Published in final edited form as:

Ann Neurol. 2011 September ; 70(3): 437–444. doi:10.1002/ana.22454.

Treatable Neurological Disorders Misdiagnosed as Creutzfeldt - Jakob disease

Numthip Chitravas, MD¹, Richard S. Jung, MD¹, Diane M. Kofskey³, Janis E. Blevins³, Pierluigi Gambetti, MD³, R. John Leigh, MD¹, and Mark L. Cohen, MD²

¹ Department of Neurology, University Hospitals Case Medical Center, Cleveland Ohio

² Department of Pathology, University Hospitals Case Medical Center, Cleveland Ohio

³ National Prion Disease Pathology Surveillance Center (NPDPSC), Case Western Reserve University, Cleveland Ohio

Abstract

Objective—Heightened awareness of Creutzfeldt-Jakob disease (CJD) among physicians and the lay public has led to its frequent consideration in the differential diagnosis of patients with rapidly progressive dementia (RPD). Our goal was to determine which treatable disorders are most commonly mistaken for CJD.

Methods—We performed a retrospective clinical and neuropathological review of prion-negative brain autopsy cases referred to the US National Prion Disease Pathology Surveillance Center (NPDPSC) at Case Western Reserve University from January 2006 through December 2009.

Results—Of 1,106 brain autopsies, 352 (32%) were negative for prion disease, 304 of which had adequate tissue for histopathological analysis. Alzheimer disease (154) and vascular dementia (36) were the two most frequent diagnoses. Seventy one patients had potentially treatable diseases. Clinical findings included dementia (42 cases), pyramidal (20), cerebellar (14), or extrapyramidal (12) signs, myoclonus (12), visual disturbance (9) and akinetic mutism (5); a typical electroencephalogram occurred only once. Neuropathological diagnoses included immune-mediated disorders (26), neoplasia (25, most often lymphoma), infections (14), and metabolic disorders (6).

Interpretation—In patients with RPD, treatable disorders should be considered and excluded before diagnosing CJD. Misdiagnosed patients often did not fulfill WHO criteria. RPD with positive 14-3-3 CSF protein should not be regarded as sufficient for the diagnosis of CJD. Adherence to revised criteria for CJD, which include distinctive MRI features of prion disease, is likely to improve diagnostic accuracy.

Introduction

Increasing awareness of transmissible spongiform encephalopathies has led to more frequent diagnostic consideration of sporadic Creutzfeldt-Jakob disease (sCJD). The National Prion Disease Pathology Surveillance Center (NPDPSC, Case Western Reserve University, Cleveland, Ohio) assists clinicians and pathologists in analyzing surgical and autopsy brain tissue from patients with suspected prion disease. Referrals to the NPDPSC from across the United States have gradually increased over the past decade; details are available at <http://www.cjdsurveillance.com/casetable.html>. Comprehensive biochemical and

immunohistochemical analyses of these cases demonstrate that many do not have prion disease. Possible reasons for referral of prion-negative cases include: 1) higher prevalence of non-prion disorders causing rapidly progressive dementia (RPD);¹ 2) over-reliance of cerebrospinal fluid (CSF) 14-3-3 protein;^{2, 3} and 3) growing awareness of services provided by NPDPSC, leading to referral of cases for which the diagnosis of CJD was considered possible, but not likely.

Studies from other prion disease referral centers have reported that the most common prion-negative etiologies of rapidly progressive dementia (RPD) are Alzheimer disease, vascular dementia, frontotemporal dementia and dementia with Lewy bodies.^{1, 4-7} Treatable disorders, such as Hashimoto encephalitis, toxic or metabolic encephalopathies, and cerebral lymphoma have also been reported.^{1, 5, 6} Supplementary Table 1 summarizes disorders misdiagnosed as CJD disease drawing on two prior studies. Due to the limited numbers of pathology-proven diagnoses, the frequency and range of treatable diseases has not been defined. The goal of our study was to interrogate our large autopsy database in order to identify and enumerate diseases misdiagnosed as CJD, in particular those disorders amenable to therapeutic intervention.

Methods

We retrospectively reviewed pathological findings of prion-negative autopsy brain tissue for cases initially registered by the NPDPSC from January 2006 through December 2009. Initial registration occurred upon receipt of any CSF, brain biopsy or autopsy tissue. The NPDPSC referral protocols were obtained by referring physicians suspicious of prion disease, available at the website <http://www.cjdsurveillance.com/>. All brain autopsy samples sent to the center must have autopsy consent, a testing and reporting policies form, and patient clinical history and medical records. Previously performed laboratory or imaging details are not required.

Per protocol, frozen brain samples were stored at -80 degrees Celsius. Half-brains were fixed in 10% formalin for a minimum of two weeks. Representative sections were obtained from 16 brain regions, decontaminated for one hour in concentrated formic acid, and embedded in paraffin. Paraffin sections (5 micrometers) were stained with hematoxylin and eosin. Representative sections of neocortex, basal ganglia, hippocampus, cerebellum, and midbrain were also stained immunocytochemically with 3F4 monoclonal antibodies directed against the human prion protein.⁸

Prion negative specimens were evaluated by two neuropathologists (MLC, PG) blinded to the clinical history. The patients' clinical records were reviewed separately by two neurologists (NC, RSJ). This information was provided to the neuropathologists who then re-reviewed the histopathological samples to assess compatibility of the clinical and pathological diagnoses. Abstracted data included demographic, clinical, laboratory and imaging findings. Disease onset was defined as the month in which the patient, family, or any witness (including physicians) noted the first neurological manifestation of a degenerative process. Neurological signs, symptoms, and electroencephalogram (EEG) results were compiled according to currently defined World Health Organization (WHO) criteria for sCJD (Table 1).⁹ Data were coded as missing when adequate documentation was unavailable. When available, brain magnetic resonance imaging (MRI) and CSF results were also obtained from the submitted medical records. We also reviewed CSF 14-3-3 protein western blot results generated in our laboratory throughout the course of the illnesses. We included all autopsy cases with both negative prion immunoblot and immunohistochemical analyses. Cases lacking immunoblot analyses were excluded unless the histopathologic findings were judged sufficient to explain the clinical illness.

We defined potentially treatable disorders as conditions for which therapy could either cure or prolong the life of the patient. These included immunological disorders, tumors, infections, and metabolic disturbances affecting the central nervous system. For the purposes of this study, we considered neurodegenerative disorders such as Alzheimer disease and frontotemporal lobar degeneration untreatable, since symptomatic therapies are not known to modify the disease course.

This study was conducted under a protocol approved by our Institutional Review Board. The subjects remained anonymous, and their nearest of kin were not contacted. Descriptive analysis was performed using statistical software, SPSS version 17.

Results

From cases registered during the study period, the NPDPSA analyzed 1,106 brain autopsies from across the United States. Of these, 352 cases (32%) were negative for prion disease. Although the protocol requires both fixed and frozen brain tissue for analysis, we received and excluded 48 cases with only fixed samples. This left 304 cases available for analysis (Figure 1). Among these 304 cases, only 7 had brain biopsied prior to autopsy; their results are summarized in Supplementary Table 2.

Our analysis confirmed Alzheimer disease (154, 50%) as the most common neurological disorder misdiagnosed as prion disease, followed by vascular dementia (36, 12%); Table 2 lists these and other diagnosed incurable diseases. In this majority group, the median age was 70 years, and median duration of illness was seven months. Since the main focus of this study was to analyze potentially treatable diseases, further characterization of these currently incurable diseases (*i.e.* specific immunostaining) was not performed.

Seventy-one individuals (23% of prion-negative cases) had potentially treatable neurological diseases. Demographic and clinical features of these 71 patients are summarized in Table 3. Median age was 65 (23–87) years, median disease duration was three months (0.5–16), and 55% were male. From our review of available medical records, all patients had cognitive decline and sCJD was listed as one of the differential diagnoses. Eleven percent of the patients met WHO diagnostic criteria for “probable” sCJD, and 18% for “possible” sCJD (Table 4). The remaining 71% of patients had cognitive decline plus only one of the following findings: pyramidal, extrapyramidal, visual, cerebellar, akinetic mutism or myoclonus; thus, in these patients, CJD was suspected but insufficient to meet the WHO criteria. Among these 71 patients, 42 had dementia, 12 had myoclonus, 20 demonstrated pyramidal symptoms, 12 exhibited extrapyramidal symptoms, 14 showed cerebellar dysfunction, nine had visual disturbances, and five developed akinetic mutism. Only one out of 21 available EEG reports was found to have the typical 1 Hz focal or diffuse periodic epileptiform discharges; the pathological diagnosis in this case was glioblastoma multiforme. The majority of the rest of the EEG results revealed a diffused generalized slowing pattern (Table 3).

The results of the CSF 14-3-3 protein tests were available for 56 patients. This test was reported positive (elevated 14-3-3 protein) in more than 50% of these cases (Table 3). CSF tau results were incomplete or missing from many of the medical records submitted by referral physicians and could not be included in the analyses.

MRI reports were available in 39 patients; these are summarized in Supplementary Table 3. Various findings were reported including normal brain, generalized cerebral atrophy, non-specific white matter changes, and signal hyperintensity in thalamus, putamen, internal capsule and brain stem.

The final pathological diagnoses for this potentially treatable group of 71 patients are summarized in Table 5. We divided them into four subgroups: immune-mediated (26), neoplastic (25), infectious (14), and metabolic (6). One representative patient from each of these diagnostic categories, all of whom presented with rapidly progressive dementia (disease duration 3–4 months) and positive CSF 14-3-3 protein, is illustrated in Figure 2,

In the *immune-mediated subgroup*, the median age was 64 years and median disease duration was four months. Diagnoses included primary angiitis of the central nervous system (PACNS, 7), acute disseminated encephalomyelitis (6), limbic encephalitis (6), neurosarcoidosis (4), Wegener granulomatosis (1), and paraneoplastic cerebellar degeneration (2). Figure 2a depicts a histopathological section of thalamus demonstrating granulomatous arteriolar inflammation consistent with primary angiitis of the CNS. Seven of the immune-mediated cases had pre-mortem serologic evidence of anti-neuronal antibodies. Only one case, with a pathological diagnosis of PACNS, was positive for serum adenylate kinase 5; an antibody recently associated with limbic encephalitis.¹⁰ One patient had a pre-mortem diagnosis of lung cancer. Only one medical record provided an anti-thyroid autoantibody result, which was negative.

The *neoplastic subgroup* was the second largest (25); median age was 71 years and median disease duration was three months. Most harbored a variety of malignant lymphoid processes within their central nervous systems (18). These included primary CNS lymphoma (8), angiotrophic lymphoma (8), and leptomeningeal lymphoma (2). The remaining patients had either malignant glioma (5) or leptomeningeal carcinomatosis (2). Lymphomas in our series tended to be widely infiltrative without a dominant mass lesion, (“lymphomatosis cerebri”). Figure 2b shows angiocentric thalamic infiltration by large, pleomorphic lymphoid cells diagnostic of primary central nervous system lymphoma. Of note, this patient had unremarkable CSF cytology and flow cytometry.

In the *infectious subgroup* (14), the median age was 67 years and median disease duration was 2.5 months. A variety of fungal (5), viral (5) and parasitic (4) infections were identified or suspected. *Coccidioides* was the most common fungal pathogen (3) in our series, followed by *Aspergillus* and *Cryptococcus*. Most cases in this group had positive CSF 14-3-3 protein results, as shown in Table 5. Two autopsy cases revealed severe necrotizing eosinophilic meningoencephalitis with identified roundworms. Morphologic preservation in one of these allowed identification of lateral spines, consistent with *Baylisascaris* species (Figure 2c). Two other autopsies revealed necrotizing eosinophilic meningoencephalitis with giant cells consistent with parasitic infection. However, organisms could not be identified. Four autopsies demonstrated lymphocytic meningoencephalitis, consistent with viral infection.

Patients in the *metabolic subgroup* (6) were the youngest; median age was 52 years. Median disease duration of two months was also shortest among the subgroups. Three patients demonstrated ophthalmoplegia, ataxia, and global confusion. Autopsy demonstrated spongiform degeneration in the hypothalamus and brainstem with neuronal sparing, typical of Wernicke encephalopathy. Figure 2d shows a mammillary body from a malnourished patient who suffered from chronic abdominal pain and vomiting. Three autopsies demonstrated metabolic astrocytosis of uncertain etiology.

Discussion

The resources of the NPDPS enabled us to conduct the largest clinicopathological study of treatable neurological disorders misdiagnosed as sCJD to date. We found that one-third of our autopsy-referral cases were negative for prion disease, and almost a quarter of these

patients had been suffering from potentially treatable disorders – a finding of potential importance to many clinicians. Among these prion-negative cases, the commonest incurable pathological diagnoses were Alzheimer disease, vascular dementia, frontotemporal lobar degeneration, mesial temporal sclerosis and diffuse Lewy body dementia. Our data thus corroborate those reported in previous autopsy studies,^{4, 5, 711–13} but also broaden the range of disorders that may mimic prion disease to now include hereditary diffuse leukoencephalopathy with spheroids, adult polyglucosan body disease, Marchiafava-Bignami disease and superficial siderosis of the CNS.

One notable finding was the substantial number of cases of vascular dementia. This may be due to the neuropathology-based design of this study. The prevalence of vascular dementia from prior clinically based studies is possibly underestimated due to the use of clinical diagnostic criteria unconfirmed by autopsy.¹⁴

Our most important finding was that a significant number (71) of patients clinically diagnosed as having prion disease suffered from potentially treatable diseases, including several disorders not previously reported.^{1, 5, 12} Table 5 lists the potentially treatable diseases derived from our study.

Limitations of our study derive from its retrospective design and constraints imposed by the protocols for referring cases. The center was sometimes not able to obtain a comprehensive set of medical records including MRI reports and the actual images from referring physicians. The mission of the NPDPS is to aid physicians in diagnosis and to monitor the occurrence of prion diseases. Referring physicians are encouraged, but not required, to provide a complete medical record. The majority of incomplete records are from cases registered in 2006 and 2007; data collection improved over the course of the study.

From the analysis of available data, approximately two-thirds of our potentially treatable prion-negative cases did not meet WHO criteria (Table 1) for “probable” or “possible” sCJD. Several factors could contribute to this discrepancy. First, the WHO criteria were designed for epidemiological purposes and not for early diagnosis of sCJD. Thus, WHO criteria do not specify behavioral disturbances, and yet many sCJD patients initially present with cognitive impairment, or other deficits of higher cortical function.^{15, 16} For example, a recent cohort study found that 40% of patients have only cognitive impairment as their first symptom.¹⁷ Second, the clinical picture of rapidly evolving dementia of unclear etiology may prompt physicians to investigate for sCJD, since the mean survival of patients affected by the most common subtype of CJD is approximately 4 to 5 months, with nearly 90% dying within five months.^{8, 18, 19} Third, as the center is also concerned with monitoring the U.S. population for variant CJD, physicians may refer cases not fulfilling WHO diagnostic criteria for sporadic CJD. Fourth, laboratory tests are unreliable in establishing a diagnosis of CJD, including the periodic sharp-and-slow complexes on EEG often manifest late in the disease course.^{20, 21} Clinicians may also rely too heavily on CSF 14-3-3 testing, which is a sensitive, but not specific, laboratory assay.^{22, 23} Many of our prion negative cases had positive CSF 14-3-3 results, especially those with other CNS infections. Elevation of 14-3-3 protein in the CSF is believed to result from acute neuronal damage, and is not a direct assay for pathogenic prion proteins within the CNS.³ The presence of CSF 14-3-3 is valuable only when interpreted in the appropriate clinical context.

Thus, great variability and delayed appearance of typical clinical manifestations, low sensitivity of EEG, and the non-specificity of CSF protein 14-3-3 elevation may provoke a high degree of suspicion for sCJD in patients with RPD. The danger then exists that once the diagnosis of sCJD has been made, a patient’s rapid decline might lead to withdrawal of

care. The results of our study suggest careful exclusion of a restricted set of possible neurologic disorders before settling on a diagnosis of sCJD.

Recent studies have demonstrated the value of brain MRI in securing a diagnosis of sCJD, when increased signal intensity on fluid attenuated inversion recovery (FLAIR) or restricted pattern on diffusion-weight imaging magnetic resonance imaging (DWI-MRI) is detected in cerebral cortex, caudate or putamen.²⁴ In our study, we have available MRIs report from 39 out of our 71 patients with potentially treatable disorders (Supplementary Table 3). In the reports, some have abnormal contrast enhancement of leptomeningeal or cerebral cortical regions, pointing toward other diagnoses, such as CNS neoplasm or infectious diseases. In those of our patients with DWI-MRI restriction and T2 hyperintensity signal in paramedian thalamus, hypothalamus and periaqueductal gray, the pathological diagnosis was Wernicke's encephalopathy. The involvement of these regions in the MRI may be found in vCJD, but very rarely in sCJD;^{25, 26} thus, these findings are more strongly suggestive of Wernicke's encephalopathy.

Immune-mediated disorders including angiitis and neurosarcoidosis require careful consideration in the differential diagnosis of sCJD (Table 5). Hashimoto encephalitis or voltage-gated potassium channel autoimmunity associated encephalopathy has also been described as mimicking prion disease,^{1, 5, 27, 28} but we were not able to diagnose these conditions in the absence of serologic data.

Among patients with CNS infections, half had fever and four out of six available CSF studies demonstrated CSF pleocytosis (5 to 600 cells/ml). All three patients with *Coccidioides* infection were immunocompetent. The patient with *Aspergillus* meningoencephalitis had a history of anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis and was being treated with prednisone and cyclophosphamide. More than half of the patients with CNS infections had a positive CSF protein 14-3-3 result, including the patient with cryptococcal meningoencephalitis. Prior publications reporting CNS infections presenting with dementia^{29, 30} have demonstrated that CSF pleocytosis should preclude a diagnosis of sCJD. We suspect that the finding of elevated CSF 14-3-3 protein result may have obfuscated the differential diagnosis.

Several prion referral centers have reported neoplastic CJD mimics, including both primary and secondary malignancies. CNS lymphomas accounted for more than 70% of the neoplastic cases in our series. Cytology was negative in all available CSF studies.

Bertrand and colleagues recently stressed the need to consider Wernicke encephalopathy in the differential diagnosis of CJD;³¹ our findings support this view. Three of our cases presented with classic clinical, imaging and pathological findings of Wernicke encephalopathy and two patients developed RPD after bariatric surgery, a treatment for obesity that is now commonly practiced in the US.

In summary, our findings indicate that heightened awareness of CJD has led to a tendency to over-diagnose this condition, and that many of these misdiagnosed patients suffer from potentially treatable diseases. The findings, derived from our study, that militate against the diagnosis of sCJD are listed in Supplementary Table 4. Application of revised consensus criteria should decrease the number of false-positive diagnoses. Especially promising are recently validated MRI features of prion-infected brains.²⁴ Physicians caring for patients with rapidly progressive brain conditions need to be aware of sCJD, but should consider other potential treatable neurological disorders before making the diagnosis of this rare, untreatable, and inexorable disease. The present study provides data that may help physicians identify patients for whom life-extending treatment can, and should, be given.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to Dr. Steven L. Galetta for suggesting this study and to all NPDPS staff involved for support in obtaining and elaborating the data. The NPDPS is supported by NIH P01 AG-14359, CDC UR8/CCU515004 and Charles S. Britton Fund to Dr. Pierluigi Gambetti. Dr. R. John Leigh is supported by NIH R01EY06717 and the Department of Veterans Affairs.

References

1. Geschwind MD, Shu H, Haman A, et al. Rapidly progressive dementia. *Ann Neurol*. 2008; 64:97–108. [PubMed: 18668637]
2. 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; 60:813–816. [PubMed: 12810484]
3. 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; 41:216–225. [PubMed: 10343153]
4. 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; 71:33–39. [PubMed: 11413259]
5. 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. [PubMed: 10581227]
6. Gelpi E, Heinzl H, Hofberger R, et al. Creutzfeldt-Jakob disease in Austria: an autopsy-controlled study. *Neuroepidemiology*. 2008; 30:215–221. [PubMed: 18424902]
7. Van Everbroeck B, Dobbeleir I, De Waele M, et al. Differential diagnosis of 201 possible Creutzfeldt-Jakob disease patients. *J Neurol*. 2004; 251:298–304. [PubMed: 15015009]
8. 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; 46:224–233. [PubMed: 10443888]
9. Organization WH. Global Surveillance, diagnosis and therapy of human transmissible spongiform encephalopathies: report of a WHO consultation. 1998.
www.who.int/csr/resources/publications/bse/WHO_EMZ_ZDI_98_9/en/
10. Tuzun E, Rossi JE, Karner SF, et al. Adenylate kinase 5 autoimmunity in treatment refractory limbic encephalitis. *J Neuroimmunol*. 2007; 186:177–180. [PubMed: 17462746]
11. Zerr I, Poser S. Clinical diagnosis and differential diagnosis of CJD and vCJD. With special emphasis on laboratory tests. *Apmis*. 2002; 110:88–98. [PubMed: 12064260]
12. Josephs KA, Ahlskog JE, Parisi JE, et al. Rapidly progressive neurodegenerative dementias. *Arch Neurol*. 2009; 66:201–207. [PubMed: 19204156]
13. Heinemann U, Krasnianski A, Meissner B, et al. Creutzfeldt-Jakob disease in Germany: a prospective 12-year surveillance. *Brain*. 2007; 130:1350–1359. [PubMed: 17472986]
14. Desmond DW. Vascular dementia: a construct in evolution. *Cerebrovasc Brain Metab Rev*. 1996; 8:296–325. [PubMed: 8969867]
15. 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; 20:597–602. [PubMed: 3539001]
16. Sy MS, Gambetti P, Wong BS. Human prion diseases. *Med Clin North Am*. 2002; 86:551–571. vi–vii. [PubMed: 12168559]
17. Rabinovici GD, Wang PN, Levin J, et al. First symptom in sporadic Creutzfeldt-Jakob disease. *Neurology*. 2006; 66:286–287. [PubMed: 16434680]

18. Cali I, Castellani R, Alshekhlee A, et al. Co-existence of scrapie prion protein types 1 and 2 in sporadic Creutzfeldt-Jakob disease: its effect on the phenotype and prion-type characteristics. *Brain*. 2009; 132:2643–2658. [PubMed: 19734292]
19. Gambetti P, Kong Q, Zou W, et al. Sporadic and familial CJD: classification and characterisation. *Br Med Bull*. 2003; 66:213–239. [PubMed: 14522861]
20. Steinhoff BJ, Zerr I, Glatting M, et al. Diagnostic value of periodic complexes in Creutzfeldt-Jakob disease. *Ann Neurol*. 2004; 56:702–708. [PubMed: 15449324]
21. Zerr I, Pocchiari M, Collins S, et al. Analysis of EEG and CSF 14–3–3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. *Neurology*. 2000; 55:811–815. [PubMed: 10994001]
22. Burkhard PR, Sanchez JC, Landis T, Hochstrasser DF. CSF detection of the 14–3–3 protein in unselected patients with dementia. *Neurology*. 2001; 56:1528–1533. [PubMed: 11402110]
23. Chohan G, Pennington C, Mackenzie JM, et al. 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*. 81:1243–1248. [PubMed: 20855493]
24. Zerr I, Kallenberg K, Summers DM, et al. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. *Brain*. 2009; 132:2659–2668. [PubMed: 19773352]
25. Collie DA, Summers DM, Sellar RJ, et al. Diagnosing variant Creutzfeldt-Jakob disease with the pulvinar sign: MR imaging findings in 86 neuropathologically confirmed cases. *AJNR Am J Neuroradiol*. 2003; 24:1560–1569. [PubMed: 13679271]
26. Zeidler M, Sellar RJ, Collie DA, et al. The pulvinar sign on magnetic resonance imaging in variant Creutzfeldt-Jakob disease. *Lancet*. 2000; 355:1412–1418. [PubMed: 10791525]
27. Geschwind MD, Tan KM, Lennon VA, et al. Voltage-gated potassium channel autoimmunity mimicking creutzfeldt-jakob disease. *Arch Neurol*. 2008; 65:1341–1346. [PubMed: 18852349]
28. Mahad DJ, Staugaitis S, Ruggieri P, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis and primary CNS demyelination. *J Neurol Sci*. 2005; 228:3–5. [PubMed: 15607202]
29. Ala TA, Doss RC, Sullivan CJ. Reversible dementia: a case of cryptococcal meningitis masquerading as Alzheimer's disease. *J Alzheimers Dis*. 2004; 6:503–508. [PubMed: 15505372]
30. Almeida OP, Lautenschlager NT. Dementia associated with infectious diseases. *Int Psychogeriatr*. 2005; 17 (Suppl 1):S65–77. [PubMed: 16240484]
31. Bertrand A, Brandel JP, Grignon Y, et al. Wernicke encephalopathy and Creutzfeldt-Jakob disease. *J Neurol*. 2009; 256:904–909. [PubMed: 19252796]

Figure 1.
Summary of autopsy results.

Figure 2.

Representative cases from each clinicopathologic category. **a** Histopathological section through the thalamus of an 85-year-old woman who presented with cognitive decline, lower limb weakness, myoclonic jerks, and EEG with diffuse generalized slowing, showing granulomatous arteriolar inflammation consistent with primary angiitis of the CNS. **b** Primary central nervous system lymphoma in a section of thalamus from a 68-year-old woman with progressive memory decline, personality change, limb and gait ataxia. Her MRI showed periventricular white matter changes; CSF cytology and flow cytometry were negative. **c** A 54-year-old man presenting with rapid cognitive decline and spastic paraparesis underwent cervical decompression without improvement. His MRI showed bilateral thalamic and frontal hyperintensities. His brain revealed necrotizing eosinophilic meningoencephalitis containing roundworms with lateral spines consistent with *Baylisascaris* infection. **d** A section of mammillary body from a 58-year-old woman who had undergone gastric bypass surgery, followed by abdominal pain, nausea, vomiting, weight loss and cognitive decline, dying within 3 months. Her brain showed spongioform degeneration with neuronal sparing in the mammillary body, typical of Wernicke encephalopathy.

Table 1

World Health Organization criteria for the diagnosis of sporadic Creutzfeldt-Jakob disease (sCJD)⁷

Criteria	
I	Progressive dementia
II A	Myoclonus
B	Visual or Cerebellar problem
C	Pyramidal or extrapyramidal features
D	Akinetic mutism
III A	Typical EEG
B	Positive CSF 14-3-3

Possible CJD: I and 2 of II and duration less than 2 years

Probable CJD: I and 2 of II and D either typical EEG and/or Positive CSF 14-3-3 with a total disease duration of less than 2 years and routine investigations should not suggest an alternative diagnosis.

Definite CJD: Neuropathologically confirmed diagnosis

Table 2

Pathology of incurable neurological disorders misdiagnosed as CJD

Diseases	Total (n = 233)
Alzheimer disease	154
Vascular dementia	36
Unspecified degenerative brain disease	10
Frontotemporal lobar degeneration (FTLD)	9
Mesial temporal lobe sclerosis	5
Diffuse Lewy body disease	4
Tauopathy, NOS	4
Hereditary diffuse leukoencephalopathy with spheroids	3
Progressive supranuclear palsy	3
Corticobasal ganglionic degeneration	1
Adult polyglucosan body disease	1
Huntington disease	1
Marchiafava-Bignami disease	1
Superficial siderosis	1

Table 3

Clinical and demographic data of potentially treatable patients

Median age in years (min-max)	65 (23–87)
Median duration of illness (months)	3 (0.5–16)
Sex (male)	55%
Symptoms	(Total n = 71)
Dementia	42
Myoclonus	12
Cerebellar	14
Visual	9
Pyramidal	20
Extrapyramidal	12
Akinetic Mutism	5
Psychiatric ^f	17
Seizure	10
Available CSF 14-3-3 Protein results	n = 56
Positive	29
Negative	27
Available EEG results	n = 21
Typical*	1
Diffuse generalized slowing pattern	17
Normal	3

^fPsychiatric symptoms includes auditory and visual hallucination, depression, and delusion.

* Typical EEG is 1-Hz focal or diffuse periodic epileptiform discharges.

Table 4

Patients with treatable disorders meeting WHO criteria for sCJD

WHO CRITERIA	N	PERCENT (%)
Probable CJD	8	11
Possible CJD	13	18
Dementia [^]	22	31
Delirium [^]	7	10
Insufficient clinical Data	21	30

[^] Patients showing delirium or dementia plus one of pyramidal, extrapyramidal, visual, cerebellar, akinetic mutism or myoclonus

Table 5

Pathologic diagnoses of potentially treatable neurological disorders misdiagnosed as CJD.

Neurological diseases	N = 71
<i>Immune mediated disorders</i>	26
Median age in years (min-max)	64 (29–81)
Median duration of illness in months (min-max)	4 (0.8–16)
14-3-3 positive	8
Primary angiitis of the CNS	7
Acute disseminated encephalomyelitis	6
Limbic encephalitis	6
Neurosarcoidosis	4
Paraneoplastic cerebellar degeneration	2
Wegener granulomatosis	1
<i>Neoplasms</i>	25
Median age in years (min-max)	71 (44–87)
Median duration of illness in months (min-max)	2.7 (0.8–10.1)
14-3-3 positive	7
Primary CNS lymphoma	8
Intravascular lymphoma	8
Leptomeningeal lymphoma	2
Malignant glioma	5
Leptomeningeal carcinomatosis	2
<i>Infections</i>	14
Median age in years (min-max)	67 (45–86)
Median duration of illness in months (min-max)	2.5 (1.2–3.8)
14-3-3 positive	9
Fungal infection	
Coccidioides immitis	3
Aspergillus fumigates	1
Cryptococcus neoformans	1
Viral meningoencephalitis	5
Parasitic infestation	
Round worms	2
Other parasitic infection	2
<i>Metabolic or toxic encephalopathies</i>	6
Median age in years (min-max)	52 (23–79)
Median duration of illness in months (min-max)	2.4 (0.5–7.5)
14-3-3 positive	4
Wernicke encephalopathy	3
Other metabolic disorders	3