UCSF

Title

Differential Diagnosis of Jakob-Creutzfeldt Disease

Authors

Paterson, Ross W
Torres-Chae, Charles C
Kuo, Amy L
et al.

Differential Diagnosis of Jakob-Creutzfeldt Disease

Ross W. Paterson, MRCP; Charles C. Torres-Chae, MPA; Amy L. Kuo, MS, RN, GNP; Tim Ando, BA;
Elizabeth A. Nguyen, BS; Katherine Wong, BS; Stephen J. DeArmond, MD, PhD; Aissa Haman, MD;
Paul Garcia, MD; David Y. Johnson; Bruce L. Miller, MD; Michael D. Geschwind, MD, PhD

Objectives: To identify the misdiagnoses of patients with sporadic Jakob-Creutzfeldt disease (sCJD) during the course of their disease and determine which medical specialties saw patients with sCJD prior to the correct diagnosis being made and at what point in the disease course a correct diagnosis was made.

Design: Retrospective medical record review.

Setting: A specialty referral center of a tertiary academic medical center.

Participants: One hundred sixty-three serial patients over a 5.5-year period who ultimately had pathologically proven sCJD. The study used the subset of 97 patients for whom we had adequate medical records.

Main Outcome Measures: Other diagnoses considered in the differential diagnosis and types of medical specialties assessing patients with sCJD.

Results: Ninety-seven subjects' records were used in the final analysis. The most common disease categories of misdiagnosis were neurodegenerative, autoimmune/paraneoplastic, infectious, and toxic/metabolic disorders. The most common individual misdiagnoses were viral encephalitis, paraneoplastic disorder, depression, vertigo, Alzheimer disease, stroke, unspecified dementia, central nervous system vasculitis, peripheral neuropathy, and Hashimoto encephalopathy. The physicians who most commonly made these misdiagnoses were primary care physicians and neurologists; in the 18% of patients who were diagnosed correctly at their first assessment, the diagnosis was almost always by a neurologist. The mean time from onset to diagnosis was 7.9 months, an average of two-thirds of the way through their disease course.

Conclusions: Diagnosis of sCJD is quite delayed. When evaluating patients with rapidly progressive dementia with suspected neurodegenerative, autoimmune, infectious, or toxic/metabolic etiology, sCJD should also be included in the differential diagnosis, and appropriate diagnostic tests, such as diffusion brain magnetic resonance imaging, should be considered. Primary care physicians and neurologists need improved training in sCJD diagnosis.

Arch Neurol. 2012;69(12):1578-1582. Published online September 24, 2012. doi:10.1001/2013.jamaneurol.79

THERE ARE OFTEN LONG DElays between the time that a patient with sporadic Jakob-Creutzfeldt disease (sCJD) first presents to the physician and the time that a correct diagnosis is made. Sporadic CJD is misdiagnosed for many reasons, including the variability of early symptoms and signs,[1-4]

the variability in disease duration, and lack of recognition of this condition in the medical community.[5] Depending on where prions accumulate in the brain, the clinical presentation can be variable[6,7] and sCJD is easily mistaken for other neurodegenerative conditions such as Alzheimer disease, corticobasal degeneration, and dementia with Lewy bodies.[8-10]

As a major center for referral of human prion diseases, we have noted that many of the families of patients with sCJD complain of the delay in diagnosis and the multitude of misdiagnoses that were given prior to sCJD being properly identified. This prompted our retrospective study to determine the most common early misdiagnoses, determine at what point in the disease course the correct diagnosis of sCJD was made, and identify which medical specialties were making the misdiagnoses. Expediting an sCJD diagnosis will help avoid potential infection control issues and extensive and costly evaluations for other conditions, allow families to focus on patient care and end-of-life planning, and facilitate early enrollment in ongoing and future treatment trials.
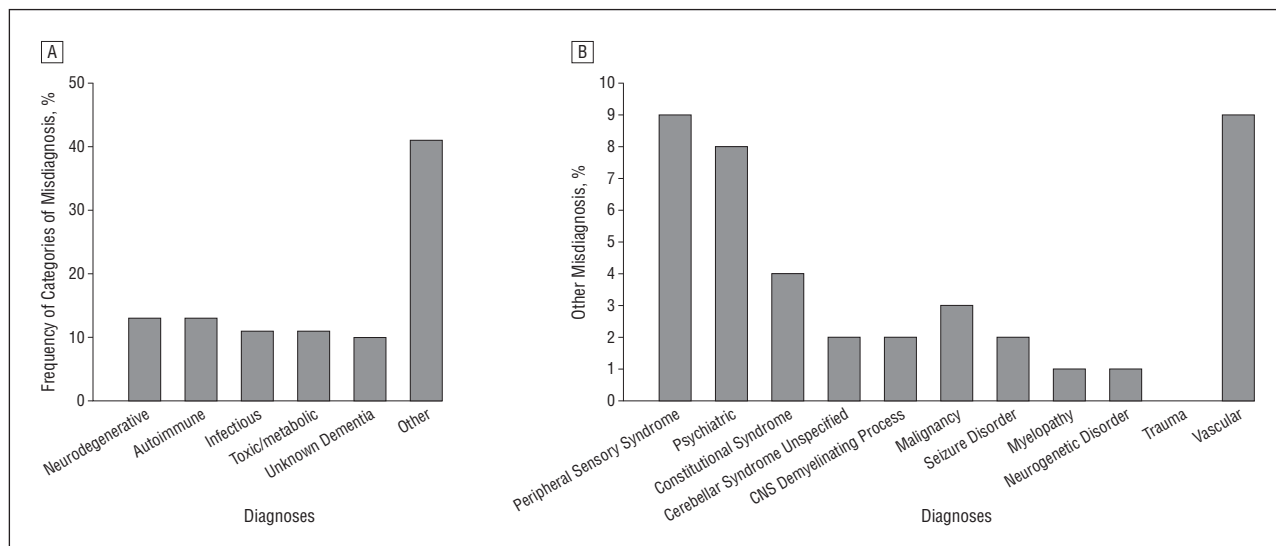
Author Affiliations:
Departments of Neurology (Drs Paterson, Haman, Garcia, Miller, and Geschwind, Messrs Torres-Chae, Ando, and Johnson, and Mss Kuo, Nguyen, and Wong) and Pathology (Dr DeArmond), University of California, San Francisco.

Figure. Frequencies of categories of misdiagnoses in patients with sporadic Jakob-Creutzfeldt disease. A, General diagnostic categories. B, Misdiagnoses within the "Other" category. CNS indicates central nervous system.

STUDY POPULATION AND DATA COLLECTION

We received approval for this study from our institution's internal review board. For this study, we retrospectively reviewed all cases referred to the UCSF Memory and Aging Center rapidly progressive dementia and CJD clinical research program between August 2001 and February 2007. This included patients initially assessed through our inpatient National Institutes of Health research unit, evaluated in our neurobehavioral clinic, or admitted to the inpatient neurology service or those who were not seen at University of California, San Francisco but who had extensive record review.

Subjects were included in the study if they had pathology-proven sCJD and records included most or all of their physician and hospital visits; if only 1 or 2 visit summaries were missing, the records were still included unless the missing summaries included the patient's first physician consultation. Qualifying records were then reviewed to determine all non-CJD diagnoses considered up to when probable sCJD became the single most likely diagnosis or when the patient received a diagnosis at our center, whichever came first. Non-CJD diagnoses were given a confidence probability value on a Likert scale of 1 to 5[11] based on what we perceived from the record review the diagnosing physician's diagnostic confidence level to be: 1 meant the diagnosis was considered most likely; 2, likely; 3, possible (but other conditions also possible); 4, unlikely; and 5, highly unlikely but wanted to rule it out. Only non-CJD diagnoses with a confidence probability value of 1 and 2 were used for this analysis. The time taken to make a diagnosis of sCJD was calculated for each subject. This was possible in 92 of 97 subjects with a documented first symptom date, diagnosis date, and date of death (date of first symptom not available for 3 and diagnosis date not available for 2 subjects).

STATISTICAL ANALYSES

To simplify data analysis, misdiagnoses were first classified into 16 general diagnostic categories, classified by etiology (eg, infectious and neurodegenerative).

COHORT CHARACTERISTICS

Between August 2001 and February 2007, our center collected 976 records, and at the time of the analysis, we had received pathological confirmation on 163 of the 976 patients. We identified 97 patients with pathology-proven sCJD for whom we had sufficient medical records. Forty were female and 57, male, with ages from 26 to 83 years (mean [SD] age, 62 [11.2] years).

MISDIAGNOSES

Our cohort of 97 patients with sCJD received a combined total of 373 alternative diagnoses prior to their diagnosis of likely CJD, with an average of 3.8 misdiagnoses per subject. The **Figure** shows the 16 general diagnostic categories of misdiagnosis and their frequency in this cohort. Neurodegenerative, autoimmune, infectious, toxic/metabolic, and unknown dementias were the categories under which patients with sCJD were most commonly misdiagnosed. **Table 1** shows the 10 most common specific conditions misdiagnosed for CJD. **Table 2** shows some of the common conditions found in each of the 5 most common (of 16) diagnostic categories. Seventy-five percent of patients were initially assessed by either a primary care physician (40%) or a neurologist (36%). Most patients were first seen by their primary care physician and then referred to a neurologist. Only 25% of patients were first seen by a specialist other than a neurologist. The first specialists to see these 97 patients were neurologists (n=70), ophthalmologists (n=6), psychiatrists (n=4), cardiologists (n=4), otolaryngologists (n=2), orthopedists (n=2), and neuro-oncologists (n=1) (**Table 3**). The types of all physicians to see these patients prior to being given a diagnosis of likely sCJD (eg, diagnostic confidence category 1

Table 1. Top 10 Individual Misdiagnoses for Sporadic Jakob-Creutzfeldt Disease in Decreasing Frequency

Misdiagnosis

1. Viral encephalitis
2. Paraneoplastic disorder
3. Depression
4. Peripheral vertigo
5. Alzheimer disease
6. Stroke
7. Dementia, nonspecified
8. Central nervous system vasculitis
9. Peripheral neuropathy
10. Hashimoto encephalopathy

Table 2. Most Common Misdiagnoses Within Top 5 Major Diagnostic Categories[a]

Diagnostic Category	% of Patients
Neurodegenerative	13
Alzheimer disease	4
Dementia with Lewy bodies	1
Frontotemporal dementia	2
Corticobasal degeneration	1
Normal-pressure hydrocephalus	1
Multiple-system atrophy	0[b]
Motor neuron disease	0[b]
Parkinsonian disorder	2
Neurodegenerative, not specified	2
Autoimmune	13
Paraneoplastic	5
Vasculitis	3
Neurosarcoidosis	0[b]
Hashimoto encephalitis	1
Autoimmune process	3
Infectious	11
Encephalitis	6
Whipple disease	1
Infectious/inflammatory process	2
Rabies	1
Herpes simplex virus	1
Postinfectious syndrome	1
Toxic/metabolic	11
Vitamin B_{12} deficiency	1
Metabolic process	2
Hypothyroidism	1
Drug adverse effect	2
Wernicke-Korsakoff syndrome	1
Urinary tract infection	1
Other	4
Unknown dementia	10
Encephalopathy	2
Mild cognitive impairment	1
"Dementia"	6
Other	4
Total	**100**

[a] Three hundred ninety-three misdiagnoses among 97 subjects with sporadic Jakob-Creutzfeldt disease.
[b] There was only 1 case.

Table 3. First Specialist to See Patient[a]

Specialist	No. (%)
Neurologist	71 (73)
Ophthalmologist	6 (6)
Psychiatrist	5 (5)
Cardiologist	4 (4)
Optometrist	3 (3)
Otolaryngologist	2 (2)
Pulmonologist	2 (2)
Orthopedic surgeon	2 (2)
Neuro-oncologist	1 (1)
Gastroenterologist	1 (1)

[a] N = 97 patients.

Table 4. All Physicians to Have Made an Incorrect Assessment in Cohort[a]

Specialist Type	No. (%)
Neurologist	95 (42.4)
Internist	51 (22.8)
Unspecified	15 (6.7)
Family physician	14 (6.3)
Ophthalmologist	8 (3.6)
Cardiologist	6 (2.7)
Physiatrist	6 (2.7)
Pulmonologist	5 (2.2)
Psychiatrist	5 (2.2)
Otolaryngologist	3 (1.3)
Geriatrician	2 (0.9)
Optometrist	2 (0.9)
Orthopedic surgeon	2 (0.9)
Neuro-oncologist	1 (0.4)
Gastroenterologist	1 (0.4)
Rheumatologist	1 (0.4)
Neuro-ophthalmologist	1 (0.4)
Speech pathologist	1 (0.4)
Infectious diseases specialist	1 (0.4)
Neurosurgeon	1 (0.4)
Neurotologist	1 (0.4)
Total	**222 (100)**

[a] N = 97 patients.

diagnoses were made by neurologists and 1, by a rehabilitation physician. **Table 5** shows the time taken for sCJD to be considered in the differential diagnosis and also the time then taken for the diagnosis of CJD to be made ("likely CJD").

COMMENT

To our knowledge, this is the first large study of pathologically proven cases of sCJD that retrospectively determines what misdiagnoses are made in the workup of sCJD, who makes these misdiagnoses, and how long it takes to reach the correct diagnosis. We found that CJD is rarely the first diagnosis made and it is usually confused with a wide range of other conditions. It is not surprising that the top misdiagnoses categories were neurodegenerative, autoimmune/paraneoplastic, infectious, and toxic/metabolic conditions, as these are common forms of nonprion rapidly progressive dementia.[9,12,13] That

or 2) are shown in **Table 4**; neurologists and internists comprised the vast majority of the physicians making the misdiagnoses. Of the 17 subjects (18%) who received the correct diagnosis on first assessment, 16 of these correct

Table 5. Disease Duration and Significant Diagnosing Event

	Disease Course, mo	Time From First Symptoms to CJD Mentioned in the Differential, mo	Time From First Symptoms to CJD "Likely" Diagnosis or Contacting UCSF, mo[a]	% of Disease Course Before Contacting UCSF or CJD Diagnosis[b]
Sample size[c]	94	60	92	92
Mean (SD)	12.0 (10.3)	6.7 (6.5)	7.8 (6.9)	67.7 (0.2)
Median (range)	12.0 (0.8-57.7)	4.9 (0.4-39.1)	6.0 (0.9-39.2)	68.9 (18.6-99.4)

Abbreviations: CJD, Jakob-Creutzfeldt disease; UCSF, University of California, San Francisco.
[a] Time used for whichever comes first: patient being referred to UCSF CJD/rapidly progressive dementia program or medical records suggesting CJD as the likely diagnosis.
[b] Either probable clinical diagnosis or definite (pathology-proven) diagnosis.
[c] Number of subjects available for each analysis; for 5 subjects, records were not sufficient to identify specific dates.

the most common individual misdiagnosis was viral encephalitis is probably due to the multifocality, acuity, and rapidity of symptoms seen in sCJD. Despite a neurologist being the first specialist to see most patients with sCJD, there were many misdiagnoses, with each subject receiving almost 4 other diagnoses before CJD became the likely diagnosis. Consequently, subjects were diagnosed late, two-thirds of the way through their disease course.

One possible reason misdiagnosis is so common is that the diagnostic criteria for sCJD are insensitive to early symptoms.[1] Whereas sCJD can only be definitively confirmed through pathology, there are a variety of probable CJD diagnostic criteria.[14-17] Most of these criteria were designed for epidemiologic surveillance purposes to diagnose sCJD post mortem in patients whose disease was not pathologically proven.[15] World Health Organization probable sCJD criteria[15] rely heavily on the presence of cerebrospinal fluid 14-3-3 protein, the utility of which is dubious.[18-20] More recent research has found magnetic resonance imaging (MRI) findings to be more sensitive and specific than 14-3-3.[17,21] Physicians relying on certain criteria might not properly include CJD in the differential diagnosis nor appreciate the value of diffusion-weighted imaging and apparent diffusion coefficient sequences that improve MRI sensitivity to around 91% to 96%[21-24] and specificity to around 91% to 95%.[21-23]

Based on this study, if neurodegenerative, autoimmune, infectious, or toxic/metabolic etiologies appear on the list of differential diagnoses of a patient with a rapidly progressive dementia, then the clinician should also consider sCJD. Equally, if evidence to support a diagnosis of viral encephalitis, paraneoplastic disorder, depression, peripheral vertigo, Alzheimer disease, stroke, dementia (nonspecified), central nervous system vasculitis, peripheral neuropathy, or Hashimoto encephalopathy is lacking, then the clinician should think about requesting an MRI with diffusion-weighted imaging/apparent diffusion coefficient sequences to look for changes associated with sCJD. Unfortunately, even the pathognomonic MRI findings of CJD are missed by about two-thirds of radiology reports,[25] and thus, it is critical that physicians be aware of MRI findings in prion disease[21] and read their patients' MRIs.

In any patient with a rapidly progressive dementia who has been given multiple potential diagnoses, sCJD must be considered. Although neurologists were more likely to make the correct diagnosis on first assessment than other physicians, this occurred uncommonly and neurologists were also the type of physician to most commonly assess these patients and therefore make misdiagnoses, followed by internists. Education about the diagnosis of CJD perhaps should focus on these 2 specialties. About 25% of patients were first seen by a nonneurology specialist; education of these other specialists about early signs of sCJD might also improve earlier diagnosis.

Although this current study focused on patients with sCJD being misdiagnosed with other conditions, the contrary—patients with non-CJD diagnoses being diagnosed with CJD—is equally, if not more, harmful, as many of these non-CJD rapidly progressive dementias are treatable if not even curable. Chitravas et al[12] recently demonstrated that 32% of subjects referred to the US National Prion Disease Pathology Surveillance Center for autopsy with suspected CJD had a non-CJD diagnosis, and 7% of all cases had a treatable etiology. The experience in our center and other centers evaluating many rapidly progressive dementias is similar.[9,13,26,27] Furthermore, subjects might fulfill clinical criteria, particularly symptom criteria, for more than 1 disease. In 1 study, patients with pathologically proven sCJD fulfilled the "probable" criteria for dementia with Lewy bodies (29%) and Alzheimer disease (45%).[28] Similarly, in a recent article from our own group, we found 46% of subjects with sCJD met probable dementia with Lewy bodies criteria and 40% of subjects with dementia with Lewy bodies met probable CJD criteria. The value of a thorough diagnostic workup is therefore critical.[9]

Early and accurate diagnosis of sCJD is of value for public health reasons and to allow for potential treatments to be tested as early as possible in the disease course.[29,30] Avoiding iatrogenic transmission of human prion disease by early diagnosis is also critical.[31,32] It would therefore be valuable to improve early and accurate diagnosis of sCJD premortem to identify at-risk persons, allowing for public health measures that would prevent transmission to healthy individuals through blood donation, infected surgical equipment, and or other medical procedures.[33]

Correspondence: Michael Geschwind, MD, PhD, University of California, San Francisco, Box 1207, San Fran-

REFERENCES

1. Rabinovici GD, Wang PN, Levin J, et al. First symptom in sporadic Creutzfeldt-Jakob disease. *Neurology.* 2006;66(2):286-287.
2. Will RG, Matthews WB. A retrospective study of Creutzfeldt-Jakob disease in England and Wales 1970-79, I: clinical features. *J Neurol Neurosurg Psychiatry.* 1984;47(2):134-140.
3. Brown P, Cathala F, Castaigne P, Gajdusek DC. Creutzfeldt-Jakob disease: clinical analysis of a consecutive series of 230 neuropathologically verified cases. *Ann Neurol.* 1986;20(5):597-602.
4. Tsuji S, Kuroiwa Y. Creutzfeldt-Jakob disease in Japan. *Neurology.* 1983;33(11):1503-1506.
5. Parchi P, Giese A, Capellari S, et al. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. *Ann Neurol.* 1999;46(2):224-233.
6. Heidenhain A. Klinische und anatomische Untersuchungen u¨ber eine eigenartige organische Erkrankung des Zentralnervensystems im Praesenium. *Z Gesamte Neurol Psychiatr.* 1929;118:49-114.
7. Akai J, Kumagai N, Imai S, Tsuchiya Y, Kato Y. Creutzfeldt-Jakob disease, an ataxic type (Brownell-Oppenheimer) [in Japanese]. *Rinsho Shinkeigaku.* 1976;16(2):124-131.
8. Tschampa HJ, Neumann M, Zerr I, et al. Patients with Alzheimer's disease and dementia with Lewy bodies mistaken for Creutzfeldt-Jakob disease. *J Neurol Neurosurg Psychiatry.* 2001;71(1):33-39.
9. Geschwind MD, Shu H, Haman A, Sejvar JJ, Miller BL. Rapidly progressive dementia. *Ann Neurol.* 2008;64(1):97-108.
10. Tartaglia MC, Johnson DY, Thai JN, et al. Clinical overlap between Jakob-Creutzfeldt disease and Lewy body disease. *Can J Neurol Sci.* 2012;39(3):304-310.
11. Likert R, Roslow S, Murphy G. A simple and reliable method of scoring the Thurstone Attitude Scales. *J Soc Psychol.* 1934;5(2):228-238. doi:10.1080/00224545.1934.9919450.
12. Chitravas N, Jung RS, Kofskey DM, et al. Treatable neurological disorders misdiagnosed as Creutzfeldt-Jakob disease. *Ann Neurol.* 2011;70(3):437-444.
13. Poser S, Mollenhauer B, Kraubeta A, et al. How to improve the clinical diagnosis of Creutzfeldt-Jakob disease. *Brain.* 1999;122(pt 12):2345-2351.
14. Masters CL, Harris JO, Gajdusek DC, Gibbs CJ Jr, Bernoulli C, Asher DM. Creutzfeldt-Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. *Ann Neurol.* 1979;5(2):177-188.
15. WHO. *Global Surveillance, Diagnosis, and Therapy of Human Transmissible Spongiform Encephalopathies: Report of a WHO Consultation.* Geneva, Switzerland: World Health Organization; 1998.
16. Geschwind MD, Josephs KA, Parisi JE, Keegan BM. A 54-year-old man with slowness of movement and confusion. *Neurology.* 2007;69(19):1881-1887.
17. Zerr I, Kallenberg K, Summers DM, et al. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. *Brain.* 2009;132(pt 10):2659-2668.
18. Geschwind MD, Martindale J, Miller D, et al. Challenging the clinical utility of the 14-3-3 protein for the diagnosis of sporadic Creutzfeldt-Jakob disease. *Arch Neurol.* 2003;60(6):813-816.
19. Chapman T, McKeel DW Jr, Morris JC. Misleading results with the 14-3-3 assay for the diagnosis of Creutzfeldt-Jakob disease. *Neurology.* 2000;55(9):1396-1397.
20. Satoh J, Kurohara K, Yukitake M, Kuroda Y. The 14-3-3 protein detectable in the cerebrospinal fluid of patients with prion-unrelated neurological diseases is expressed constitutively in neurons and glial cells in culture. *Eur Neurol.* 1999;41(4):216-225.
21. Vitali P, Maccagnano E, Caverzasi E, et al. Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. *Neurology.* 2011;76(20):1711-1719.
22. Shiga Y, Miyazawa K, Sato S, et al. Diffusion-weighted MRI abnormalities as an early diagnostic marker for Creutzfeldt-Jakob disease. *Neurology.* 2004;63(3):443-449.
23. Young GS, Geschwind MD, Fischbein NJ, et al. Diffusion-weighted and fluid-attenuated inversion recovery imaging in Creutzfeldt-Jakob disease: high sensitivity and specificity for diagnosis. *AJNR Am J Neuroradiol.* 2005;26(6):1551-1562.
24. Tschampa HJ, Zerr I, Urbach H. Radiological assessment of Creutzfeldt-Jakob disease. *Eur Radiol.* 2007;17(5):1200-1211.
25. Geschwind MK, Kuryan C, Cattaruzza T, Vitali P, DeArmond S, Wong KS. Brain MRI in Sporadic Jakob-Creutzfeldt disease is often misread [abstract]. *Neurology.* 2010(suppl 2):74.
26. Geschwind MD, Haman A, Miller BL. Rapidly progressive dementia. *Neurol Clin.* 2007;25(3):783-807.
27. Papageorgiou SG, Kontaxis T, Bonakis A, Karahalios G, Kalfakis N, Vassilopoulos D. Rapidly progressive dementia: causes found in a Greek tertiary referral center in Athens. *Alzheimer Dis Assoc Disord.* 2009;23(4):337-346.
28. Van Everbroeck B, Dobbeleir I, De Waele M, De Deyn P, Martin JJ, Cras P. Differential diagnosis of 201 possible Creutzfeldt-Jakob disease patients. *J Neurol.* 2004;251(3):298-304.
29. Korth C, Peters PJ. Emerging pharmacotherapies for Creutzfeldt-Jakob disease. *Arch Neurol.* 2006;63(4):497-501.
30. Geschwind MD. Clinical trials for prion disease: difficult challenges, but hope for the future. *Lancet Neurol.* 2009;8(4):304-306.
31. Will RG. Acquired prion disease: iatrogenic CJD, variant CJD, kuru. *Br Med Bull.* 2003;66:255-265.
32. Brown P, Brandel JP, Preece M, Sato T. Iatrogenic Creutzfeldt-Jakob disease: the waning of an era [published correction appears in *Neurology.* 2006;67(8):1528]. *Neurology.* 2006;67(3):389-393.
33. Peden A, McCardle L, Head MW, et al. Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. *Haemophilia.* 2010;16(2):296-304.