Gray and white matter abnormalities in patients with nocturnal frontal lobe epilepsy

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Target audience Neurologists and neuroradiologists working on differential diagnosis of motor sleep disorders and pathophysiology of epilepsy.

Purpose Nocturnal frontal lobe epilepsy (NFLE) includes paroxysmal episodes with polymorphic semeiology, and variable intensity and duration appearing almost exclusively during sleep. [1] The pathophysiology of the seizures in NFLE is not yet fully understood. Conventional MR images are normal in patients with NFLE. The only previous MRI study of a group of patients shows mild and widespread abnormalities of the entire brain with no correlates to clinical score. [2] The aim of this study was to investigate the role of both cortical and subcortical-microstructural abnormalities in the physiopathology and diagnosis of NFLE.

Methods From July 2011 to June 2012, 20 patients (age: 36 ±10 years, 12 F) with clinical diagnosis of NFLE were evaluated with a standardized MRI protocol. Each patient underwent MRI examination using a 1.5 T GE Signa scanner, following the same protocol including: T1-weighted volumetric imaging (FSPGR, TR/TE 12.3/5.2 ms; 1 mm isotropic resolution); Diffusion Tensor imaging (DTI; TR/TE 104/82 ms, 32 acquisitions with non-collinear field gradients b-value=900 mm^2 s^{-1}, axial oblique FOV 32 cm; 128×128 in-plane resolution; 2.5 mm slices). 16 healthy subjects were used as controls for morphometric analysis (age: 34 ±10 years, 9 F), while 20 healthy subjects were used as controls for TBSS analysis (age: 35 ±10 years, 9 F)

Voxel-based morphometry (VBM) was performed by segmenting all volumetric images (SPM; UCL) into three brain tissue types, followed by non-linear registration to a study specific template using DARTEL (SPM; UCL), after which non-parametric voxel-wise inference was performed for gray (GM) and white matter (WM) using randomize (FSL/FMRIB, U Oxford). To evaluate DTI images, standard pre-processing was followed by the generation of tensor metric maps (FA, MD) non-linear registration of FA maps to a study-specific template, and identification of major white matter tracts (TBSS), all within the FSL/FMRIB software protocol. Again, voxel-wise inference within these tracts was performed using randomise (FSL/FMRIB). Patient and control group mean values were compared using as regressors age (and total intracranial volume for VBM). Likewise, severely and mildly impaired patient groups were compared, using the frequency of epileptic attacks as a marker as severity.

Results The patients were divided in two groups: 9 patients had at least one attack a week and were considered as severely impaired while 11 had no more than one a year and were considered as mildly impaired. With regard to white matter diffusivity, patients showed a widespread decrease of FA in several areas, including corpus callosum in particular, but also the middle and anterior cingulate and optic radiations. The VBM analysis of white matter also showed localized changes, including a decrease in the right limbic lobe at the level of right hippocampus close to parahippocampal gyrus, and in the left WM cortex, close to the post-central gyrus. No differences were found in WM between less and more affected patients either in diffusivity or tissue volume. In gray matter, no volume differences were found between the NFLE group and normal controls, while GM was reduced in the right frontal cortex of severely- compared to mildly-affected patients.

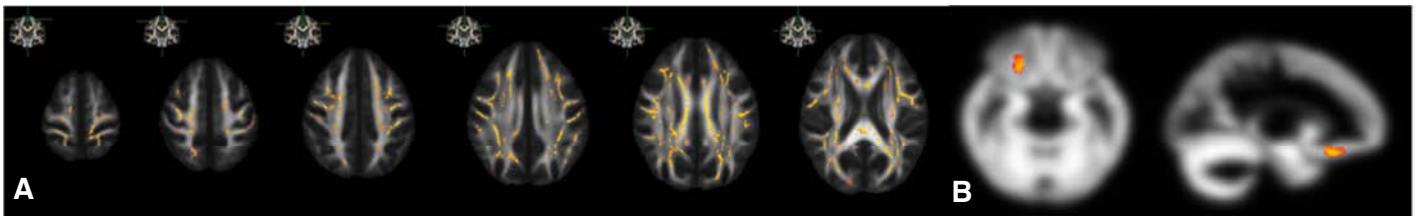

Figure. (A) Areas of reduced FA on TBSS WM skeleton in patients compared to controls, projected onto representative axial slices study-specific FA template. (B) Area of reduced GM in more severely affected patients, disclosed by VBM (p=0.01), projected onto study-specific GM template, shown in axial and sagittal planes.

Discussion Widespread alteration of white matter were found in NFLE patients, independently of disease severity, in line with previous report[2]. Right frontal-orbital gray matter decrease was found in more severely affected patients, although we cannot establish whether this finding is related to the cause or to a consequence of the disease. Distinguishing NFLE seizures from paroxysmal non-epileptic sleep disorders is often difficult and sometimes impossible on clinical grounds alone. Local alteration of gray or white matter demonstrated in the current study may be reflected in a wider NFLE patient population, and may in the future aid differential diagnosis between NFLE and other non-epileptic motor phenomena arising from sleep.

Conclusion We have demonstrated by using TBSS and VBM differences in the brains of NFLE patients compared to healthy controls even in absence of conventional MRI alterations. White matter is widely affected in the patient group. Gray matter is focally decreased in severe impaired patients.

References [1]Tinuper P, Provini F, Bisulli F, Vignatelli L, Plazzi G, Vetrugno R, Lugaresi, E. Movement disorders in sleep: guidelines for differentiating epileptic from non-epileptic motor phenomena arising from sleep. Sleep Med Rev 2007;11: 255-267.

[2]Ferini-Strambi L, Bozzali M, Cercignani M, Oldani A, Zucconi M, Filippi M. Magnetization transfer and diffusion-weighted imaging in nocturnal frontal lobe epilepsy. Neurology. 2000 Jun 27;54(12):2331-3.