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ORIGINAL ARTICLE

Usefulness of high b-value diffusion-weighted MRI in the diagnosis of Creutzfeldt-Jakob disease ☆

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Abstract
Background: Current diagnostic criteria of probable Creutzfeldt-Jakob disease (CJD) include a combination of clinical, EEG and analytic data. Recent data indicate that brain MRI including fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) sequences can be a valid and reliable tool for the diagnosis of CJD. We describe our experience with high b-value (3000s/mm^2) diffusion-weighted imaging (DWI) in patients with probable or definite CJD and compare it with standard b-value (1000s/mm^2) DWI.
Methods: We performed a retrospective analysis of patients admitted to our Hospital Service between 2002 and 2008 with a final diagnosis of probable or definite CJD. Patients were examined using either a 1.5 Tesla or a 3 Tesla MRI. The MRI protocol included T1-weigthed spin-echo sequences, T2-weighted fast spin-echo, FLAIR and DWI sequences with high b-value and standard b-value.
Results: During the study period there were 7 patients with probable or definite CJD. Only 3 patients (43%) showed changes on FLAIR sequence consistent with CJD. All the cases were detected with high b-value DWI, including 2 cases (28%) that would have been missed using standard b-value (1000s/mm^2) DWI. In all the patients the changes were more conspicuous and extensive at high b-value DWI (b=3000s/mm^2).

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Conclusion: Our data indicate that high b-value DWI may improve the sensitivity of brain MRI for the diagnosis of CJD, allowing the detection of some cases that would have been overlooked by conventional sequences.

PALABRAS CLAVE
Enfermedad de Creutzfeldt-Jakob;
Resonancia magnética cerebral;
Secuencias potenciadas en difusión;
DWI;
Valor b

Utilidad de la resonancia magnética cerebral con secuencia de difusión y valor b alto en el diagnóstico de la enfermedad de Creutzfeldt-Jakob

Resumen
Introducción: Los criterios diagnósticos actuales de la enfermedad de Creutzfeldt-Jakob (ECJ) probable incluyen la combinación de datos clínicos, electroencefalográficos y analíticos. En los últimos años se ha demostrado que la RM craneal con el uso de secuencias FLAIR y difusión (DWI) puede ser una herramienta útil en el diagnóstico de esta enfermedad. Describimos nuestra experiencia en la utilización de la DWI convencional (b: 1000s/mm^2) y DWI con valor b alto (3000s/mm^2) en el diagnóstico de la ECJ probable o definitiva.
Pacientes y métodos: Realizamos un análisis retrospectivo de los pacientes atendidos en nuestro hospital diagnosticados de ECJ probable o definitiva, desde el año 2002 al 2008. A todos ellos se les realizó una RM craneal con un protocolo que incluyó secuencias potenciadas en T1, T2, FLAIR y dos secuencias DWI, una con valor b convencional (1000s/mm^2) y otra con valor b alto (3000s/mm^2).
Resultados: Se atendieron a 7 pacientes con diagnóstico de ECJ probable o definitiva. En tres de ellos (43%) la secuencia FLAIR mostró cambios de señal compatibles con ECJ. En todos los pacientes en la secuencia DWI con valor b alto se observaron alteraciones características de la enfermedad, incluyendo dos casos (28%) en los que todas las secuencias realizadas, incluida la DWI convencional, fueron normales. Adicionalmente en los 7 casos (100%) las alteraciones radiológicas fueron más fáciles de identificar y más extensas con valores altos b de DWI.
Conclusión: La utilización de un valor b alto (3000s/mm^2) en la secuencia DWI puede aumentar la sensibilidad de la RM craneal en el diagnóstico de la ECJ, permitiendo la detección de casos en los que la DWI convencional es normal.

Introduction

Prion diseases are a group of degenerative processes that affect both humans and animals, and are characterised by the presence of abnormal prion protein isoforms.[1] Although they are rare processes, for which there is no effective treatment, they present a potential public health problem due to their seriousness and potential transmission. The most common form in humans is Creutzfeldt-Jakob disease (CJD), with a yearly incidence rate of 0.5 to 1.5 cases per million inhabitants. Creutzfeldt-Jakob Disease includes sporadic (sCJD), familial (fCJD), iatrogenic (iCJD) and variant (vCJD) forms. Definitive diagnosis of CJD requires pathological confirmation.[2] The current diagnostic criteria include a combination of clinical (rapidly progressive dementia associated to ataxia, myoclonus or pyramidal or extrapyramidal signs), electroencephalographic (periodic complexes) and analytical data (14-3-3 protein in CSF).[2] The diagnostic capacity of these criteria is limited, especially in the initial phases of the disease and in atypical presentations.[3,4] During the last few years, we have identified findings in brain MRI both in FLAIR sequences as well as diffusion-weighted imaging (DWI), that can help in the diagnosis of this disease.[5,6] The characteristic findings of sCJD consist of a hypersensitivity of the signal located in the cerebral striate and/or cortex. In vCJD, the pulvinar sign is included in the diagnostic criteria,[6] although false positives have been described in patients with sCJD.[7] We have shown that in patients who presented symptoms suggesting this disease, brain MRI with FLAIR and DWI sequences increased the sensitivity of the current diagnostic criteria by up to 98%[8] Conventional brain MRI protocols currently use diffusion sequences with a b-value of 1000s/mm^2.[6,8]

If higher b-values are applied (3000s/mm^2) in the DWI, this can show radiological alterations that go unnoticed with conventional b-values, findings that could have clinical implications.[6] We present our experience in CJD diagnosis using high b-value DWI sequences, compared to DWI with a conventional b-value.

Patients and methods

We undertook a retrospective analysis of patients diagnosed with probable or definite CJD who were seen in the neurology department and sent to the neuroradiology department at the Ruber International Hospital between 2002 and 2008. The brain MRI studies were assessed by one of the two neuroradiologists (JL, JE), who received the available clinical information. The examinations were carried out using a 1.5 Tesla Signa LX (GEHC) or a 3 Tesla Signa HDX (GEHC) MRI. The MRI protocol included T1-weighted spin-echo sequences (TR/TE 600/14), T2-weighted fast spin-echo sequences (TR/TE 5,400/85), FLAIR (TR/TE/TI 9,000/105/2,100) and DWI sequences. The parameters for the images with a b-value of 1,000 obtained with the 1.5 T MRI were: TR=10,000; TE=105ms; transversal sections=20; section thickness=5mm; interval between sections=1mm; matrix=96 x 96; field of view (FOV)=250mm and number of excitations (NEX)=1. The parameters for the images with a b-value of 3,000 obtained with the 1.5 T MRI were: TR=10,000; TE=136ms; transversal sections=20; section thickness=5mm; interval between sections=1mm; matrix=96 x 90; FOV=250mm and NEX=4. The parameters for the images with a b-value of 1,000 obtained with the 3 T MRI were: TR=6,000; TE: 71ms; transversal sections=20; section thickness=5mm; interval between sections=1mm; matrix=128 x 128; FOV=250mm and NEX=1. The parameters for the images with a b-value of 3,000 obtained with the 3 T MRI were: TR=7.000; TE=91ms; transversal sections=20; section thickness=5mm; interval between sections=1mm; matrix=128 x 128; FOV=250mm and NEX=4.

The MRI findings, which previously had been validated, were considered consistent with the diagnosis of sCJD and included the following[8]: a) gyriform abnormalities in at least two regions (temporal, occipital or parietal) in the FLAIR or DWI images and b) unilateral or bilateral hyperintensity of the caudate nucleus head and putamen in T2-weighted, FLAIR or DWI images. A pulvinar sign in sCJD was defined as hypersensitivity of the symmetric signal and exclusive to both thalamic nuclei pulvinares.[9]

Results

We identified 7 patients (5 females and 2 males; mean age: 58.6 years; range: 26-74 years) with probable or definite CJD diagnosis. Four of them were diagnosed with definite CJD from a post-mortem study. The mean survival rate from symptom onset was 6.4 months (range: 2-12 months) and the mean duration of the disease at the time of diagnosis was 4 months (range: 1-11 months). We could not carry out any clinical follow-up on two patients. The clinical data, demographic characteristics and the brain MRI findings of these patients are summarised in table 1. Three patients (43%) showed radiological alterations in the FLAIR sequences consistent with sCJD. In 5 patients (71%), diffusion-weighted MRI with conventional b-values (b=1,000s/mm^2) showed characteristic alterations in the cerebral cortex and/or basal ganglia. In two patients (28%), the radiological study with conventional FLAIR and DWI sequences (b=1,000s/

Table 1 Clinical and radiological characteristics of the patients studied

Age (years)	26	50	60	70	70	74	60
Gender	Female	Female	Male	Female	Female	Male	Female
Initial symptoms	Dementia	Dementia and ataxia	Subacute ataxia	Visual symptoms	Dementia	Dementia	Dementia
Mean survival (months)	12	4	9	2	5	Unknown	Unknown
EEG	Focal slowing	Focal epileptiform activity	Normal	Focal slowing	Periodic complexes	Focal slowing	Focal slowing
Protein 14.3.3	+	Unknown	-	+	+	+	+
HPPG	MM	E200K, MM	MV	MV	VV	MM	VV
Diagnosis.	Definite vCJD	Definite fCJD	Definite sCJD	Definite sCJD	Probable sCJD	Probable sCJD	Probable sCJD
FLAIR	+	+	-	-	+	-	-
DWI. b 1000	+	+	-	+	+	+	-
DWI. b 3000	++	++	+	++	++	++	+

+: findings in the brain MRI consistent with CJD; -: normal brain MRI;++: more extensive and evident radiological findings; E200K: mutation that causes a change of Glu by Lys at codon 200; HPPG: human prion protein gene; MM: homozygous for methionine at codon 129; MV: heterozygous methionine / valine at codon 129; VV: homozygous for valine at codon 129.

Figure 1 Patient with definite sCJD. A and B. Conventional FLAIR and DWI sequences (b=1,000s/mm^2), axial cuts, normal. C. DWI Image with a high b-value (b: 3,000s/ mm^2) that shows an increase in the abnormal signal of the patient's right putamen.

Figure 2 Patient with definite vCJD. A. Conventional DWI sequence (b=1,000s/mm^2), axial cut, with an increased signal in both putamen and bilateral occipital cortex. B. DWI sequence with a high b-value (b=3,000s/mm^2) where we can see that the radiological changes are more extensive and evident.

Figure 3 Patient with definite sCJD. A. Conventional DWI sequence (b=1000s/mm^2), axial cut, with dubious signal change in the bilateral occipital cortex. B. DWI sequence with a high b-value (b=3,000s/mm^2) where the change in the signal of the bilateral occipital cortex is more evident and extensive.

mm^2) was normal. We saw significant radiological changes when we used high b-values (b=3,000s/mm^2) in the DWI (fig. 1). The radiological alterations in the 7 patients were easier to identify and more extensive in high b-values of DWI (b=3000s/mm^2) (figs. 2 and 3). A patient with definite vCJD showed extensive signal changes in the basal ganglia, whose radiological characteristics were different from the pulvinar sign.

Discussion

The results of our work showed that the DWI sequence with b-value of 3000s/mm^2 can increase the sensitivity of the brain MRI in the diagnosis of CJD, allowing its identification in patients where the conventional DWI sequences (b: 1000s/mm^2) are normal. This data supports the results of other studies that show how the brain MRI protocol used determines the diagnosis of this disease.[5,6,8] Previous studies have described a sensitivity diagnosis of 79% when T2 -weighted brain MRI sequences or proton density are used. The use of protocols that include conventional FLAIR and DWI sequences could increase the sensitivity and specificity of the brain MRI by up to 80%-100% and 94%-100%, respectively.[1,8] However, we should highlight that in our 7-patient series, two of them with definite CJD and probable CJD did not show radiological alterations in the conventional sequences but did so in the DWI with high b-values. It is known that in some cases of sCJD the brain MRI studies with conventional DWI sequences can be normal. Therefore, if CJD is suspected, it may be a good idea to add DWI sequences with high b-values to the study. In our series of patients, they all showed characteristic radiological alterations when high b-value DWI sequences (3000s/mm^2) were included. However, this study has important limitations, as it is a retrospective analysis, with a small number of patients.

Despite these limitations, the findings described are similar to those recently published in a study that compared DWI sequences with both values (1000s/mm^2 and 3000s/mm^2) in 10 patients diagnosed with CJD (sCJD and vCJD).[10] There were signal alterations in the basal ganglia and/or the cortex in the conventional DWI of all of the patients and, in 9 of them, the changes were more evident when a high b-value was used. These authors, unlike our study, did not describe any patient whose conventional DWI was normal and the DWI with high b-values showed characteristic CJD changes.

We have recently seen the use of DWI with high b-values for diagnosing other neurological diseases.[11] So that we can correctly interpret the studies with DWI sequences, we should look at the appearance the different brain structures acquire when using different b-values. The cerebral cortex and the basal ganglia appear hyperintensive with respect to the white matter when used in conventional DWI sequences (b value=1,000s/mm^2). When higher b-values are used, the signal from the different brain structures changes. This is particularly true for the white matter and, above all, for the fibres of the internal capsule, which present a greater signal when compared to the basal ganglia and the cerebral cortex. Therefore, there is an inversion of the visual appearance in the DWI sequences according to the b-value used. The hyperintensity that the basal ganglia and cortex show in normal conditions of DWI sequences with b=1,000s/mm^2 can make the detection of the pathological increase of this signal difficult. However, a b-value=3000s/mm^2 would show the grey matter diffusion restriction much more clearly. This can help in the diagnosis of different diseases such as CJD, where the changes of cortex signal and basal ganglia predominate. Undertaking brain MRIs using DWI sequences with high b-values does not need different software or equipment to that normally used and it can be carried out by just increasing the examination time by only a few seconds. Although we have seen that there is a much better diagnosis with high-b-value DWI over the normal ones in some diseases, we still have to determine the best b-value for each disease.[12,13]

To conclude, the use of DWI sequences with a high b-value (3,000s/mm^2) can help in CJD diagnosis, especially in those patients with atypical symptoms or where the conventional brain MRI sequences are normal or provide ambiguous data.

Conflict of interest

The authors declare no conflict of interest.

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