J Neurol (2005) 252 : 338–342
DOI 10.1007/s00415-005-0648-8

ORIGINAL COMMUNICATION

Heike Russmann
Francois Vingerhoets
Judith Miklossy
Philippe Maeder
Markus Glatzel
Adriano Aguzzi
Julien Bogousslavsky

Sporadic Creutzfeldt-Jakob disease

A comparison of pathological findings and diffusion weighted imaging

Received: 24 February 2004
Received in revised form: 18 July 2004
Accepted: 20 July 2004
Published online: 3 March 2005

H. Russmann, MD · Dr. F. J. G. Vingerhoets, Priv.-Doz. (✉) · J. Bogousslavsky, MD
Dept. of Neurology
Centre Hospitalier Universitaire Vaudois
Route de Bugnon 11
CH-1011 Lausanne, Switzerland
Tel.: +41-21/314-1111
Fax: +41-21/3141287
E-Mail: F.Vingerhoets@chuv.hospvd.ch

P. Maeder, MD
Dep. of Radiology
Centre Hospitalier Universitaire Lausanne
Lausanne, Switzerland

J. Miklossy, MD
Dept. of Pathology
Centre Hospitalier Universitaire Lausanne
Lausanne, Switzerland

M. Glatzel, MD · A. Aguzzi, MD
Dept. of Pathology
Centre Hospitalier Universitaire Zurich
Zurich, Switzerland

Abstract To investigate a possible relationship between the severity of pathological and radiological lesions in diffusion-weighted MRI (DWI) we compared DWI findings from 6 sequential brain MRI scans with pathological features of numerous tissue blocks of different cortical and subcortical regions in a case of autopsy-proven sporadic CJD. Whereas DWI and pathological examination revealed multifocal, cortical and deep hyperintensities at corresponding localizations, no correlation between the degree of severity of radiologically visible and pathological damage was found.

The characteristic focal involvement and extension of lesions of the cortex and the basal ganglia bilaterally shown by DWI may be an argument for the spreading of the disease per contiguitatem.

Key words Creutzfeldt-Jakob disease · current diagnostic criteria for clinical diagnosis · diffusion-weighted MRI · cerebral spongiosis · gliosis

Introduction

Sporadic Creutzfeldt-Jakob disease (CJD) is diagnosed on the basis of clinical criteria, characteristic EEG signs, and neuropathological abnormalities demonstrated by light microscopy and immunohistochemistry. Clinical criteria are progressive dementia, myoclonus, visual or cerebellar disturbances, pyramidal or extrapyramidal features, and characteristic EEG abnormalities [1, 2], while neuropathological criteria are morphologic changes on light-microscopy with trias spongiform degeneration, neuronal loss, and astrocytic gliosis [3]. The [4] premortem diagnosis of CJD is supported by the presence of 14-3-3 protein [4] and radiological abnormalities, such as hyperintense signals on T1-, T2-, and/or diffusion weighted MRI images [5–8].

We describe a patient of histopathologically confirmed Creutzfeldt-Jakob disease, who had MRI and pathological lesions at similar localizations and looked for correlation between the degree of severity of radiological and neuropathological findings.

Clinical history

A 48-year-old woman, without familial or personal history of neurological disease or transplantation or hormone treatment except contraception, initially presented with problems of comprehension and memory. On admission to the Neurology Department six months after the first symptoms, neuropsychological examination showed intermittent disorientation, speech disorders with comprehension deficits, dyspraxia, and frontal signs. Neurological examination showed right visual hemiextinction, saccadic pursuit, augmentation of mus-

JON 1648

cle tone, asterixis and spontaneous myoclonus, ataxia, and gait disorder with titubation. Laboratory blood tests revealed a slight inflammatory reaction and high titers of anti-thyroglobulin and anti-microsomal antibodies with normal TSH and FT4 values, leading to the diagnosis of Hashimoto's thyroiditis. There were no other abnormalities on extensive laboratory and radiological screening. CSF examination was normal except for the presence of 14-3-3 protein.

Despite treatment with steroids and immunosuppressors, which led to a decrease in anti-microsomal antibody titers, the patient developed akinetic mutism during the first ten days of hospitalization. Death occurred two months after admission, eleven months after the first symptoms. The EEG showed periodic triphasic complexes with loss of background activity and the presence of intermittent epileptic activity.

Radiology

The patient underwent conventional sagittal and transverse spin echo for T1-WI, T2-WI and proton density-weighted images of 5-mm thickness using a Siemens Magnetom 63SP 1.5 T. Matrix was 256 × 256, and field of view was 230 mm. Contrast-enhanced T1-WI sagittal and transverse 5-mm-thick MRI slices were obtained using gadolinium-diethylenetriamine-pentaacetic acid. Diffusion weighted (DW) sequences were performed using a single shot spin-echo planar imaging technique, giving a diffusion weighting (b-value) of 1100 s/mm^2.

The diffusion gradient was applied in the transverse (x) direction. In selected procedures we also applied the diffusion gradient in the sagittal and coronal directions to rule out normal anisotropy. Apparent diffusion coefficient (ADC) was calculated for 11 regions of interest.

Six DW MRI scans (days 1; 7; 21; 31; 38; 46) were performed during hospitalization, the last one six weeks before the death of the patient. The first one (day 1) showed focal signal hyperintensities localized in the left frontal cortex, the parietal cortex bilaterally, with left predominance, the head of the caudate with left predominance, the cingulate gyrus, the anterior part of the left putamen, and the left temporal cortex. There was extension and intensification of signal hyperintensities in the head of the right caudate and the right parietal cortex on the MRI-scan (2) one week later. On day 21 (3) there was intensification of the previously described hypersignals in the left caudate nucleus and left anterior putamen, as well as extension to the right putamen. On day 31 (4) there was further extension of signal hyperintensities on the right putamen as well as bilateral intensification of signal hyperintensities on the heads of the caudate nucleus and the left parietal cortex. One week later (5: day 38) signal intensification extended further down in both putamen. The last MRI (6: day 48) performed six weeks before death, showed extension of signal hyperintensities to the left frontal operculum and left temporal cortex, as well as signal intensification of the previously described lesions, especially those in both caudate nuclei, both putamen, and the cerebellum. In contrast to a previous report [9], no significant visible atrophy was present.

Neuropathological investigation

From the formalin fixed brain samples from 25 representative levels of eleven regions of interest were taken and were embedded in paraffin. These representative regions included the frontal, temporal, parietal and occipital cortical areas, hippocampus, basal ganglia, thalamus, mesencephalon and cerebellum, including vermis (see Fig. 2).

Paraffin sections (5 µm thick) were stained with Hematoxylin and Eosin (H&E), Van Gieson – luxol fast blue, Thioflavin-S and with the Gallyas silver technique for the demonstration of neurofibrillary tangles. For the detection of prion protein (PrP), paraffin sections were immunostained with a monoclonal antibody (clone 3F4), which recognizes amino acids 109–112 epitope of the prion protein (PrP). In order to exclude Alzheimer's disease and the possibility of other neurodegenerative disorders, further immunohistochemical investigations were performed.

In addition to the presence of specific neuropathological changes (spongiosis, neuronal loss and gliosis) in all cortical areas tested, the detection of PrP using 3F4 antibody definitely confirmed the clinical diagnosis of sporadic CJD. A semiquantitative assessment of the severity of spongiosis, neuronal loss and gliosis was performed. The density of spongiosis was determined on H&E-stained sections, the severity of neuronal loss on H&E and synaptophysin immunostained sections using monoclonal antibody, M0776, clone SY 38 (DAKO Corporation, Carpinteria, California). The density of astrocytic gliosis was analysed on H&E and on immunostained sections using anti glial fibrillary acidic protein (GFAP) antibody (Z334, DAKO Corporation, Carpinteria, California). The densities of neuronal loss, spongiosis and gliosis were graded from "0 to 3" (0: absent, 1: low density, 2: medium density, 3: high density). The semiquantitative analysis was performed in all brain regions indicated in Fig. 2. The neuropathologist was blinded about the imaging results.

The semiquantitative assessment of the severity of spongiform alteration, neuronal loss and gliosis in several brain regions performed by a pathologist, blinded to the MRI results, were compared with the findings of the last MRI-scan (day 48).

Statistics were performed for corresponding neuropathological and MRI data, available for all 11 regions

of interest. The degree of severity (0–3) of histopathological changes was correlated with the ADC coefficient of the corresponding region using Spearman rank correlation.

Results

There was a reduction in the apparent diffusion coefficient (ADC) in all regions with spongiform alterations (Table 1). However, no correlation was found between the degree of spongiform alterations and the decrease in the ADC (correlation coefficient for spongiosis: 0.12, neuronal loss: –0.28 and gliosis: –0.28). ADC was most reduced in the basal ganglia (caudate nucleus and putamen) while spongiosis was more severe in the cortical regions (central gyrus and temporal and parietal cortex, Fig. 2). Gliosis and neuronal loss occurred at similar levels in these regions, but were more severe in the frontal and occipital cortex and the cerebellum.

Discussion

Our serial study consisted of six DWI MRI-scans over a period of six weeks in a case of histologically confirmed CJD, which fulfilled the current criteria for CJD in the premortem phase and it shows two findings: a) during the radiological follow-up consisting of six MRI scans in the first six weeks after admission, the increasing intensity and extension of these hyperintense signals correlated with disease progression and revealed multifocal regions of increased cortical signal intensity in basal ganglia and cortical regions; b) there was no correlation between the degree of radiological and histopathological abnormalities.

Table 1 Results of ADC and histopathological examination for 11 regions of interest

	DWI		Pathology		
Localization	ADC	SD	Spongiosis	Neuronal Loss	Gliosis
Central Gyrus left	64.8	16.5	3	3	3
Frontal left	71.1	14.2	1	3	3
Temporal left	89.2	11.1	3	2	2
Hippocampus	86.6	9.9	2	1	1
Parietal left	77.7	23.0	3	3	3
Occipital left	76.0	18.8	2	3	3
Caudate nucleus	62.1	12.7	2	2	2
Putamen	49.0	4.6	2	2	2
Mesencephalon	78.6	10.4	1	0	1
Thalamus	76.5	7.1	2	2	2
Vermis	68.9	12.0	2	3	3

Concerning the first result brain MRI may show focal hyperintensities in T2-weighted images in the striatum and thalamus [10, 11] and in the occipital gyri [12], and hyperintensity in T1- and T2-weighted images in the globus pallidus [7], but late in the disease. The CJD-specific hyperintensities detected by diffusion-weighted MRI result from cell damage with characteristic vacuolization of the neuropil [8, 13] with vacuoles with a diameter of less than 20 μm, gliosis [8, 13] or astrocytosis [13] that provide restricted diffusion compared with normal tissue [14], resulting in an increased DWI signal [15]. DWI can therefore detect cortical areas affected by CJD that appear normal in T1 and T2 studies [9, 16, 17].

The sites of the most pronounced lesions in our patient were similar to those previously reported, with involvement of the caudate nucleus, putamen, and cerebral cortex [5, 18]. The images showed intensification, expansion, and migration of cortical and deep matter lesions during the studied time-course (Fig. 1).

Concerning the second result, spongiform changes and gliosis were present in all histologically examined regions, with hyperintensity signals in DWI, due to a reduced ADC (Fig. 2). Comparison of the ADC and cellular damage as shown by histopathology showed corresponding localizations but no quantitative relation in terms of the degree of severity (Fig. 2).

The lack of a quantitative relationship between the degree of severity of radiological and pathological abnormalities might indicate differences in the reflection of cellular damage and changes in water diffusion in different brain regions by radiological images. Interestingly the ADC is lowest in the basal ganglia (putamen 49, caudate nucleus 62.1) but spongiosis, gliosis and neuronal loss had only degree 2 using a score between 0–3 whereas in some cortical regions with a severity-degree of 3 ADC was quite high (parietal left: 77.7, frontal left: 71.1). Compared with the study of Mittal et al. [14] who reported a detailed correlation with Diffusion-Weighted MRI with neuropathology in CJD, there might be methodological differences in the measurement of the raw data. It has to be taken into account that the score for the grading of the severity of pathological lesions is a semiquantitative score which depends on the observer.

We conclude that DWI-imaging is a non-invasive technique for follow-up in premortem phase, but that ADC measurement does not permit an estimate of the degree of the severity of cellular damage. The pattern of focal cortical involvement and the extension of the lesions from the left basal ganglia to the right basal ganglia might argue for spreading of damage per contiguitatem.

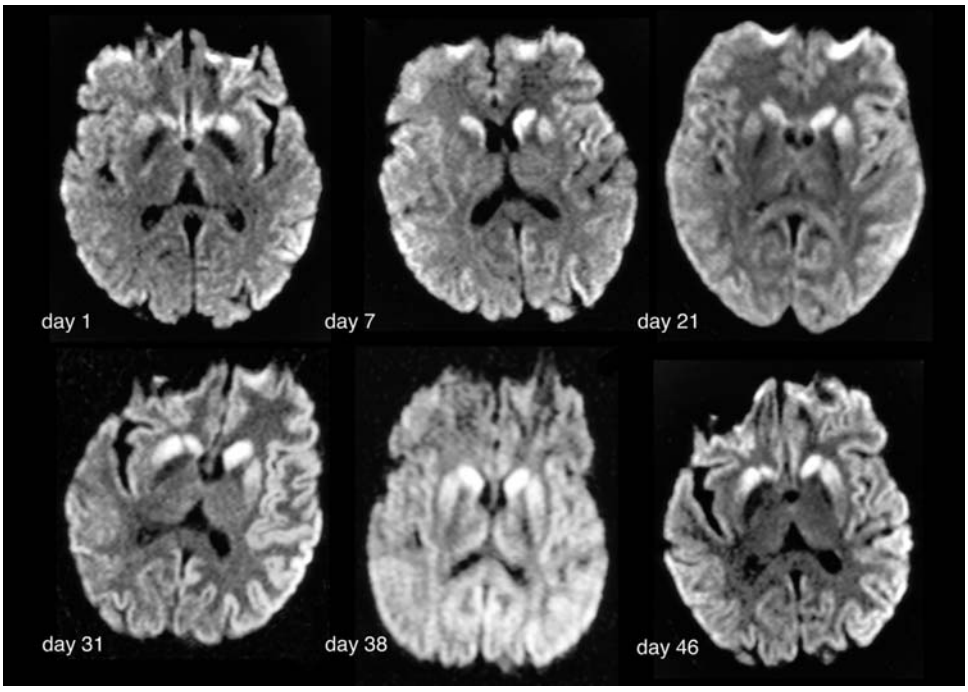

Fig. 1 Progression of extension and intensity on sequential DWI in a case of sporadic CJD

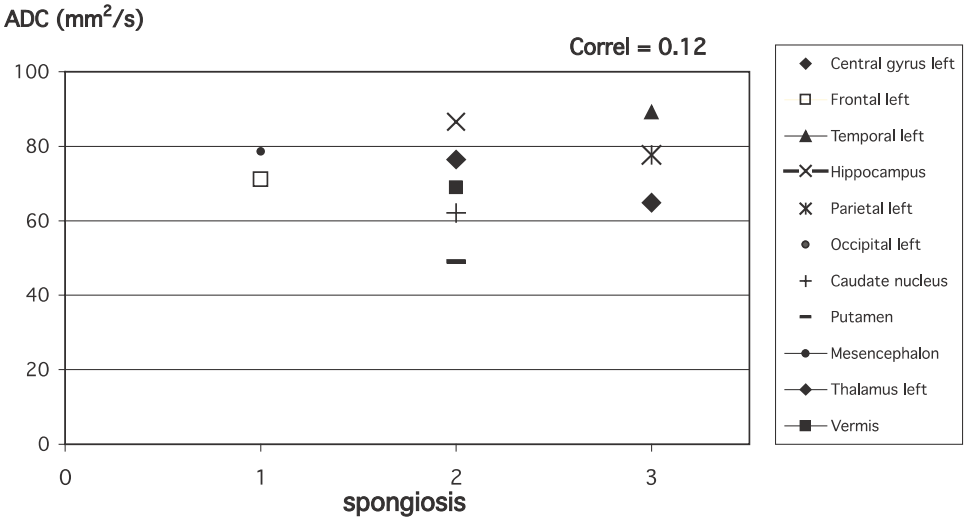

Fig. 2 Comparison of the ADC with the degree of spongiosis

References

1. Budka H, Aguzzi A, Brown P, Brucher JM, Bugiani O, Collinge J, et al. (1995) Tissue handling in suspected Creutzfeldt-Jakob disease (CJD) and other human spongiform encephalopathies (prion diseases). Brain Pathol 5: 319–322
2. Chiofalo N, Fuentes A, Galvez S (1980) Serial EEG findings in 27 cases of Creutzfeldt-Jakob disease. Arch Neurol 37:143–145
3. Kretzschmar HA, Ironside JW, De Armond SJ, Tateishi J (1996) Diagnostic criteria for sporadic Creutzfeldt-Jakob disease. Arch Neurol 53:913–920
4. Hsich G, Kenney K, Gibbs CJ, Lee KH, Harrington MG (1996) The 14-3-3 brain protein in cerebrospinal fluid as a marker for transmissible spongiform encephalopathies. N Engl J Med 335: 924–930
5. Bahn MM, Parchi P (1999) Abnormal diffusion-weighted magnetic resonance images in Creutzfeldt-Jakob disease. Arch Neurol 56:577–583
6. Bahn MM, Kido DK, Lin W, Pearlman AL (1997) Brain magnetic resonance diffusion abnormalities in Creutzfeldt-Jakob disease. Arch Neurol 54: 1411–1415

7. de Priester JA, Jansen GH, de Kruijk JR, Wilmink JT (1999) New MRI findings in Creutzfeldt-Jakob disease: high signal in the globus pallidus on T1-weighted images. Neuroradiology 41: 265–268
8. Demaerel P, Heiner L, Robberecht W, Sciot R, Wilms G (1999) Diffusion-weighted MRI in sporadic Creutzfeldt-Jakob disease. Neurology 52:205–208
9. Galvez S, Cartier L (1984) Computed tomography findings in 15 cases of Creutzfeldt-Jakob disease with histological verification. J Neurol Neurosurg Psychiatry 47(11):1244–1246
10. Finkenstaedt M, Szudra A, Zerr I, Poser S, Hise JH, Stoebner JM, et al. (1996) MR imaging of Creutzfeldt-Jakob disease. Radiology 199:793–798
11. Gertz HJ, Henkes H, Cervos-Navarro J (1988) Creutzfeldt-Jakob disease: correlation of MRI and neuropathologic findings. Neurology 38:1481–1482
12. Kropp S, Schulz-Schaeffer WJ, Finkenstaedt M, Riedemann C, Windl O, Steinhoff BJ, et al. (1999) The Heidenhain variant of Creutzfeldt-Jakob disease. Arch Neurol 56:55–61
13. Urbach H, Klisch J, Wolf HK, Brechtelsbauer D, Gass S, Solymosi L (1998) MRI in sporadic Creutzfeldt-Jakob disease: correlation with clinical and neuropathological data. Neuroradiology 40:65–70
14. Mittal S, Farmer P, Kalina P, Kingsley PB, Halperin J (2002) Correlation of diffusion-weighted magnetic resonance imaging with neuropathology in Creutzfeldt-Jakob disease. Arch Neurol 59:128–134
15. Na DL, Suh CK, Choi SH, Moon HS, Seo DW, Kim SE, et al. (1999) Diffusion-weighted magnetic resonance imaging in probable Creutzfeldt-Jakob disease: a clinical-anatomic correlation. Arch Neurol 56:951–957
16. Yee AS, Simon JH, Anderson CA, Sze CI, Filley CM (1999) Diffusion-weighted MRI of right-hemisphere dysfunction in Creutzfeldt-Jakob disease. Neurology 52:1514–1515
17. Demaerel P, Baert AL, Vanopdenbosch L, Robberecht W, Dom R (1997) Diffusion-weighted magnetic resonance imaging in Creutzfeldt-Jakob disease. Lancet 349(9055):847–848
18. Shiga YSS, Syuichi H, Shoki T, Yasuto I (2000) Diffusion-Weighted Magnetic Resonance Imaging of Creutzfeldt-Jakob Disease. Neurology (Suppl 3): A54–A100