Neuroimaging in human prion disease: Searching in the mist

Panayotis Ioannides, Dimitris Karacostas

Panayotis Ioannides, Dimitris Karacostas, B’ Department of Neurology, AHEPA University Hospital, Thessaloniki 54636, Greece

Author contributions: Ioannides P and Karacostas D studied the conception, design of the study, collected, analyzed and interpreted the data, wrote and revised the manuscript.

Correspondence to: Dimitris Karacostas, MD, PhD, B’ Department of Neurology, AHEPA University Hospital, Thessaloniki 54636, Greece. bneurol@med.auth.gr

Telephone: +30-2310-994677 Fax: +30-2310-994689

Received: November 18, 2009 Revised: December 22, 2009 Accepted: December 25, 2009 Published online: December 31, 2009

Abstract

Human prion disease is a rare, uniformly fatal neurodegenerative disorder. Its precise pathogenesis is obscure. The clinical profile of the disease differs among its various forms. There are no definitive diagnostic tests (except for brain biopsy) or proven treatment. To increase the clinical diagnostic sensitivity and specificity, three laboratory tests, including electroencephalogram, cerebrospinal fluid testing for 14-3-3 protein, and magnetic resonance imaging, are currently used. Additionally, proton magnetic resonance spectroscopy, positron emission tomography and single photon emission computed tomography can provide interesting and novel results in the research of human prion disease.

© 2009 Baishideng. All rights reserved.

Key words: Human prion disease; Creutzfeldt-Jakob disease; Neuroimaging; Magnetic resonance imaging

INTRODUCTION

Human prion disease is a rare, uniformly fatal progressive neurodegenerative disorder, characterized by the deposition of an abnormal prion protein (PrP) in the central nervous system[1]. The most common form of human prion disease is Creutzfeldt-Jakob disease (CJD) and the whole nosological spectrum has been further divided into four categories. (1) Sporadic CJD (sCJD) arising from either a spontaneous PrP gene mutation or from a stochastic PrP structural change to the abnormal form. The host codon 129 genotype and the molecular strain of the deposited prion agent affect the phenotype[1,2]; (2) Iatrogenic prion disease, caused by infection (prion transmission) from medical (blood transfusion, human growth hormone) or surgical (corneal, dura mater grafts) procedures[1,2]; (3) Variant CJD (vCJD) which is causally linked to bovine (cattle) spongiform encephalopathy prion agent[1-3]; and (4) Inherited or genetic prion disease, caused by autosomal dominant PrP gene mutations (such as E220k, P102L) or insertions (such as ins144bp, ins24bp) on human chromosome 20[4,5]. The clinicopathological spectrum is further influenced by polymorphisms at codon 129 of the PrP gene[6].

The precise pathogenetic mechanism underlying the neurological illness is at present obscure. The clinical profile of the disease differs among its various forms. Early ante-mortem diagnosis is challengingly difficult and no definitive diagnostic tests (except for brain
biopsy) or proven treatment modalities are available. Most importantly, other potentially treatable diseases including infectious, inflammatory, autoimmune, toxic, and metabolic diseases should initially be excluded.

In addition to abnormal PrP staining, the neuropathological changes are characterized by neuronal loss, astrocytic gliosis, and spongiform change. The initial diagnostic suspicion of prion disease is clinical, usually raised by various combinations of rapidly progressive cognitive impairment, psychiatric features, cerebellar ataxia, myoclonus, visual disturbances, pyramidal or extrapyramidal signs and terminal akinetic mutism. However, significant clinical heterogeneity and different phenotypes occur in all forms of human prion disease (sCJD, vCJD, genetic and iatrogenic CJD (iCJD)), and are paralleled to variations in neuropathology.

DIAGNOSTIC LABORATORY TESTS

Three laboratory tests, including electroencephalogram (EEG), cerebrospinal fluid (CSF) testing for 14-3-3 protein, and magnetic resonance imaging (MRI) are currently used to increase the clinical diagnostic sensitivity and specificity, and have been included in the World Health Organization (WHO) diagnostic criteria for vCJD and sCJD. The EEG, in around two thirds of cases, may show progressive deterioration with the appearance of periodic sharp wave complexes, the absence of which does not exclude the diagnosis. Also, these EEG complexes may be present in other conditions, such as hepatic encephalopathy, drug-heavy metals toxicity and Alzheimer’s disease, while they are absent in vCJD.

CSF 14-3-3 is a normal neuronal protein that is released into the CSF following neuronal damage, with no specific connection to CJD. However, it shows a surprisingly high specificity and sensitivity (around 94%) to sCJD and therefore it should be only valid in the appropriate clinical setting. When this test is used in unselected patients with rapidly progressive dementia, false positive results can be found in 12% of them. Furthermore, fatal insomnia, a rare inherited form of prion disease, does not increase the CSF levels of 14-3-3 protein, in almost all cases.

Over the past decade, the non-invasive nature of MRI, the improved MR sequences used, and the availability of clinical-imaging-neuropathological correlations, have all contributed to an increased importance of MRI in the diagnosis of human prion disease, and have been included in the diagnostic criteria for vCJD. Additionally, proton magnetic resonance spectroscopy (MRS), positron emission tomography (PET) and single photon emission computed tomography (SPECT) can provide interesting and novel but sometimes puzzling results in the research of human prion disease.

NEUROIMAGING FINDINGS ON MRI

A symmetric high signal in the caudate and putamen is typical on fluid-attenuated inversion recovery (FLAIR) and diffusion weighted images (DWI) in sCJD. More recent reports have added to the above the significance of “cortical ribbon” hyper-intensity, with a higher sensitivity to DWI (Figure 1A and B). Nevertheless, the findings in a comprehensive, multicenter international study, strongly argue that characteristic MR lesion profiles may occur in each molecular subtype of sCJD. However, in another study, no abnormality on any MR sequence was found, in 5 of 8 patients with methionine homozygotes (MM2 subtype). Although the mechanism underlying the MR signal change is controversial, a recent small study found that apparent diffusion coefficient (ADC) values, decrease with increasing spongiform change (P < 0.001) and PrP deposition (P = 0.003) in deep gray matter and increased signals in DWI are characterized by reduced ADC values, which quantify regional water diffusion (Figure 1B and C). Serial DWI has shown that the extension of high signals increases with disease progression. In contrast, initial hyper intensity disappeared in the late disease stages.

In iCJD, incubation periods range from months to up to 30 years and the imaging patterns observed in recipients seem to differ according to the type of donor materials. In human growth hormone recipients, bilaterally symmetric high signals can be observed in caudate head and putamen. Similar findings have been reported in case reports of dura mater recipients. However, atrophy is the only imaging finding in larger series of dural grafts. In prion infection due to blood transfusion from asymptomatic donors who later developed vCJD, the pre-mortem MRI is normal or the pulvinar sign becomes evident as the disease clinically progresses.

In vCJD, bilateral symmetric high pulvinar signal, as seen on T2 weighted imaging (T2WI), FLAIR (most sensitive) and DWI has been included in the WHO diagnostic criteria. When this pulvinar sign is associated with hyper-intensity in dorsomedial thalamic nuclei, the “hockey stick” sign develops (Figure 1F-H). The above mentioned pulvinar or hockey stick signs are the most consistent MRI findings in any human prion disease, possibly because only one molecular strain of the disease has been found in vCJD. Finally, in confused or agitated patients with their standard MR sequences degraded by movement artefact, only DWI can provide important diagnostic data (Figure 11 and J).

In inherited prion disease, MR changes are non-specific. However, imaging is required to exclude other prion and non-prion diseases. Imaging reports indicate normal findings, cortical or cerebellar atrophy or decreased basal ganglia signals (Figure 1D and E). Also,
there is no evidence suggesting the most useful MR sequences in the diagnosis of this inherited disorder[3].

**FINDINGS ON PROTON MRS**

This non-invasive method is used to assess the spectra of several brain metabolites, such as N-acetylaspartate (NAA), creatine and myo-inositol (MI) and to measure these compounds in both absolute values and ratios, in specific brain regions[2,4]. Considering the NAA a neuronal marker[29], and MI a glial marker[4], proton MRS used as an additional tool along with other MR sequences (FLAIR, DWI, T2WI) is of value in the study of human prion disease. Reduced absolute levels or ratios of NAA and increased MI values, have been reported in sporadic[4,30], variant[30,31], iatrogenic[23] and inherited[32] CJD. The pattern of these metabolic changes on MRS matches the MRI findings on FLAIR, T2WI, and DWI[14]. However, this hypo-metabolism is more pronounced in the cerebellum and cortex than in the thalamus and striatum[15], unmatching the distribution of lesions seen on MRI.

Accordingly, widespread hypoperfusion has been demonstrated using SPECT in all forms of human prion disease[3]. The majority of sCJD patients reveal decreased cerebral perfusion, including the occipital cortex, cerebellum or the entire hemisphere[16]. Also, more regional changes in perfusion with SPECT can be detected in early stages of the disease than MRI changes[34].

**CONCLUSION**

As different types of disease arise, changes in the neuroimaging patterns of human prion disease continue to puzzle clinicians and researchers alike.

At present, the most consistent MRI change is the pulvinar sign in vCJD patients. When the dorsomedial thalamic nuclei are involved, the “hockey stick” sign provides additional clues[3,8,27]. Since bilateral high signals are observed in the caudate and putamen, and “cortical ribbon” hyper-intensity is found on DWI of...
sCJD patients\textsuperscript{12,17,18}, the diagnostic sensitivity of MRI is further augmented. Newer imaging techniques, such as proton MRS and SPECT seem to provide useful data for identifying the patterns in all forms of human prion disease\textsuperscript{13,14,19}.

Future research should eventually aim at studying the increasing number of “probable” prion cases, through multicenter international studies, utilizing combined imaging modalities, such as serial DWI with MRS, SPECT with MR perfusion imaging and MRI with \textit{in vivo} PET probe to label prion plaques\textsuperscript{20,21}. Hopefully, this perspective will elucidate some of the debatable issues presented and the “mist” will start to resolve.

REFERENCES

1. Knight RS, Will RG. Prion diseases. J Neurol Neurosurg Psychiatry 2004; 75 Suppl 1: i36-i42
2. Macfarlane RG, Wroe SJ, Collinge J, Yousry TA, Jäger HR. Neuroimaging findings in human prion disease. J Neurol Neurosurg Psychiatry 2007; 78: 664-670
3. Collinge J. Prion diseases of humans and animals: their causes and molecular basis. Annu Rev Neurosci 2001; 24: 519-550
4. Lodi R, Parchi P, Tonon C, Manners D, Capellari S, Strafmanniello, 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 imaging and spectroscopy study. Brain 2009; 132: 2669-2679
5. Collinge J. Human prion diseases: etiology and clinical features. In: Growdon JH, Rossor MN, editors. The Dementias. Boston: Butterworth-Heinemann, 1998: 113-150
6. Zerr I, Pocchiari M, Collins S, Brandel JP, de Pedro Cuesta J, Knight RS, Bernheimer H, Cardone F, Dalsenriever-Lauprêtre N, Cuadrado Corrales N, Ladogana A, Bodemer M, Fletcher A, Awan T, Ruiz-Bermón A, Budka H, Laplanche JL, Will RG, Poser S. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. Neurology 2000; 55: 811-815
7. Steinhoff BJ, Zerr I, Glutting M, Schulz-Schaeffer W, Poser S, Kretzschmar HA. Diagnostic value of periodic complexes in Creutzfeldt-Jakob disease. Ann Neurol 2004; 56: 702-708
8. World Health Organization. The Revision of the Surveillance Case Definition for variant Creutzfeldt-Jakob Disease: Report of a WHO Consultation, Edinburg, World Health Organ Tech Rep Ser 2004
9. Mastrianni JA. Prion diseases: transmissible spongiform encephalopathies. In: Noseworthy JH, editor. Neurological pathogenesis: principles and practice. Oxon: Informa Health Care, 2006: 1163-1168
10. Burkhard PR, Sanchez JC, Landis T, Hochstrasser DS. CSF detection of the 14-3-3 protein in unselected patients with dementia. Neurology 2001; 56: 1528-1533
11. Krasnianski A, Bartl M, Sanchez Juan PJ, Heinemann U, Meissner B, Varges D, Schulze-Sturm U, Kretzschmar HA, Schulz-Schaeffer WJ, Zerr I. Fatal familial insomnia: Clinical features and early identification. Ann Neurol 2008; 63: 658-661
12. Meissner B, Kallenberg K, Sanchez-Juan P, Collie D, Summers DM, Almonti S, Collins SJ, Smith P, Crau P, Jansen GH, Brandel JP, Coulthart MB, Roberts H, Van Everbroeck B, Galanauad D, Mellina V, Will RG, Zerr I. MRI lesion profiles in sporadic Creutzfeldt-Jakob disease. Neurology 2009; 72: 1994-2001
13. Manners DN, Parchi P, Tonon C, Capellari S, Straffmanniello 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
14. Tschampa HJ, Zerr I, Urbach H. Radiological assessment of Creutzfeldt-Jakob disease. Eur Radiol 2007; 17: 1200-1211
15. Engler H, Lundberg PO, Ekborn K, Nennesmo I, Nilsson A, Bergström M, Tsukada H, Hartvig P, Längström B. Multitracer study with positron emission tomography in Creutzfeldt-Jakob disease. Eur J Nucl Med Mol Imaging 2003; 30: 187
16. Henkel K, Meller J, Zerr I, Schulz-Schaeffer W, Schroeter A, Tschampa HJ, Kretzschmar HA, Becker W, Poser S. Single photon emission computed tomography (SPECT) in 19 patients with Creutzfeldt-Jakob disease. J Neurol 1999; 246 (Suppl 1): 400
17. Schröter A, Zerr I, Henkel K, Tschampa HJ, Finkenstaedt M, Poser S. Magnetic resonance imaging in the clinical diagnosis of Creutzfeldt-Jakob disease. Arch Neurol 2000; 57: 1751-1757
18. Shiga Y, Miyazawa K, Sato S, Fukushima R, Shibuya S, Sato Y, Konno H, Do-hura K, Mugikura S, Tamura H, Higano S, Takahashi S, Itoyama Y. Diffusion-weighted MRI abnormalities as an early diagnostic marker for Creutzfeldt-Jakob disease. Neurology 2004; 63: 443-449
19. Krasnianski A, Meissner B, Schulz-Schaeffer W, Kallenberg K, Bartl M, Heinemann U, Vargus D, Kretzschmar HA, Zerr I. Clinical features and diagnosis of the MM2 cortical subtype of sporadic Creutzfeldt-Jakob disease. Arch Neurol 2006; 63: 876-880
20. Uksis R, Kushihashi T, Kitanosono T, Fujisawa H, Takenaka H, Oghiya Y, Gokan T, Unechika H. Serial diffusion-weighted MRI of Creutzfeldt-Jakob disease. AJR Am J Roentgenol 2005; 184: 560-566
21. Russmann H, Vingerhoets F, Miklosy J, Maeder P, Glatzel M, Aguzzi A, Bogousslavsky J. Sporadic Creutzfeldt-Jakob disease: a comparison of pathological findings and diffusion weighted imaging. J Neurol 2005; 252: 338-342
22. Matoba M, Tonami H, Miyaji H, Yokota H, Yamamoto I. Creutzfeldt-Jakob disease: serial changes on diffusion-weighted MRI. J Comput Assist Tomogr 2001; 25: 274-277
23. Oppenheim C, Zuber M, Galanauad D, Detilleux M, Bolgert F, Mas JL, Chiras J, Meder JF. Spectroscopy and serial diffusion MR findings in sGH-Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry 2004; 75: 1066-1069
24. Preusser M, Ströbel T, Gelpi E, Eiler M, Broessner G, Schmutzhard E, Budka H. Alzheimer-type neuropathology in a 28 year old patient with iatrogenic Creutzfeldt-Jakob disease after dural grafting. J Neurol Neurosurg Psychiatry 2006; 77: 413-416
25. Martinez-Lage JF, Poza M, Sola J, Tortosa JG, Brown P, Cervenakova L, Esteban JA, Mendoza A. Accidental transmission of Creutzfeldt-Jakob disease by dural cadaveric grafts. J Neurol Neurosurg Psychiatry 1994; 57: 1091-1094
26. Wroe SJ, Pal S, Siddique D, Hyare H, Macfarlane R, Joiner S, Linehan JM, Brandner S, Wadsworth JD, Hewitt P, Collinge J. Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report. Lancet 2006; 368: 2061-2067
27. Zeidler M, Sellar RJ, Collie DA, Knight R, Stewart G, Macleod MA, Ironside JW, Couzens S, Colchester AC, Hadley DM, Will RG. The pulvinar sign on magnetic resonance imaging in variant Creutzfeldt-Jakob disease. Lancet 2000; 355: 1412-1418
28. Zerr I, Giese A, Windl O, Kropp S, Schulz-Schaeffer W, Riedemann C, Skworic K, Bodemer M, Kretzschmar HA, Poser S. Phenotypic variability in fatal familial insomnia (D178N-129M) genotype. Neurology 1998; 51: 1398-1405
29. Kantarci K, Knopman DS, Dickson DW, Parisi JE, Whitwell
JL, Weigand SD, Josephs KA, Boeve BF, Petersen RC, Jack CR Jr. Alzheimer disease: postmortem neuropathologic correlates of antemortem 1H MR spectroscopy metabolite measurements. Radiology 2008; 248: 210-220

30 Pandya HG, Coley SC, Wilkinson ID, Griffiths PD. Magnetic resonance spectroscopic abnormalities in sporadic and variant Creutzfeldt-Jakob disease. Clin Radiol 2003; 58: 148-153

31 Cordery RJ, MacManus D, Godbolt A, Rossor MN, Waldman AD. Short TE quantitative proton magnetic resonance spectroscopy in variant Creutzfeldt-Jakob disease. Eur Radiol 2006; 16: 1692-1698

32 Waldman AD, Cordery RJ, MacManus DG, Godbolt A, Collinge J, Rossor MN. Regional brain metabolite abnormalities in inherited prion disease and asymptomatic gene carriers demonstrated in vivo by quantitative proton magnetic resonance spectroscopy. Neuroradiology 2006; 48: 428-433

33 Goldman S, Laird A, Flamant-Durand J, Luxen A, Bidaut LM, Stanus E, Hildebrand J, Przedborski S. Positron emission tomography and histopathology in Creutzfeldt-Jakob disease. Neurology 1993; 43: 1828-1830

34 Arata H, Takashima H, Hirano R, Tomimitsu H, Machigashira K, Izumi K, Kikuno M, Ng AR, Umehara F, Arisato T, Ohkubo R, Nakabeppu Y, Nakajo M, Osame M, Arimura K. Early clinical signs and imaging findings in Gerstmann-Sträussler-Scheinker syndrome (Pro102Leu). Neurology 2006; 66: 1672-1678

S- Editor Wang JL  L- Editor Wang XL  E- Editor Zheng XM