An in vivo proton magnetic resonance spectroscopy study of thalamus in prion disease.

R. Lodi[1], P. Parchi[2], C. Tonon[1], D. N. Manners[1], S. Capellari[2], A. Filla[3], E. Malucelli[1], G. Pierangeli[2], P. Cortelli[2], P. Montagna[2], B. Barbiroli[1]

[1]Dipartimento di Medicina Clinica e Biotecnologia Applicata "Campanacci", Policlinico S.Orsola, Università di Bologna, Bologna, Italy, [2]Dipartimento di Scienze Neurologiche, Università di Bologna, Bologna, Italy, [3]Dipartimento di Scienze Neurologiche, Università "Federico II", Napoli, Italy

Synopsis

The *intra vitam* diagnosis of prion diseases is challenging and a definite diagnosis still relies on neuropathological examination. This study was performed to test the usefulness of ^{1}H-MRS in identifying *in vivo* brain diagnostic indicators of prion disease in eleven patients with probable or possible prion disease. ^{1}H-MRS demonstrated a significant reduction of thalamic NAA/Cr in five patients with confirmed prion disease compared to the healthy control group and the patient control group where the clinical follow-up excluded a prion disease. These results suggest that ^{1}H-MRS should be introduced in the diagnostic assessment of patients with a rapidly progressive dementia.

Introduction

Prion diseases are rare, fatal, neurodegenerative disorders of the central nervous system that can be familial, sporadic or acquired by infection (1). The *intra vitam* diagnosis is challenging and a number of dementing disorders either degenerative or vascular must be considered in the differential diagnosis. The sporadic form is called Creutzfeldt-Jakob disease (sCJD) while the inherited disorders include familial CJD (fCJD), Gerstmann Sträussler-Scheinker (GSS) disease and fatal familial insomnia (FFI). At present there is no non-invasive *in vivo* diagnostic test and a definite diagnosis still requires neuropathological examination in non-familial cases. Proton MR spectroscopy (^{1}H-MRS) allows *in vivo* quantification of several brain metabolites including N-acetyl-aspartate (NAA), a putative marker of neuronal integrity and density. Aim of this study was to test the diagnostic usefulness of *in vivo* ^{1}H-MRS in the investigation of subjects with clinical diagnosis of probable or possible prion disease.

Methods

Eleven consecutive patients (3 males, 31-72 years, age range) with probable or possible prion disease (2) were recruited. Seven sex- and age-matched healthy subjects (3 males, 30-60 years) were also studied. All patients underwent neurological examinations, EEG, poligraphic studies, CSF examination for the detection of 14-3-3 protein and ^{1}H-MRS. ^{1}H-MRS studies were performed in a 1.5T General Electrics Medical Systems (Milwaukee, Wisconsin) Signa Horizon LX whole-body scanner using a 25cm diameter quadrature birdcage head coil. MRI study included axial FSPGR (fast spoiled gradient echo) T1 images (slice thickness=3 mm, slice gap=0 mm, TE= 2.4 ms, TR=250 ms, matrix=256x256, FOV=24x24cm). A voxel (volume: 4-5 cm^3) was selected to include the bilateral dorso-medial thalamic nuclei and spectra were acquired using the PRESS single voxel localisation sequence (TE=35 ms; TR= 4000 ms, number of acquisitions=128). Peak area for NAA at 2.02 ppm, for creatine-phosphocreatine (Cr) at 3.03 ppm, for choline (Cho) at 3.22 ppm, and for myo-inositol (mI) at 3.56 ppm were calculated using the time domain fitting program AMARES/MRUI (http://carbon.uab.es/mrui). Peak integral values were expressed relative to the Cr peak. Statistical significance, determined by the Student *t* test for unpaired data, was taken as $p<0.05$.

Results

Definite diagnosis of prion disease was made in five patients. Two related patients harboured the Gerstmann-Sträussler-Scheinker mutation P102L in the PRNP gene, whereas diagnosis was established by post-mortem examination in the remaining three patients. Clinical follow-up excluded the prion disease diagnosis in the other six patients. In the prion disease patient group, thalamic NAA to Cr ratio (1.00±0.18, mean±SD) was significantly reduced compared to the healthy control group (1.39±0.09; $p<0.001$) and patient control group (1.43±0.07; $p<0.001$) where prion disease was excluded. However, thalamic NAA/Cr was similar in healthy and patient control groups ($p=0.46$). None of the five patients with definite prion disease presented thalamic NAA/Cr values (0.82-1.29, range) within the normal range (1.31-1.56). On the other hand, in none of the six patients without prion disease did thalamic NAA/Cr (1.34-1.56) fall below the normal range (figure 2).

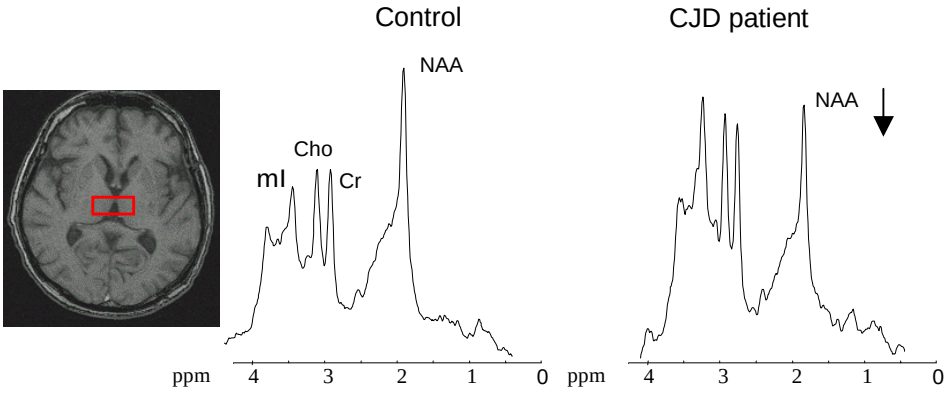

Figure 1. *Left*: Axial FSPGR T1 image (TE=2.4ms, TR=250ms) showing medial thalamic nuclei localitation *Centre and right*: ^{1}H-MRS spectra (TR=4000ms; TE=35ms) from a healthy volunteer and a prion patient.

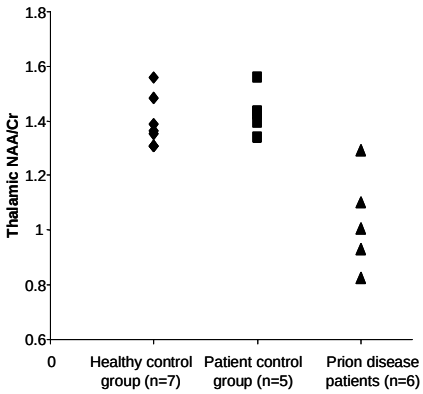

Figure 2. Distribution of thalamic NAA/Cr in the healthy control group, patient control group and prion disease patients .

Discussion

^{1}H-MRS demonstrated a significant reduction of NAA/Cr in the thalamus of prion disease patients, while no reduction in NAA to Cr ratio was found in patients with possible/probable prion disease at presentation, where the clinical follow-up excluded a prion disease. These preliminary results indicate that ^{1}H-MRS is a sensitive and specific tool for the *in vivo* identification of diagnostic markers in prion diseases and should be included in the assessment of patients with a history of rapidly progressive dementia.

References

1. Prusiner Sb et al, *Brain Pathol* 1998, 8:499-513
2. Zerr I et al, *Neurology*, 2000, 55 (6):811-5