



Prion Infections of the Brain

Ryan Wada, MD, FRCPC, Walter Kucharczyk, MD, FRCPC*

- The variant form of Creutzfeldt-Jakob disease
- Iatrogenic prion disease
- Inherited prion disease
- The Heidenhain variant
- The relationship of genotype to phenotype and to MR imaging appearance
- The correlation between histopathology and MRI in Creutzfeldt-Jakob disease
- Colocalization of electroencephalogram abnormalities with MRI-visible lesions
- Summary
- References

Prions (proteinaceous infectious particles) are infective agents comprised of protein, lacking nucleic acid. The actual protein, termed *cellular prion protein* (PrP^C), is a normal cellular constituent. The infective particle is an isoform of PrP, termed *scrapie prion protein* (PrP^{Sc}), resulting from partial refolding into a beta-sheet configuration, which can then induce further conversion of the normal protein into the infective form. PrP^{Sc} has reduced solubility and partial resistance to proteases, making standard sterilization procedures difficult. Clinically relevant infection occurs in the central nervous system in animals and humans, resulting in varying degrees of spongiform neuronal degeneration, neuronal loss, reactive astrocytic gliosis, and amyloid-like plaques predominantly affecting gray matter structures [1].

Human forms of prion infection include sporadic, familial (inherited), and acquired. The sporadic forms are divided into sporadic Creutzfeldt-Jakob disease (sCJD) and sporadic fatal insomnia. sCJD is further divided into several subtypes, largely based on which amino acids are encoded by codon 129 in the prion gene. The familial prion diseases consist of familial CJD, fatal

familial insomnia, and Gerstmann-Sträussler-Scheinker disease (GSS). The acquired diseases are kuru, iatrogenic CJD, and new variant CJD (vCJD) or “mad cow disease.” Kuru largely disappeared with the end of cannibalism among the Fore people of New Guinea.

sCJD (Fig. 1) accounts for approximately 85% of human cases, with the remainder being predominantly hereditary, including familial CJD, GSS, and fatal familial insomnia [2]. The hereditary forms are related to mutations associated with different codons of the PrP encoding gene, *PRNP* [3]. Iatrogenic causes include dura mater grafts, corneal implants, and contaminated human growth hormone [4–6]. vCJD, which is believed to be transmitted through contaminated meat from cows infected with bovine spongiform encephalopathy, has gained recognition from a public health perspective [7,8].

Overall, CJD is rare, with an incidence of less than one per million. The sporadic form is more common among elderly individuals, whereas the variant form is seen in younger patients. sCJD is characterized by rapidly progressive dementia resulting in death over weeks to months. As the

Department of Medical Imaging, University of Toronto, 150 College Street, Room 112, Toronto, Ontario, M5S 3E2 Canada

* Corresponding author.

E-mail address: w.kucharczyk@utoronto.ca (W. Kucharczyk).

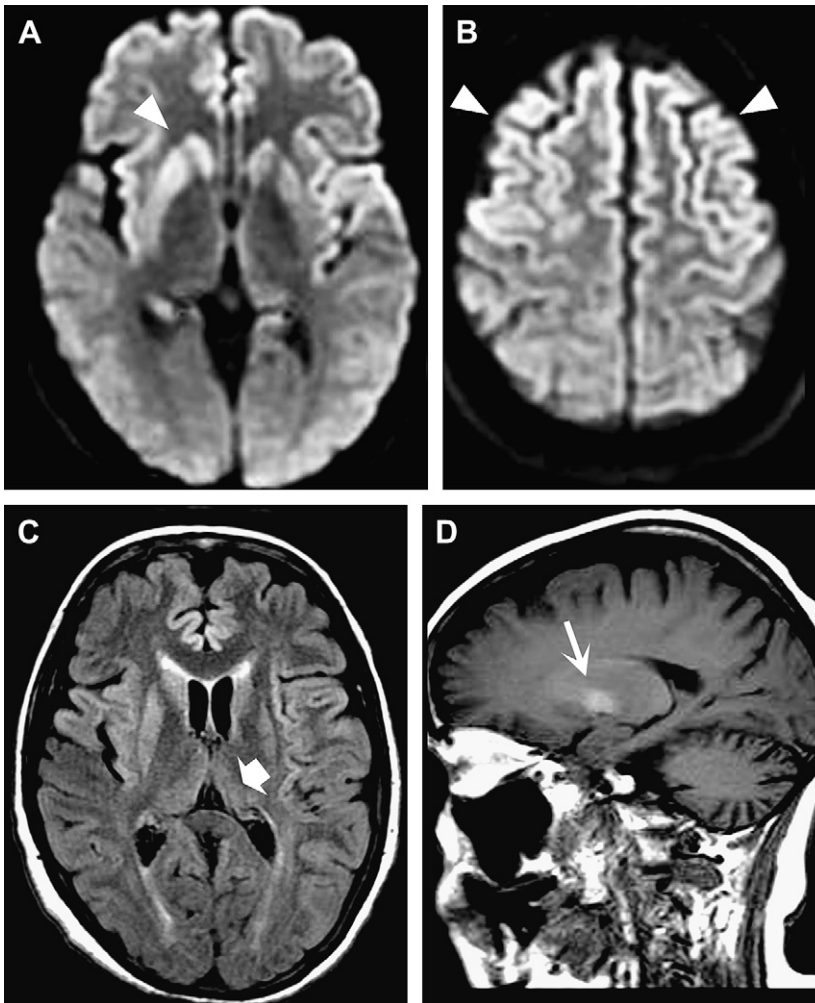


Fig. 1. Sporadic Creutzfeldt-Jakob disease in 52-year-old woman, previously healthy, who has rapidly progressive dementia and mutism. Axial diffusion-weighted images (A, B) shows striatal and cortical restricted diffusion (arrowheads) with corresponding hyperintensity on fluid-attenuated inversion recovery (FLAIR) (C). Note the medial thalami are also hyperintense on FLAIR (solid arrow), but it is less pronounced than the striatal abnormalities. Sagittal T1-weighted image (D) shows pallidal hyperintensity (thin arrow), which may relate to prion protein accumulation.

disease advances, typical symptoms include the development of motor dysfunction, myoclonus, and, in the later stages, akinetic mutism, with death frequently occurring secondary to respiratory infection. The variant form has prominent psychiatric features early in the disease and a slower progressive course, with a reported median survival of 14 months [9,10]. According to World Health Organization (WHO) criteria, definitive diagnosis of sCJD is made through histopathologic analysis; however, characteristic periodic sharp wave complexes (PSWC) on electroencephalogram (EEG) or positive cerebral spinal fluid (CSF) 14-3-3 protein assay in the appropriate clinical setting contribute to a probable diagnosis [2]. vCJD does not tend to

display typical EEG or CSF findings and has separate diagnostic criteria, in which imaging studies have an important role [10].

MR imaging is more sensitive than CT [11] and remains the mainstay of imaging investigation. Typical findings of sCJD on conventional sequences include symmetric T2 hyperintensity involving the basal ganglia, in particular the corpus striatum [12,13]. Less common features include asymmetric striatal involvement [14,15] and signal abnormality in the thalamus and periaqueductal gray matter [13]. Cerebral cortical signal abnormality, either symmetric or asymmetric, may be seen in the absence of striatal involvement [11] and has become a well-recognized feature, particularly

with the greater use of fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted images (DWI) and because these images have greater sensitivity for detecting cortical lesions [16–18]. Evidence shows that DWI is the most sensitive sequence in CJD evaluation [19–22]. DWI shows persistent restricted diffusion in the typical areas of involvement that have been reported to progress over the disease course but may normalize in the later stages, possibly related to gliosis [23,24]. T1 hyperintensity may be seen in the globus pallidi, postulated to be related to prion deposition [25]. Cortical perirolandic sparing has been reported [21], but subsequent quantitative analysis of apparent diffusion coefficients has shown a similar degree of involvement in these “spared” areas, suggesting that local effects may be masking true regional pathology [26]. MR imaging findings can precede the onset of characteristic clinical disease, particularly with the use of DWI [24,27]. No mass effect or enhancement is seen, and progression to atrophy occurs in the terminal stages [28]. When only cortical involvement is present, radiologic mimics may include mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke; venous hypertensive disease [29]; and posterior reversible encephalopathy [30]. With respect to other imaging tests, MR spectroscopy has shown decreased *N*-acetyl aspartate (NAA), reflecting neuronal loss, but is nonspecific [29,31]. Positron emission tomography and single photon emission CT (SPECT) have been shown to be sensitive for early changes, with diminished lobar metabolism/perfusion [32–35]. Although the specificity has not been well established, good correlation between SPECT and DWI has been reported [29].

In a recent, large, multinational study from 1992 to 2002, MR imaging examination of 1036 patients who had definite sCJD showed characteristic imaging findings in only 40%, which was significantly less sensitive than either EEG (60%) or 14-3-3 CSF assays (90%). However, FLAIR and DWI were not used systematically [36]. Both DWI and FLAIR have greater sensitivity than T2-weighted sequences. Smaller cohorts directly examining DWI have shown greater than 90% sensitivity and specificity for patients who have a definite or probable diagnosis, even in the presence of negative EEG and CSF results [18,21], and therefore experts have suggested that it be included in the diagnostic criteria for sCJD [37].

In a recently published series of 36 cases, 26 of which underwent DWI imaging, Shiga and colleagues [21] emphasized the value of DWI as an early diagnostic marker for CJD. They compared the percentages of DWI abnormalities, PSWCs on the EEG, detection of CSF 14-3-3 protein, and

increase of CSF neuron-specific enolase (25 ng/mL) on the first examination. Disease controls consisted of 32 patients, aged 31 to 84 years, who had progressive dementia or impaired consciousness. DWI showed abnormalities in 92.3% of cases, PSWCs were seen in 50%, 14-3-3 protein was detected in 84%, and neuron-specific enolase increase was seen in 73.3%. Of the 32 control subjects, 2 had false-positive results on DWI. The sensitivity of DWI was 92.3% and specificity was 93.8%. In 17 patients who did not show PSWCs on the first EEG, abnormal DWI findings were still clearly detected. Four patients who had negative results for 14-3-3 protein also showed DWI abnormalities. DWI abnormalities were detected at 3 weeks of symptom duration in four patients in whom PSWCs were not yet evident.

In 26 patients who had CJD, DWI was examined 3 to 25 weeks after onset with a mean duration of 10.7 weeks. Of these patients, 24 showed high-intensity brain lesions on DWI examination, 3 (12.5%) showed lesions only in the caudate heads and putamen, 10 (41.7%) showed linear lesions only in the cerebral cortex, and 11 (45.8%) showed lesions in the basal ganglia and cerebral cortex. Only 3 patients (12.5%) showed lesions in the thalamus. No patients showed high-intensity lesions in the cerebellum. In some cases, the high-intensity lesions detected with sequential DWI did not always progress with the advance of the disease, and in some lesions the signal intensity decreased with disease progression. In some cases, the cortical high signal varied in intensity and anatomic distribution. In the terminal stage with profound brain atrophy, the high-intensity lesions became unclear [21].

The variant form of Creutzfeldt-Jakob disease

vCJD shows distinctive imaging findings; in particular, symmetric high signal in the pulvinar compared with the signal in the remainder of the basal ganglia. This finding is termed the *pulvinar sign* (Fig. 2) [38]. The WHO criteria for vCJD includes the pulvinar sign as a component of a probable diagnosis [10]. In a prospective study of 86 patients who had histopathologically confirmed vCJD, symmetric high signal on T2-weighted, proton density-weighted, or FLAIR images was present in more than 90% [39]. The finding was rarely asymmetric. FLAIR also showed dorsomedial thalamic involvement, termed the *hockey stick sign*, to be positive in more than 90% of patients. Other common areas of abnormality are similar to the sporadic form and include the striatum and periaqueductal gray matter. Less

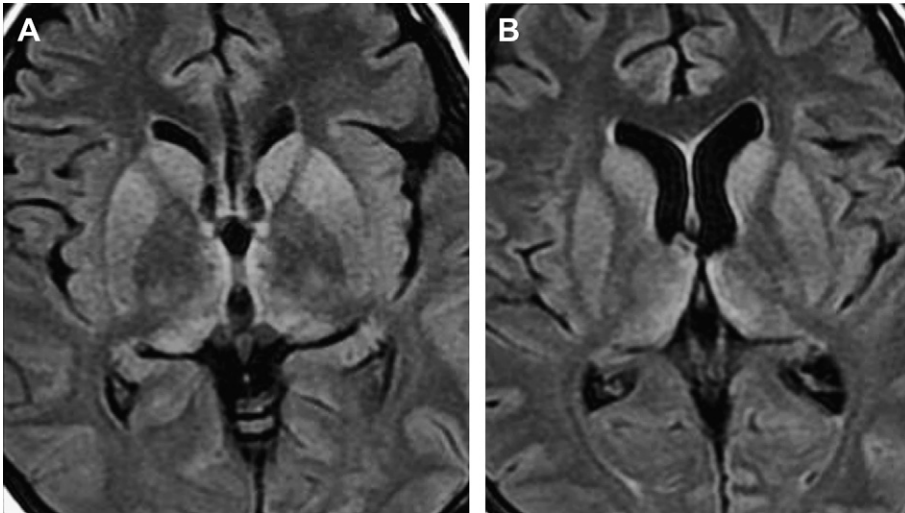


Fig. 2. The pulvinar and hockey stick signs. This pair of axial fluid-attenuated inversion recovery images through the level of the thalami and basal ganglia show bilaterally symmetric hyperintense lesions in the pulvinar region (A) and in the dorsomedial thalami (B). The latter has been called the *hockey stick sign*. However, the caudate and putamen are as hyperintense as the lesions in the thalami, and thus this case would not fulfill the World Health Organization (WHO) criteria for the pulvinar sign. The WHO criteria for the pulvinar sign in new variant Creutzfeldt-Jakob disease requires that the pulvinar be brighter than the signal in the other deep gray matter nuclei. The case proved to be sporadic Creutzfeldt-Jakob disease.

commonly, parietooccipital white matter hyperintensity and cerebral and cerebellar atrophy have been noted [39]. Case reports have described pulvinar signal abnormality in the sporadic form as a potential mimic [40,41]; however, experts have noted that true variant cases should have pulvinar involvement greater than the basal ganglia, and that this relative hyperintensity is more specific than simple pulvinar signal abnormality [42]. In other words, pulvinar hyperintensity is an excellent but not pathognomonic indication of vCJD [40,41,43]. However, not all of these cases fulfilled the WHO criteria for this sign, which specify that the pulvinar signal must be brighter than the signal in other deep nuclei. In two reports, the WHO criteria were fulfilled, with pulvinar intensity being higher than other deep gray matter nuclei [44,45]. The pulvinar sign is also seen occasionally with other diseases, such as limbic encephalitis [46]. Apparent diffusion coefficient values may vary within the structures involved [47].

Iatrogenic prion disease

Fewer than 300 cases of human iatrogenic prion disease have been noted worldwide [48]. Most of these infections were caused by cadaveric human growth hormone, dura mater, and corneal grafts. The most frequent MR imaging finding in these cases has been bilateral symmetric hyperintensity

of the caudate head and putamen, with the abnormalities appearing earlier on DWI than on T2-weighted imaging [6,49–51]. Asymmetric pulvinar hyperintensity has also been reported after a cadaveric dura mater graft [52]. In the single reported case of MR imaging performed on a patient who had a history of corneal grafts, caudate and putamen hyperintensity was found, and FLAIR and DWI showed cortical hyperintensity [53].

Inherited prion disease

Inherited prion diseases comprise approximately 15% of human cases. Few reports on imaging findings have been published. GSS disease is one of the inherited prion diseases. Clinically, prominent cerebellar ataxia is seen. MR imaging reports on GSS are much less common than with CJD, but these diseases share common MR imaging findings. Most notably, DWI has shown bilateral discontinuous ribbon-like hyperintensities throughout the cerebral cortex and progressive cortical atrophy [54]. Cerebral hypoperfusion on SPECT [55] and diminished NAA may precede findings on conventional MRI [56]. Imaging findings described in other inherited forms include cortical atrophy, cerebellar atrophy, and hypointensity on T2-weighted imaging in the basal ganglia [57–59]. Some patients have shown no MRI abnormality at all. Some symptomatic patients who had normal

MR imaging examinations had ^{123}I SPECT imaging that showed patchy decreases across the entire cerebrum [55]. In fatal familial insomnia, MR imaging did not show any specific abnormality, or merely mild atrophy [57,59]. In some presymptomatic carriers, early atrophy was seen [60].

The Heidenhain variant

Some types of prion disease have been attached with eponymous names because of one or more prominent clinical features. In the Heidenhain variant of sCJD, visual symptoms occur first and persist throughout the disease course. The first change in behavior may be that patients stop reading or watching television because of deteriorating vision. Funduscopic examination usually shows little abnormality. Onset of dementia occurs later. In this clinical setting, MR imaging is extremely valuable because the diagnosis of CJD is rarely suspected. In one series of 11 cases, MR imaging showed symmetric hyperintensities in the basal ganglia in seven patients and marked signal increase in the occipital visual cortex in four. Two cases also showed isolated atrophy in the visual cortex [61]. In another recent series, Cooper and colleagues [62] reported that the Heidenhain variant of CJD accounted for 22 of 594 cases of sCJD. Their patients presented with early, prominent, visual complaints, and in some the only complaints were visual. Of these patients, 77% initially presented to ophthalmologists before consulting any

other specialist. Hyperintense cortical ribbons or typical CJD basal ganglia lesions on MR imaging should immediately indicate inclusion of CJD in the differential diagnosis. MR imaging leads to a much more rapid definitive diagnosis than would otherwise be achieved, circumventing the need for many other diagnostic tests (Fig. 3).

The relationship of genotype to phenotype and to MR imaging appearance

The PrP genotype and PrP^{Sc} type have a major influence on the disease phenotype in human prion diseases. Gambetti and colleagues [63] and Parchi and colleagues [64] classified and characterized CJD as a function of these disease determinants. Parchi and colleagues linked clinical phenotype with six molecular subtypes as defined by a combination of homozygosity or heterozygosity for methionine (M) or valine (V) at codon 129 of the prion protein gene and the size of the protease-resistant fragment of the pathologic prion protein (types 1 and 2). The MM1 and MV1 subtypes correlate with the classical phenotype of sCJD, namely rapidly progressive dementia with short illness duration and usually a periodic EEG. The other (nonclassical) molecular subtypes are associated with less-typical features, such as young age at onset (VV1), ataxia at presentation (MV2 and VV2), and a slower course and the lack of periodic EEG appearance. Approximately 30% of cases are of this nonclassical subtype and these patients may be difficult to diagnose

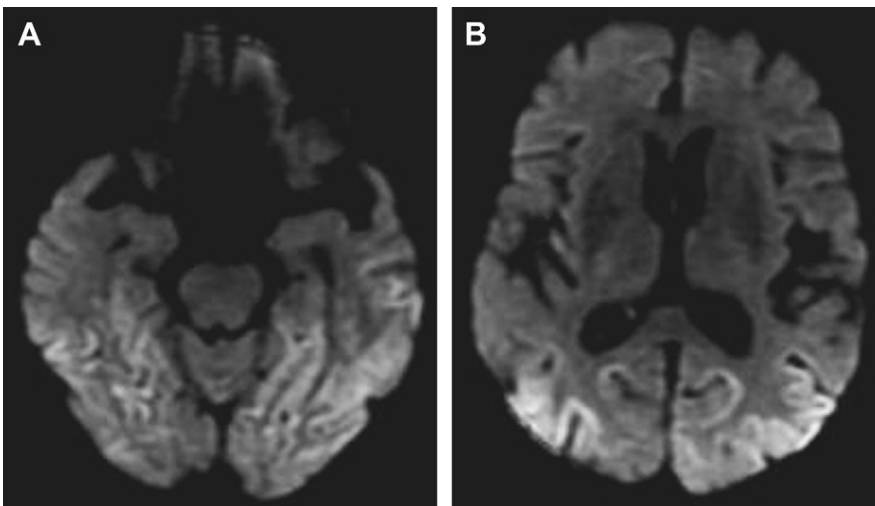


Fig. 3. The Heidenhain variant of Creutzfeldt-Jakob disease. This woman's presenting complaint was deterioration of vision. Dementia followed later. This pair of diffusion-weighted images shows striking, bilaterally symmetric, cortical hyperintensities involving most of the occipital cortex and the temporal cortex. These lesions were also clearly visible on fluid-attenuated inversion recovery images (not shown) but very inconspicuous on T2-weighted image (not shown), partially because of their proximity to and the masking effect of very bright cerebrospinal fluid in the adjacent sulci. Note that the basal ganglia and thalami are normal.

clinically, particularly in the early stages [65]. Some correlation exists between MR imaging findings and these molecular subtypes. Hyperintensity in the caudate and putamen has been found in more than 90% of patients in several series that are codon 129 heterozygotes [45,66,67]. Methionine homozygotes account for more than 70% of the sCJD population, but patterns of MR imaging change are less consistent. Patients who have the rare VV1 subtype—a type that mimics vCJD clinically with young onset, prolonged disease course, and psychiatric symptoms—consistently have high signal in the cortex, a useful differential diagnostic imaging feature for diagnosing sCJD because cortical high signal is infrequent in vCJD [68].

The correlation between histopathology and MRI in Creutzfeldt-Jakob disease

The histopathology of CJD is characterized by cytoarchitectural loss, neuronal loss, and spongiform changes. Spongiform degeneration of the cortex occurs in virtually all cases of CJD regardless of the clinical presentation. This degeneration consists of oval vacuoles 5 to 25 μm in diameter located in the neuropil between nerve cell bodies. Late-stage disease is characterized by larger 100- μm vacuoles. DWI lesions correlate strongly with the presence of these histopathologic features [69]. In several studies, serial imaging has shown that lesions visible on MR imaging progressed with disease advancement [24,70]. This finding has been attributed to progressive spongiform degeneration [19]. Prion protein deposition has also been noted to correlate well with the anatomic location of the DWI-visible lesions [71]. In the author's experience, correlation between MRI and autopsy has shown anatomic colocalization of DWI-visible lesions and prion protein deposition on immunohistopathology. Nevertheless, the author believes that spongiform change is more likely than a change in protein concentration to alter water diffusion as measured on DWI, and hence more likely to account for the DWI visible lesions on MRI. These DWI hyperintense lesions have been reported to disappear in the late stages of disease [24,49]. This finding may be because fibrillary gliosis becomes the dominant histologic feature in end-stage CJD [72].

Colocalization of electroencephalogram abnormalities with MRI-visible lesions

Patients who have CJD frequently have EEG abnormalities, the most characteristic type being periodic sharp waves. In one study, Cambier and colleagues [73] found that the EEG abnormalities colocalized

with the MRI abnormalities. This series illustrated the correlation between the lateralized and focal clinical, EEG, and MRI FLAIR sequence abnormalities in eight patients who had CJD. EEG, MRI and CSF studies were performed in all patients. Symptoms were lateralized to the left hemisphere in five patients and to the right hemisphere in two. One patient showed bilateral occipital lobe involvement. In all patients, EEG showed lateralized or focal periodic sharp waves that colocalized with clinical cerebral dysfunction. FLAIR MRI images showed increased signal in the cortical ribbon and deep gray matter corresponding to the lateralized clinical and EEG findings in seven patients. The other patient had bilateral occipital increased signal on FLAIR MRI.

Summary

Prions are a rare cause of human disease, but very important to recognize because of their potential for transmissibility and their uniformly severe outcome. MR imaging plays an extremely important role in early diagnosis, especially with DWI and FLAIR images, which are undoubtedly the most sensitive for the depiction of prion-induced brain lesions. The lesions are characteristically shown as ribbons of cortical hyperintensity, or basal ganglia or thalamic hyperintensity. The cortical and deep lesions may appear alone or together, and although usually bilateral and symmetric, they may asymmetric or purely unilateral. When these MR imaging findings are observed in an appropriate clinical context, the diagnosis of prion disease is very likely.

References

- [1] Prusiner SB, Scott MR, DeArmond SJ, et al. Prion protein biology. *Cell* 1998;93:337–48.
- [2] Collins S, Boyd A, Fletcher A, et al. Recent advances in the pre-mortem diagnosis of Creutzfeldt-Jakob disease. *J Clin Neurosci* 2000;7:195–202.
- [3] Prusiner SB. Shattuck lecture—neurodegenerative diseases and prions. *N Engl J Med* 2001;344:1516–26.
- [4] Lang CJ, Heckmann JG, Neundorfer B. Creutzfeldt-Jakob disease via dural and corneal transplants. *J Neurol Sci* 1998;160:128–39.
- [5] Centers for Disease Control and Prevention (CDC). Update: Creutzfeldt-Jakob disease associated with cadaveric dura mater grafts—Japan, 1979–2003. *MMWR Morb Mortal Wkly Rep* 2003;52:1179–81.
- [6] Caboclo LO, Huang N, Lepski GA, et al. Iatrogenic Creutzfeldt-Jakob disease following human growth hormone therapy: case report. *Arq Neuropsiquiatr* 2002;60:458–61.

- [7] Will RG, Ironside JW, Zeidler M, et al. A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet* 1996;347:921-5.
- [8] de Pedro-Cuesta J, Glatzel M, Almazan J, et al. Human transmissible spongiform encephalopathies in eleven countries: diagnostic pattern across time, 1993-2002. *BMC Public Health* 2006;6:278.
- [9] Zeidler M, Stewart GE, Barraclough CR, et al. New variant Creutzfeldt-Jakob disease: neurological features and diagnostic tests. *Lancet* 1997; 350:903-7.
- [10] Will RG, Zeidler M, Stewart GE, et al. Diagnosis of new variant Creutzfeldt-Jakob disease. *Ann Neurol* 2000;47:575-82.
- [11] Falcone S, Quencer RM, Bowen B, et al. Creutzfeldt-Jakob disease: focal symmetrical cortical involvement demonstrated by MR imaging. *AJNR Am J Neuroradiol* 1992;13:403-6.
- [12] Finkenstaedt M, Szudra A, Zerr I, et al. MR imaging of Creutzfeldt-Jakob disease. *Radiology* 1996;199:793-8.
- [13] Schroter A, Zerr I, Henkel K, et al. Magnetic resonance imaging in the clinical diagnosis of Creutzfeldt-Jakob disease. *Arch Neurol* 2000; 57:1751-7.
- [14] Yoon SS, Chan S, Chin S, et al. MRI of Creutzfeldt-Jakob disease: asymmetric high signal intensity of the basal ganglia. *Neurology* 1995; 45:1932-3.
- [15] Bavis J, Reynolds P, Tegeler C, et al. Asymmetric neuroimaging in Creutzfeldt-Jakob disease: a ruse. *J Neuroimaging* 2003;13:376-9.
- [16] Vrancken AF, Frijns CJ, Ramos LM. FLAIR MRI in sporadic Creutzfeldt-Jakob disease. *Neurology* 2000;55:147-8.
- [17] Schwaninger M, Winter R, Hacke W, et al. Magnetic resonance imaging in Creutzfeldt-Jakob disease: evidence of focal involvement of the cortex. *J Neurol Neurosurg Psychiatry* 1997;63: 408-9.
- [18] 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;26:1551-62.
- [19] Bahn MM, Parchi P. Abnormal diffusion-weighted magnetic resonance images in Creutzfeldt-Jakob disease. *Arch Neurol* 1999;56: 577-83.
- [20] Murata T, Shiga Y, Higano S, et al. Conspicuity and evolution of lesions in Creutzfeldt-Jakob disease at diffusion-weighted imaging. *AJNR Am J Neuroradiol* 2002;23:1164-72.
- [21] Shiga Y, Miyazawa K, Sato S, et al. Diffusion-weighted MRI abnormalities as an early diagnostic marker for Creutzfeldt-Jakob disease. *Neurology* 2004;63:443-9.
- [22] Kallenberg K, Schulz-Schaeffer WJ, Jastrow U, et al. Creutzfeldt-Jakob disease: comparative analysis of MR imaging sequences. *AJNR Am J Neuroradiol* 2006;27:1459-62.
- [23] Matoba M, Tonami H, Miyaji H, et al. Creutzfeldt-Jakob disease: serial changes on diffusion-weighted MRI. *J Comput Assist Tomogr* 2001; 25:274-7.
- [24] Ukisu R, Kushihashi T, Kitanosono T, et al. Serial diffusion-weighted MRI of Creutzfeldt-Jakob disease. *AJR Am J Roentgenol* 2005;184:560-6.
- [25] de Priester JA, Jansen GH, de Kruijk JR, et al. New MRI findings in Creutzfeldt-Jakob disease: high signal in the globus pallidus on T1-weighted images. *Neuroradiology* 1999;41:265-8.
- [26] Lin YR, Young GS, Chen NK, et al. Creutzfeldt-Jakob disease involvement of rolandic cortex: a quantitative apparent diffusion coefficient evaluation. *AJNR Am J Neuroradiol* 2006;27: 1755-9.
- [27] Alvarez FJ, Bisbe J, Bisbe V, et al. Magnetic resonance imaging findings in pre-clinical Creutzfeldt-Jakob disease. *Int J Neurosci* 2005;115: 1219-25.
- [28] Uchino A, Yoshinaga M, Shiokawa O, et al. Serial MR imaging in Creutzfeldt-Jakob disease. *Neuroradiology* 1991;33:364-7.
- [29] Ukisu R, Kushihashi T, Tanaka E, et al. Diffusion-weighted MR imaging of early-stage Creutzfeldt-Jakob disease: typical and atypical manifestations. *Radiographics* 2006;26(Suppl 1): S191-204.
- [30] Sibon I, Foubert A, Menegon P, et al. Creutzfeldt-Jakob disease mimicking radiologic posterior reversible leukoencephalopathy. *Neurology* 2005;65:329.
- [31] Pandya HG, Coley SC, Wilkinson ID, et al. Magnetic resonance spectroscopic abnormalities in sporadic and variant Creutzfeldt-Jakob disease. *Clin Radiol* 2003;58:148-53.
- [32] Ogawa T, Inugami A, Fujita H, et al. Serial positron emission tomography with fludeoxyglucose F 18 in Creutzfeldt-Jakob disease. *AJNR Am J Neuroradiol* 1995;16:978-81.
- [33] Watanabe N, Seto H, Shimizu M, et al. Brain SPECT of Creutzfeldt-Jakob disease. *Clin Nucl Med* 1996;21:236-41.
- [34] Miller DA, Vitti RA, Maslack MM. The role of 99m-tc HMPAO SPECT in the diagnosis of Creutzfeldt-Jakob disease. *AJNR Am J Neuroradiol* 1998;19:454-5.
- [35] Matsuda M, Tabata K, Hattori T, et al. Brain SPECT with 123I-IMP for the early diagnosis of Creutzfeldt-Jakob disease. *J Neurol Sci* 2001; 183:5-12.
- [36] Collins SJ, Sanchez-Juan P, Masters CL, et al. Determinants of diagnostic investigation sensitivities across the clinical spectrum of sporadic Creutzfeldt-Jakob disease. *Brain* 2006;129: 2278-87.
- [37] Tschampa HJ, Kallenberg K, Urbach H, et al. MRI in the diagnosis of sporadic Creutzfeldt-Jakob disease: a study on inter-observer agreement. *Brain* 2005;128:2026-33.
- [38] Zeidler M, Sellar RJ, Collie DA, et al. The pulvinar sign on magnetic resonance imaging in

- variant Creutzfeldt-Jakob disease. *Lancet* 2000; 355:1412-8.
- [39] 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;24:1560-9.
- [40] Haik S, Brandel JP, Oppenheim C, et al. Sporadic CJD clinically mimicking variant CJD with bilateral increased signal in the pulvinar. *Neurology* 2002;58:148-9.
- [41] Martindale J, Geschwind MD, De Armond S, et al. Sporadic Creutzfeldt-Jakob disease mimicking variant Creutzfeldt-Jakob disease. *Arch Neurol* 2003;60:767-70.
- [42] Summers DM, Collie DA, Zeidler M, et al. The pulvinar sign in variant Creutzfeldt-Jakob disease. *Arch Neurol* 2004;61:446-7.
- [43] Rossetti AO, Glatzel M, Aguzzi A, et al. Clinical and radiological mimicry of vCJD in a valine homozygous PrP(Sc) type 1 sCJD patient. *J Neurol* 2003;250:491-3.
- [44] Petzold GC, Westner I, Bohner G, et al. False-positive pulvinar sign on MRI in sporadic Creutzfeldt-Jakob disease. *Neurology* 2004;62:1235-6.
- [45] Krasnianski A, Schulz-Schaeffer WJ, Kallenberg K, et al. Clinical findings and diagnostic tests in the MV2 subtype of sporadic CJD. *Brain* 2006;129(Pt 9):2288-96.
- [46] Mihara M, Sugase S, Konaka K, et al. The "pulvinar sign" in a case of paraneoplastic limbic encephalitis associated with non-Hodgkin's lymphoma. *J Neurol Neurosurg Psychiatry* 2005;76:882-4.
- [47] Waldman AD, Jarman P, Merry RT. Rapid echoplanar diffusion imaging in a case of variant Creutzfeldt-Jakob disease; where speed is of the essence. *Neuroradiology* 2003;45:528-31.
- [48] Brown P, Preece M, Brandel JP, et al. Iatrogenic Creutzfeldt-Jakob disease at the millennium. *Neurology* 2000;55:1075-81.
- [49] Oppenheim C, Zuber M, Galanaud D, et al. Spectroscopy and serial diffusion MR findings in hGH-Creutzfeldt-Jakob disease. *J Neurol Neurosurg Psychiatry* 2004;75:1066-9.
- [50] Lewis AM, Yu M, DeArmond SJ, et al. Human growth hormone-related iatrogenic Creutzfeldt-Jakob disease with abnormal imaging. *Arch Neurol* 2006;63:288-90.
- [51] Noguchi-Shinohara M, Hamaguchi T, Kitamoto T, et al. Clinical features and diagnosis of dura mater graft-associated Creutzfeldt-Jakob disease. *Neurology* 2007;69:360-7.
- [52] Wakisaka Y, Santa N, Doh-ura K, et al. Increased asymmetric pulvinar magnetic resonance imaging signals in Creutzfeldt-Jakob disease with florid plaques following a cadaveric dura mater graft. *Neuropathology* 2006;26:82-8.
- [53] Rabinstein AA, Whiteman ML, Shebert RT, et al. Abnormal diffusion-weighted magnetic resonance imaging in Creutzfeldt-Jakob disease following corneal transplantations. *Arch Neurol* 2002;59:637-9.
- [54] Yamamoto S, Kinoshita M, Furukawa S, et al. Early abnormality of diffusion-weighted magnetic resonance imaging followed by brain atrophy in a case of Gerstmann-Sträussler-Scheinker disease. *Arch Neurol* 2007;64:450-1.
- [55] Arata H, Takashima H, Hirano R, et al. Early clinical signs and imaging findings in Gerstmann-Sträussler-Scheinker syndrome (Pro102Leu). *Neurology* 2006;66:1672-8.
- [56] Konaka K, Kaido M, Okuda Y, et al. Proton magnetic resonance spectroscopy of a patient with Gerstmann-Sträussler-Scheinker disease. *Neuroradiology* 2000;42:662-5.
- [57] Zerr I, Giese A, Windl O, et al. Phenotypic variability in fatal familial insomnia (D178N-129M) genotype. *Neurology* 1998;51:1398-405.
- [58] Wimberger D, Uranitsch K, Schindler E, et al. Gerstmann-Sträussler-Scheinker syndrome: MR findings. *J Comput Assist Tomogr* 1993;17:326-7.
- [59] Almer G, Hainfellner HA, Jellinger K, et al. Fatal familial insomnia: a new Austrian family. *Brain* 1999;122:5-16.
- [60] Fox NC, Freeborough PA, Mekkaoui KF, et al. Cerebral and cerebellar atrophy on serial magnetic resonance imaging in an initially symptom free subject at risk of familial prion disease. *BMJ* 1997;315:856-7.
- [61] Kropp S, Schulz-Schaeffer WJ, Fickenstaedt M, et al. The Heidenhain variant of Creutzfeldt-Jakob Disease. *Arch Neurol* 1999;56:55-61.
- [62] Cooper SA, Murray KL, Heath CA, et al. Isolated visual symptoms at onset in sporadic Creutzfeldt-Jakob disease: the clinical phenotype of the "Heidenhain variant". *Br J Ophthalmol* 2005;89:1341-2.
- [63] Gambetti P, Kong Q, Zou W, et al. Sporadic and familial CJD: classification and characterization. *Br Med Bull* 2003;66:213-39.
- [64] 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;46:224-33.
- [65] Zeidler M, Green A. Advances in diagnosing Creutzfeldt-Jakob disease with MRI and CSF 14-3-3 protein analysis. *Neurology* 2004;63:410-1.
- [66] Meissner B, Körtner K, Bartl M, et al. Sporadic Creutzfeldt-Jakob disease: magnetic resonance imaging and clinical findings. *Neurology* 2004;63:450-6.
- [67] Zerr I, Schulz-Schaeffer WJ, Giese A, et al. Current clinical diagnosis in Creutzfeldt-Jakob disease: identification of uncommon variants. *Ann Neurol* 2000;48:323-9.
- [68] Meissner B, Westner IM, Kallenberg K, et al. Sporadic Creutzfeldt-Jakob disease: clinical and diagnostic characteristics of the rare VV1 type. *Neurology* 2005;65:1544-50.

- [69] Mittal S, Farmer P, Kalina P, et al. Correlation of DWI MRI with neuropathology in Creutzfeldt-Jakob disease. *Arch Neurol* 2002;59:128–34.
- [70] Russmann H, Vingerhoets F, Miklossy J, et al. Sporadic Creutzfeldt-Jakob disease. a comparison of pathologic findings and diffusion weighted imaging. *J Neurol* 2005;252:338–42.
- [71] Na DL, Suh CK, Choi SH, et al. Diffusion-weighted magnetic resonance imaging in probable Creutzfeldt-Jakob disease: a clinical-anatomic correlation. *Arch Neurol* 1999;56:951–7.
- [72] Masters CL, Richardson EP Jr. Subacute spongiform encephalopathy (Creutzfeldt-Jakob disease). The nature and progression of spongiform change. *Brain* 1978;101:333–44.
- [73] Cambier DM, Kantarci K, Worrell GA, et al. Lateralized and focal clinical, EEG, and FLAIR MRI abnormalities in Creutzfeldt-Jakob disease. *Clin Neurophysiol* 2003;114:1724–8.