First study of therapy follow-up of Creutzfeldt-Jakob disease by Magnetic Resonance Diffusion and Spectroscopy

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Introduction

Magnetic Resonance imaging and spectroscopy constitute the most promising and non invasive approach for early diagnosis (1) of Creutzfeldt Jakob disease (CJD). CJD is a rare and fatal neurodegenerative disorder caused by abnormal prion protein accumulation in the CNS (2). A number of subtypes are recognized: sporadic (sCJD), iatrogenic CJD (iCJD), and familial CJD (fCJD). In 1996, a new form, named variant CJD (vCJD), is believed to occur by transmission of the prion from bovine spongiform encephalopathy to humans through infected beef products. Early and accurate diagnosis of vCJD is important for prognostic and epidemiologic purposes and furthermore, for therapy development. In this context, we set up a MRI/MRS protocol to evaluate a new treatment based on the intra cerebro-ventricular infusion of Pentosan polysulfate (PSP) (3) simultaneously with biological, electrophysiological and clinical examinations by following patients longitudinally every 6 weeks.

Material and Methods

The first MR examination of the protocol was performed on 14 patients (9 male, 5 female, age =50±15y) with different form of CJD (2 iatrogenic, 2 variant, 8 sporadic, 2 familial) using a 1.5 T Sonata imager (Siemens, Germany) system before starting the PSF treatment. For control, six normal subjects were examined (3 male, 3 female, age=38±8y). Following conventional imaging sequences including 3D T1 MPR, transverse fast SE T2 and FLAIR, diffusion-weighted (DW) EPI images were acquired with three b values (0, 500, 1000 s/mm^2) and ADC maps calculated. Six single voxel spectra were localized using PRESS sequence (TR=1500 ms, 128 scans) with short echo time (TE=30 ms) from the anterior cingular cortex, the right and left side of the lenticular and the pulvinar areas, and the vermis. MR images were read by a neuroradiologist (M.H.). ADC values were measured in seven regions: right and left heads of caudate nuclei, putamen nuclei, and pulvinar areas, anterior cingular cortex, and vermis. The spectra were analyzed using the Siemens spectroscopic software. All peaks were fitted (lipids, NAA, glutamate, glutamine, creatine, choline, inositol (Ino)) and metabolite ratios were calculated using creatine (Cr) as reference. Three patients (among the 14) are actually included in the therapy follow-up protocol.

Results

1) Characterization of the subtypes disease: Visual analysis of the T2w, FLAIR and DW images showed hyper-intensities at various degrees depending on the region and the CJD form. DWI showed typical hyperintensities "hockey sign" in the pulvinar area of vCJD patients while the sCJD patients presented further increase in the caudate and putamen nuclei. Compared to normal values obtained from six volunteers, the ADC was significantly decreased in caudate (ADC=658±100.10^{-6}mm^2/s in patients vs 809±25.10^{-6}mm^2/s; p<0.0001), putamen (ADC= 564±99.10^{-6}mm^2/s in patients vs 755±18.10^{-6}mm^2/s; p<0.0001) and pulvinar regions of the patients (ADC=722±108.10^{-6}mm^2/s in patients vs 796±44.10^{-6}mm^2/s; p<0.0001). In the group of sporadic patients, Ino/Cr ratio was significantly increased in the putamen region (Ino/Cr=0.35±0.14 vs 0.21±0.05, p=0.02) compared to controls.

2) Longitudinal follow-up during 45 weeks of the first patient (iCJD subtype) treated with PSP. ADC measurements showed continuous decrease in caudate and putamen nuclei (the most impaired in this subtype) until the 12th week of therapy when they stabelized. After the 24th week, ADC increased slightly in the caudate. In contrast, ADC values started to decrease in the frontal cortex region only after the 24th week. (Fig1). The metabolic results showed an Ino/Cr ratio increased in the voxel including caudate and putamen nuclei compared to controls (Ino/Cr=0.20±0.05) and staying high in the course of time. In frontal cortex, the rise of Ino/Cr is delayed by 12 weeks.

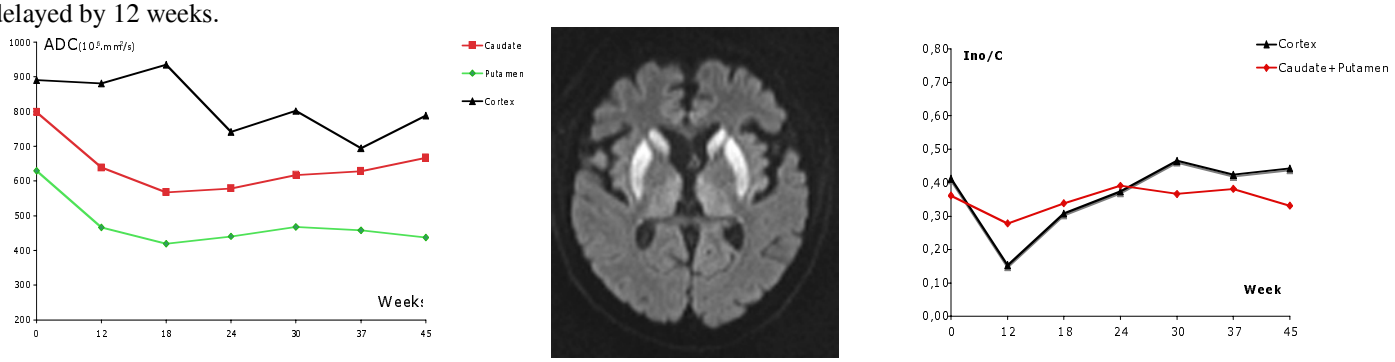

Fig.1. Follow-up of ADC (left) and Ino/Cr ratio (right) of the first patient treated with PSP during 45 weeks. DW image of the iCJD patient (middle).

Conclusion

These results demonstrated that both DWI and MRS provide complementary patterns of lesions and metabolic abnormalities to characterize CJD and constitute both sensitive and specific tools for diagnosis and non invasive therapeutic follow-up.

References

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