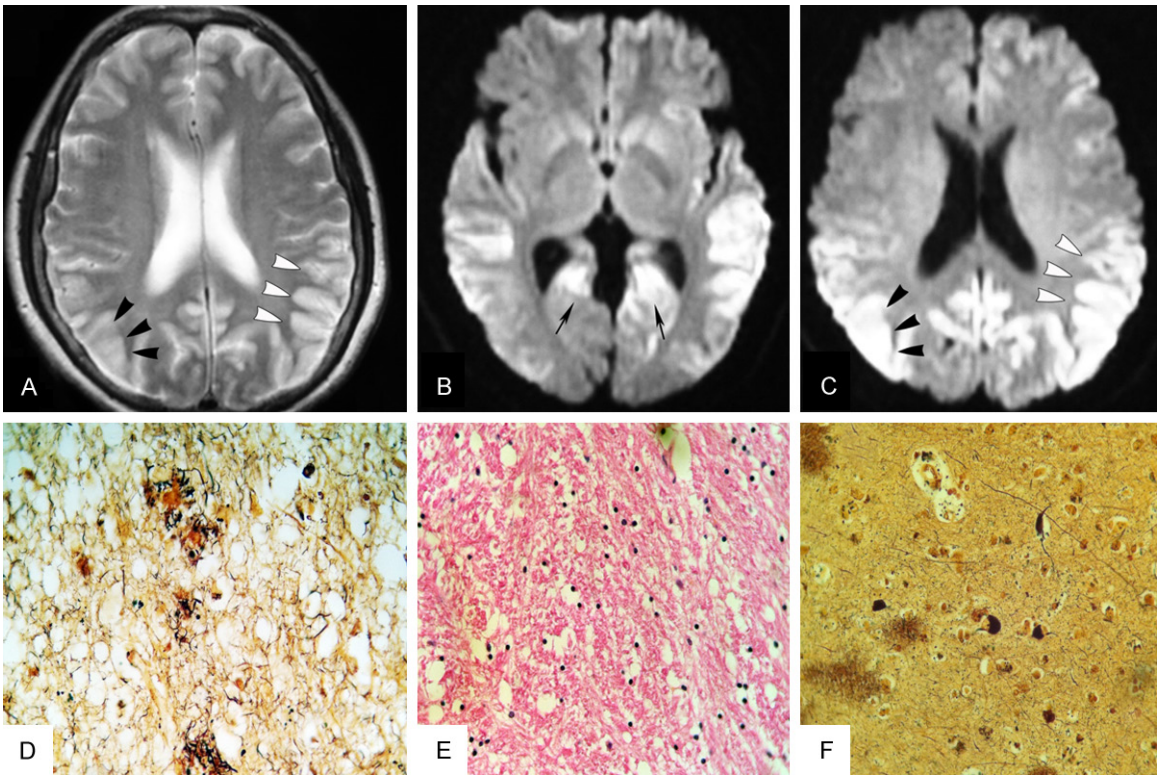

Figure 1. A. With MRI scanning, the T2 abnormal imaging high signal in the bilateral cortexes; B. An abnormal signal in the posterior thalami and ventricles on diffusion-weighted images; C. Compared T2, diffusion-weighted show more obvious images; D. Bielschowsky stain shows a marked spongiform change in the cerebral cortex; E. Florid plaques, stained with hematoxylin and eosin, high power view; F. Florid plaques, stained with silver impregnation, high power view.

in differentiation of rapid dementia forms such as CJD, but also in solid identification of patients with Alzheimer's disease. Furthermore, in some dementia due to inflammation, where a 14-3-3 test might be false positive, low levels of tau might be helpful in discriminating forms of neurodegenerative dementia [3]. This approach also allowed a reliable differential diagnosis with other neurodegenerative dementias [16, 18].

The imaging of CJD

MRI findings in early phase were correlated the onset of the characteristic pathological findings [17]. We evaluated the images for the presence and location of abnormal signal intensities. In most of cases, during the early phase, there were not abnormal findings on the T2-weighted images. However, the diffusion-weighted abnormal imaging high signal in the cortex and the basal ganglia disappeared in five patients. In two cases, bilateral putaminas and insulas showed low intensities signals on FLAIR images, similar to diffusion-weighted imaging abnormalities. During the intermediate phase, the involved range of the high signal intensities on the diffusion-weighted images had expanded and progressive cortical atrophy had become apparent, however in another patient, no abnormal high signal was seen in the basal ganglia at whole clinical course. During the terminal phase, all cases showed cerebral atrophy more obviously. In one patient, abnormal high signal intensities in the cerebral cortex and basal ganglia on the diffusion weighted images all disappeared. Bilateral pulvinar sign as low signal intensities on MRI were observed in both of vCJD patients instead (**Figure 1**).

With multisequence MRI, the classification method of human spongiform encephalopathies was available to differential diagnosis of CJD. On T2-weighted or FLAIR, PD and DW MRIs, the neuroimaging hallmark of sCJD is increased grey matter signal [4, 15, 17, 18]. In most cases, these changes would be found in bilateral symmetric markedly hyperintense cau-

date nuclei and putamina. In different cases, the thalami and the cortex are usually involved to different degree [8, 9]. In contrast, vCJD shows increased signal of the pulvinar thalami generally exceeding the signal of the caudate nuclei and putamina [9].

In a previous study, patients with suspect Creutzfeldt-Jakob's disease (CJD) have been examined with Positron Emission Tomography (PET) combining N-[11C-methyl]-L-deuterodeprenyl (DED) and [(18)F] 2-fluorodeoxyglucose (FDG) in an attempt to detect astrocytosis and neuronal dysfunction, two of the hallmarks in CJD. Increased DED uptake with pronounced hypometabolism matching the areas with high DED retention was found in the fronto-parieto-occipital areas and cerebellum of patients with confirmed CJD. However, the temporal lobes did not present such a pattern [23].

Linguraru [26] report their method further allows the quantification of intensity distributions in basal ganglia, therewith, differentiate sCJD and vCJD patients as sCJD patient FLAIR images are classified with a more significant hypersignal in external or superior nuclei of thalami.

Important of biopsy and risk of iatrogenic transmitting

Since CJD was first described in 1920, fewer than 1 percent of cases have been acquired CJD. There is no evidence that CJD is contagious through casual contact with a CJD patient. Even then, the most controversial fact to obstruct clinical biopsy or autopsy is iatrogenic infection.

There were iatrogenic cases linked to medical procedures including inadequately sterilized biopsy needle in the brain. To eliminate the risk of transmitting CJD by this route, we used disposable device as we can, and the sterilized method referenced Stanley. All Instruments were decontaminated by a combination of sodium hypochlorite and recommended autoclaving methods before subjecting them to cleaning in a washer cycle and routine sterilization [6, 19]. Scrupling the risk of transmitting CJD, since 2001, all human growth hormone used in the China has been synthesized by recombinant DNA procedures. Up to now, no human growth hormone-related disease transmission was identified [1, 3, 23].

All instances of iatrogenic transmission of CJD to date have been due to cross contamination with high-titer tissues in or adjacent to the CNS, and findings of epidemiological and observational studies have failed to provide evidence of transmission via blood transfusion or fractionated plasma products [6, 19, 24]. This evidence may not apply to vCJD, which is caused by a novel infectious agent for human beings and in which there is evidence of a peripheral pathogenesis different from other forms of human prion disease. In vCJD, prion protein is readily detectable in lymphoreticular tissues such as appendix, spleen, tonsil, and lymph nodes, whereas these tissues are negative-by comparable methods-in other forms of human prion disease [13, 16, 25].

In some institutes, most cases of CJD were no longer recommending a brain biopsy. However, the diagnosis were still uncertain even after a DWI MRI scanning or 14-3-3 protein test, brain biopsy has the experience necessary for some cases in initial course. [3, 26, 27] A brain biopsy in a patient with CJD may be negative for a variety of reasons. In some cases, prion disease is not definitely confirmed until tissue from a brain autopsy is analyzed [18].

Brain biopsy, a highly accurate method of diagnosis, therefore may be necessary; however, false-negative results sometimes are obtained because the samples were collected from an unaffected area. In China, brain biopsy is invasive, little costly and have frightening facts. It also poses a risk of secondary infection to medical personnel and, subsequently, patients. For the cases in terminal phase, usually autopsy could not be accepted by patients or their family because this process is anti-traditionalism. Under these circumstances, CJD is extremely difficult to diagnose, especially at an early stage, and it is frequently confused with other causes of dementia.

Buganza et al. [8] reported that diagnosis of sCJD should be considered in the differential diagnosis of rapidly evolving ataxic or dementing syndromes with or without epileptic seizures, regardless of the patient age. While the recognition of atypical phenotypes such as negativity in 14-3-3 protein test or MRI scanning can provide additional diagnostic challenge, it must be underlined that neuropathology is still the "gold standard" for sCJD diagnosis.

Pathology

No biopsy no neuropathology. In our quotient, the typical spongiform changes were found. With Holzer stain, the architecture of the cerebellar gray and white matter is preserved. Severe fibrillary astrocytic gliosis is visible. At aperio 20× and 40×, cerebral cortex shows extensive microvacuolar changes. In many areas, these microvacuoles are coalescent to form microcystic spaces.

Multi changes of neuropathology of CJD, particularly of the panencephalopathic type and its additional findings, were described on 6-cases quotient accepted biopsy. The panencephalopathic type of CJD was characterized by extensive degeneration of the cerebral white matter which is diffuse in the deep and circumscribed and spongy in the digital white matter. This white matter lesion could not be explained simply as secondary to cortical deterioration. Most cases of the panencephalopathic type disclosed Involvement of anatomically-interrelated systems in various combinations (inferior olivary nucleus-pontine nucleuscerebellar cortex, globus pallidus-subthalamus-substantia nigra, optic tract-lateral geniculate body-optic radiation, and primary thalamic degeneration). These associated findings which could be paralleled as those of combined multisystemic degenerations have been found not only in the panencephalopathic type but also in other subtypes of CJD including other cases of spongiform encephalopathy with multiple kuru plaques. They cannot be considered as coincidental to CJD.

Aokit et al. [24] retrospectively reviewed six CJD cases, including three with subacute spongiform encephalopathy (SSE), three with panencephalopathic type of CJD (PECJD) and six normal controls with immunohistochemical and quantitative studied. CD68, GFAP, TNF-α, IL1α used to label microglial cells, astrocytes or two cytokines. The authors implied that microglia are increased in number before demyelination and become hypertrophic while phagocytosing myelin in PECJD, and that the negative correlation between the density of microglia and astrocytes is not regulated by either cytokine.

Treatment

Treatment for all forms of CJD is largely symptomatic as no established curative agents have been identified. A number of different experimental agents are currently under investigation including quinacrine, which prevented conversion of PrPC to PrPSc during in vitro studies. Pentosan polysulphate has been shown to increase incubation time in animal studies by affecting prion production, replication, and the associated cell toxicity, but data in humans are not clear. Flupirtine has been shown to have a trend toward improving cognitive function but showed no survival improvement. Doxycycline is currently being investigated in treatment trials in Europe [12, 21].

It's tragedy that No effective treatment exists for CJD or any of its variants. A number of drugs have been tested-including steroids, antibiotics and antiviral agents- and have not shown benefits. For that reason, doctors focus on alleviating pain and other symptoms and on making people with these diseases as comfortable as possible [14, 18].

Conclusion

Even CJD cannot be cured and finally cause death. The health education to public or medical staff must be emphasized in present China. Potential susceptible herd of Creutzfeldt-Jakob disease should pay more attention to rapid mental deterioration, usually within a few months. Our multimode detections remain high evidential weight in the diagnosis of CJD. Thus, a thorough clinical work-up including transcranial biopsy of rapid dementia diagnosis should be performed to identify their origin especially with regard of potentially treatable forms. DWI is extremely useful in detecting CJD during the very early phase-even before the onset of characteristic clinical findings. CSF biomarker was regarded as important support for identify CJD. During primary phase, biopsy guided by MRI could differentiate of rapid dementia forms once other clinical process's sensibility or specificity was distrusted. A marked spongy change is evident in the gray matter of the putamen, whereas the bundles of white matter are relatively intact.

Although an intracranial biopsy procedure is invasive and carries risk of cerebral infection or hematoma, generally it is a safe, well-tolerated procedure. Special precautions to prevent the spread of prions must be taken. Disposable medical supplies must be destroyed by incineration and surgical instruments need to be autoclaved in sodium hydroxide.

Acknowledgements

This research was supported by Financial assistance from the Foundation of Medical and health general research plan of Zhejiang Province, 2014KYA103.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jianmin Zhang, Department of Neurosurgery, Second Affiliated Hospital, Zhejiang University College of Medicine, Hangzhou, China. Tel: +86-571-87784785; Fax: +86-571-87784755; E-mail: zjm135@vip.sina.com

References

[1] Muayqil T, Gronseth G, Camicioli R. Evidence-based guideline: Diagnostic accuracy of CSF 14-3-3 protein in sporadic Creutzfeldt-Jakob disease: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2012; 79: 1499-1506.

[2] Gomori AJ, Partnow MJ, Hirano A. The ataxic form of Creutzfeldt-Jakob disease. Arch Neurol 1973; 29: 318-323.

[3] Stoeck K, Sanchez-Juan P, Gawinecka J, Green A, Ladogana A, Pocchiari M, Sanchez-Valle R, Mitrova E, Sklaviadis T, Kulczycki J, Slivarichova D, Saiz A, Calero M, Knight R, Aguzzi A, Laplanche JL, Peoc'h K, Schelzke G, Karch A, van Duijn CM, Zerr I. Cerebrospinal fluid biomarker supported diagnosis of Creutzfeldt-Jakob disease and rapid dementias: a longitudinal multicentre study over 10 years. Brain 2012; 135: 3051-3061.

[4] Lodi R, Parchi P, Tonon C, Manners D, Capellari S, Strammiello R, Rinaldi R, Testa C, Malucelli E, Mostacci B, Rizzo G, Pierangeli G, Cortelli P, Montagna P, Barbiroli B. Magnetic resonance diagnostic markers in clinically sporadic prion disease: a combined brain magnetic resonance imaging and spectroscopy study. Brain 2009; 132: 2669-2679.

[5] Chohan G, Pennington C, Mackenzie JM, Andrews M, Everington D, Will RG, The role of cerebrospinal fluid 14-3-3 and other proteins in the diagnosis of sporadic Creutzfeldt-Jakob disease in the UK: a 10-year review. J Neurol Neurosurg Psychiatry 2010; 81: 1243-1248.

[6] de Pedro-Cuesta J, Mahillo-Fernandez I, Rabano A, Celero M, Cruz M, Siden A, Laursen H, Falkenhorst G, Mølbak K; EUROSURGYCJD Research Group. Nosocomial transmission of sporadic Creutzfeldt-Jakob disease: results from a risk-based assessment of surgical interventions. J Neurol Neurosurg Psychiatry 2011; 82: 204-212.

[7] Javed Q, Alam F, Krishna S, Jaganathan G. An unusual case of sporadic Creutzfeldt-Jakob disease (CJD). BMJ Case Rep 2010; 2010.

[8] Buganza M, Ferrari S, Cecchini ME, Orrico D, Monaco S, Zanusso G. The oldest old Creutzfeldt-Jakob disease case. J Neurol Neurosurg Psychiatry 2009; 80: 1140-1142.

[9] Zerr I, Kallenberg K, Summers DM, Romero C, Taratuto A, Heinemann U, Breithaupt M, Varges D, Meissner B, Ladogana A, Schuur M, Haik S, Collins SJ, Jansen GH, Stokin GB, Pimentel J, Hewer E, Collie D, Smith P, Roberts H, Brandel JP, van Duijn C, Pocchiari M, Begue C, Cras P, Will RG, Sanchez-Juan P. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. Brain 2009; 132: 2659-68.

[10] Bouwman NA, Verhagen WI, Meulstee J. EEG Abnormalities in Poikilothermia Suggesting Creutzfeldt-Jakob Disease. Clin EEG Neurosci 2009; 40: 196-199.

[11] Manners DN, Parchi P, Tonon C, Capellari S, Strammiello R, Testa C, Tani G, Malucelli E, Spagnolo C, Cortelli P, Montagna P, Lodi R, Barbiroli B. Pathologic correlates of diffusion MRI changes in Creutzfeldt-Jakob disease. Neurology 2009; 72: 1425-1431.

[12] Klug GM, Wand H, Boyd A, Law M, Whyte S, Kaldor J, Masters CL, Collins S. Enhanced geographically restricted surveillance simulates sporadic Creutzfeldt-Jakob disease cluster. Brain 2009; 132: 493-501.

[13] Brown P. Transmissible spongiform encephalopathy in the 21st century: Neuroscience for the clinical neurologist. Neurology 2008; 70: 713-722.

[14] Heinemann U, Krasnianski A, Meissner B, Varges D, Kallenberg K, Schulz-Schaeffer WJ, Steinhoff BJ, Grasbon-Frodl EM, Kretzschmar HA, Zerr I. Creutzfeldt-Jakob disease in Germany: a prospective 12-year surveillance. Brain 2007; 130: 1350-1359.

[15] Collins SJ, Sanchez-Juan P, Masters CL, Klug GM, van Duijn C, Poleggi A, Pocchiari M, Almonti S, Cuadrado-Corrales N, de Pedro-Cuesta J, Budka H, Gelpi E, Glatzel M, Tolnay M, Hewer E, Zerr I, Heinemann U, Kretszchmar HA, Jansen GH, Olsen E, Mitrova E, Alpérovitch A, Brandel JP, Mackenzie J, Murray K, Will RG. Determinants of diagnostic investigation sensitivities across the clinical spectrum of sporadic Creutzfeldt-Jakob disease. Brain 2006; 129: 2278-2287.

[16] Jara M, John B, Kreindel S, Wilk-Rivard E, DeMaria A Jr. Diagnostic Evaluation for Creutzfeldt-Jakob Disease in Massachusetts, 1991-2001. Clin Infect Dis 2005; 41: 829-833.

[17] Tschampa HJ, Kallenberg K, Urbach H, Meissner B, Nicolay C, Kretzschmar HA. MRI in the diagnosis of sporadic Creutzfeldt-Jakob dis-

ease: a study on inter-observer agreement. Brain 2005; 128: 2026-2033.
[18] Sellars RJ, Collie DA, Will RJ. Progress in Understanding Creutzfeldt-Jakob Disease. AJNR Am J Neuroradiol 2002; 23: 1070-1072.
[19] Belay ED, Schonberger LB. Variant Creutzfeldt-Jakob disease and bovine spongiform encephalopathy. Clin Lab 2002; 22: 849-62.
[20] Klug GM, Boyd A, McGlade A, Stehmann C, Masters CL, Collins SJ. Surveillance of Creutzfeldt-Jakob disease in Australia: update to December 2010. Commun Dis Intell 2011; 35: 149-53.
[21] Pocchiari M, Puopolo M, Croes EA, Budka H, Gelpi E, Collins S, Lewis V, Sutcliffe T, Guilivi A, Delasnerie-Laupretre N, Brandel JP, Alperovitch A, Zerr I, Poser S, Kretzschmar HA, Ladogana A, Rietvald I, Mitrova E, Martinez-Martin P, de Pedro-Cuesta J, Glatzel M, Aguzzi A, Cooper S, Mackenzie J, van Duijn CM, Will RG. Predictors of survival in sporadic Creutzfeldt-Jakob disease and other human transmissible spongiform encephalopathies. Brain 2004; 127: 2348-59.
[22] Tschampa HJ, Neumann M, Zerr I, Henkel K, Schröter A, Schulz-Schaeffer WJ, Steinhoff BJ, Kretzschmar HA, Poser S. Patients with Alzheimer's disease and dementia with Lewy bodies mistaken for Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry 2001; 71: 33-9.
[23] Engler H, Nennesmo I, Kumlien E, Gambini JP, Lundberg P, Savitcheva I, Långström B. Imaging astrocytosis with PET in Creutzfeldt-Jakob disease: case report with histopathological findings. Int J Clin Exp Med 2012; 5: 201-7.
[24] Aokit T, Kobayashik K, Isakik K. Microglial and astrocytic change in brains of Creutzfeldt-Jakob disease: an immunocytochemical and quantitative study. Clin Neuropathol 1999; 18: 51-60.
[25] Hsich G, Kenney K, Gibbs CJ Jr, Lee KH, Harrington MG. The 14-3-3 brain protein in cerebrospinal fluid as a marker for transmissible spongiform encephalopathies. N Engl J Med 1996; 335: 924-30.
[26] Linguraru MG, Ayache N, Bardinet E, Ballester MA, Galanaud D, Haïk S, Faucheux B, Hauw JJ, Cozzone P, Dormont D, Brandel JP. Differentiation of sCJD and vCJD forms by automated analysis of basal ganglia intensity distribution in multisequence MRI of the brain--definition and evaluation of new MRI-based ratios. Trans Med Imaging 2006; 25: 1052-67.
[27] Schuette AJ, Taub JS, Hadjipanayis CG, Olson JJ. Open biopsy in patients with acute progressive neurologic decline and absence of mass lesion. Neurology 2010; 75: 419-24.