

Case reports

Normalization of 14-3-3 in CJD

Maarten SCHROOTEN, Wouter DE VOOGHT, Sarah WECKHUYSEN, Wim VAN PAESSCHEN and Philip VAN DAMME
Department of Neurology, University of Leuven, Belgium

Abstract

We report on a 47-year-old woman with autopsy proven Creutzfeldt-Jakob disease (CJD), who had a positive initial 14-3-3 test but a subsequent negative test under pharmacologic suppression of the periodic epileptiform discharges on EEG. Multiple factors associated with a subsequent 14-3-3 test becoming negative are known. However, none of these circumstances were applicable to our patient. This case history suggests sedative therapy in CJD may induce false negative 14-3-3 testing. This appears to be a relevant finding, since the differential diagnosis between non-convulsive status epilepticus and CJD is not always evident in the initial stage of the disease and some patients with CJD present with seizures.

Key words : 14-3-3 ; Prion disease ; CJD ; Creutzfeldt-Jakob disease ; EEG ; non-convulsive status epilepticus ; epilepsy ; antiepileptic drugs.

Introduction

Sporadic Creutzfeldt-Jakob disease (CJD) is a relatively rare, degenerative, invariably fatal prion disease. A significant number of CJD patients develop periodic epileptiform discharges (PEDs) on EEG (Zerr *et al.*, 2000). These PEDs are not always easily distinguished from non-convulsive status epilepticus (NCSE) (Fernandez-Torre *et al.*, 2004). In the present text we report on a woman with autopsy proven CJD, who had a positive initial 14-3-3 test which nonetheless was followed by a negative test under pharmacologic suppression of the PEDs. To our knowledge such an instance has never been reported on before.

Case report

A 47-year-old woman was taken to the emergency department of a nearby local hospital by her family because of apathy, apraxia, forgetfulness, drunken gait with falls and visual hallucinations. The symptoms had gradually increased over a period of one month. Her medical history was notable of hypertension, a somatization disorder, an eating disorder, a borderline personality and a gastric

banding procedure. She had a daughter with epilepsy and an aunt with a psychiatric disorder. Cerebral imaging, blood tests and CSF examination were normal. EEG was consistent with NCSE. Phenytoin, valproate and aciclovir were started. Despite treatment, the woman's condition deteriorated and she was subsequently transferred to our hospital.

On admission, she was in a state of abulia. There was less spontaneous use of the left arm. Deep tendon reflexes were brisk. Plantar reflexes were normal. MRI of the brain and blood tests were normal. EEG showed 0.5-1.0 Hz PEDs (Fig. 1A). We considered both Creutzfeldt-Jakob disease and NCSE in the differential diagnosis. Since the latter condition is potentially treatable and is far more prevalent, propofol sedation was given and levetiracetam was added to phenytoin and valproate. Discontinuation of propofol led to the reappearance of the PEDs on EEG. Gabapentin and later pregabalin were added. Meanwhile, the results of the immunoblot of 14-3-3 (Van Everbroeck *et al.*, 2003) of a CSF sample taken the 2nd day of admission (i.e. 48 days before the death of the patient, approximately 32 days after the onset of symptoms, which is after 40% of the total duration of the disease) came back positive beyond doubt. Since epileptic activity can result in increased 14-3-3 levels in the CSF (Peoc'h *et al.*, 2006), we decided to continue sedation, using propofol and in a later stage thiopental, aiming at EEG (burst) suppression. In the meantime we were awaiting the results of renewed imaging and 14-3-3 test. The second MRI of the brain showed typical lesions associated with CJD (a hyperintense aspect of the cortex, the caudate nuclei and the putamina on diffusion-weighted images) (Fig. 1B). In retrospect, these were already slightly present on the first MRI. Detection of 14-3-3, however, was negative on a second CSF sample taken the 14th day of admission, which was on the 13th day of EEG (burst) suppression (i.e. 36 days before the death of the patient, approximately 44 days after onset of symptoms, which is after 55% of the total duration of the disease). This negative test result was double-checked. Since there was no clinical recovery

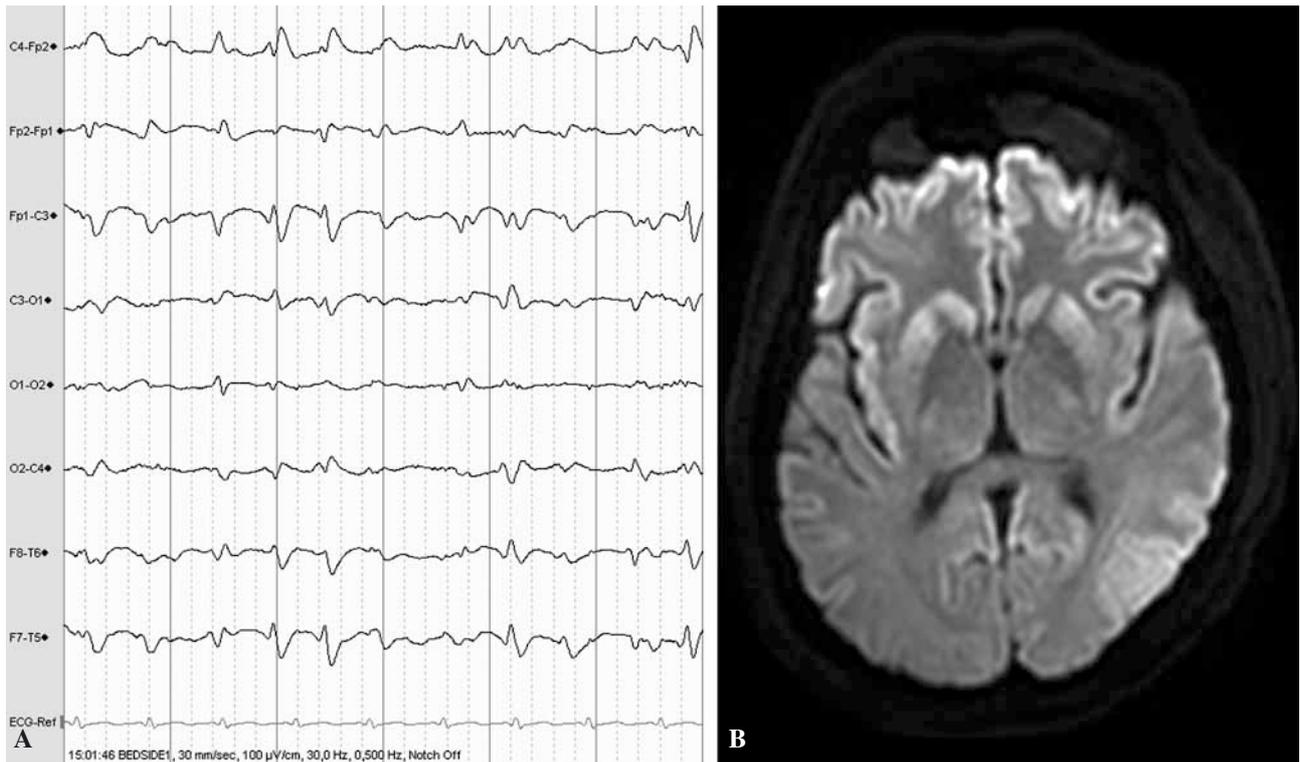


FIG. 1. — EEG on the 2nd day of admission (A) and diffusion-weighted magnetic resonance image of the brain on the 23rd day of admission (B).

after 7 weeks of treatment, a palliative approach was instituted (including the stop of sedation). Additional CSF testing in this stage was refused by the patient's family. She died after a disease duration of approximately 80 days. Post-mortem brain pathology showed a classic picture of CJD. Additional tests for variant-CJD were negative.

Discussion

Although a second 14-3-3 test on a repeated lumbar puncture after an initial negative test usually has an increased sensitivity (Sanchez-Juan *et al.*, 2006), the initial positive test turned negative on a second sample in our case. False negative CSF 14-3-3 test results have been observed in patients with CJD and long disease duration (> 1 year) (Van Everbroeck *et al.*, 2003), early or late in the disease course (the first 25% and the last 15% of the total disease duration, respectively) (Van Everbroeck *et al.*, 2003), or when severe brain atrophy was present (Shiga *et al.*, 2006). None of these circumstances were applicable to our patient. The fact that 14-3-3 tests are frequently positive in molecular CJD subtypes, which frequently present without PEDs, makes a straightforward relationship between suppression of PEDs and becoming negative of the 14-3-3 test rather unlikely (Zerr *et al.*, 2000). The release of 14-3-3 protein into CSF is generally considered a marker for extensive neuronal damage (Adembri *et al.*, 2007). Sedative therapy might reduce this release

due to a decrease in metabolic rate and possibly, a clinically insignificant, neuroprotective effect. Since the differential diagnosis between NCSE and CJD is not always evident (Fernandez-Torre *et al.*, 2004) and some patients with CJD present with seizures (Parry *et al.*, 2001 ; Cohen *et al.*, 2004), one should be aware that sedative therapy in CJD may induce false negative 14-3-3 testing. Further similar cases are certainly needed to confirm this finding.

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Maarten SCHROOTEN, M.D.,
UZ Leuven,
Department of Neurology,
Herestraat 49,
B-3000 Leuven (Belgium).
E-mail : maarten.schrooten@uzleuven.be