Subcortical MRI abnormalities and sudden electro-clinical worsening in sporadic Creutzfeldt-Jakob Disease (CJD)

Giuseppe Borzì[1]
Paolo Perrotta[2]
Laura Mumoli[1]
Miriam Sturniolo[1]
Franco Pucci[1]
Antonio Gambardella[1,2]
Angelo Labate[1,2]

[1] Institute of Neurology, University Magna Græcia, Catanzaro
[2] Neuroimaging Research Unit, Institute of Molecular Bioimaging and Physiology, National Research Council, Germaneto, Catanzaro, Italy

Corresponding author :
Angelo Labate
Institute of Neurology, University Magna Græcia
Viale Europa
88100 Catanzaro, Italy
Tel. +39-0961-3647406; Fax +39-0961-3647177
E-mail: labate@unicz.it

Abstract

***Background*: sporadic Creutzfeldt-Jakob Disease (sCJD) is a fatal disease, manifesting with progressive dementia, hallucination, ataxia, myoclonus, pyramidal and extrapyramidal sign. Diagnosis of sCJD requires pathologic confirmation by brain biopsy, but is suspected clinically when a patient presents with rapidly progressive dementia, motor dysfunction, and myoclonus. In the appropriate clinical setting, the combination of electroencephalogram (EEG) and Magnetic Resonance Imaging (MRI) typical findings are strongly supportive for the diagnosis. However, there are insufficient data regarding a correlation between subcortical lesions and surface EEG.**
***Case presentation*: a 70-year-old Italian woman presented with a 40 days history of progressive memory deficits with a mild spatial disorientation. At admission, 50 days after the onset, her neurological examination showed temporo-spatial disorientation, ideo-motor apraxia, cerebellar gait, vertical and horizontal gaze palsy and upper limb jerks. An extensive battery of routine laboratory analysis resulted normal. Lumbar puncture with CSF analysis revealed positivity for 14-3-3 and tau protein. EEG and MRI were performed at admission. The EEG showed generalized slow background activity prevalent over the left hemisphere together with frequent fronto-temporal spikes whereas FLAIR and diffusion hyperintensity on MRI was seen over the left caudate nucleus. Two weeks later, she quickly declined showing diffuse myoclonic jerks and akinetic mutism. The repeated EEG showed a definite generalized slow background activity with periodic and bilateral sharp wave complexes while MRI FLAIR and diffusion sequences disclosed hyperintensity of the caudate nucleus bilaterally.**
***Conclusion*: this case nicely demonstrates as the EEG abnormalities parallel with caudate nucleus FLAIR and diffusion hyperintensity spreading from unilateral to bilateral in two weeks.**

KEY WORDS: sporadic Creutzfeldt-Jacob Disease, MRI, EEG, prion, sCJD.

Background

Sporadic Creutzfeldt-Jakob Disease (sCJD) is a fatal disease, manifesting with progressive dementia, hallucination, ataxia, myoclonus, pyramidal and extrapyramidal sign (1). Although a definite diagnosis of sCJD requires pathologic confirmation by brain biopsy or direct examination at autopsy, not all relatives give informed consent to obtain it. Indeed, sCJD is suspected clinically when a patient presents with rapidly progressive dementia, motor dysfunction, and myoclonus. Typical electroencephalogram (EEG) findings [e.g. bilaterally synchronous periodic sharp waves (PSW) or occipital sharp slow waves] as well as brain magnetic resonance imaging (MRI) abnormalities are also considered strongly supportive of the diagnosis (1, 2). In fact, recently, basal ganglia hyperintensities have been extensively described as typical signs of sCJD and have been included in the international diagnostic criteria (1, 2). Although there are previous studies that correlate the presence of cortical hyperintensity with the presence of PSW in EEG in the early stage of disease (3), to our knowledge cases of correlations between alterations of subcortical structures, their progressive involvement during the disease progression and PSW have not been described yet. Furthermore, it is still unclear whether clinical deterioration may be related to the progressive involvement of subcortical and cortical structures. Here, we describe an intriguing observation because the caudate nucleus hyperintensity tended to parallel the rapid electro-clinical worsening.

Case presentation

A 70-year-old woman came to our observation because of a 40 days history of progressive memory deficits, started with a variable mild spatial disorientation. About two weeks before the admission at our Clinic, she developed progressive gait unbalance, upper limbs jerks and episodes of agitation. Her speech became progressively poorer too. Her past medical history was unremarkable. She never made blood donation in the past, neither surgeries. She had no family history of neurological diseases. Medical history was negative for alcohol or drug abuse. She did not have trips across Europe or other foreign countries. At admission, about 50 days after the onset, her neurological examination showed temporo-spatial disorientation, ideo-motor apraxia, ataxia, vertical and horizontal gaze palsy, right-prevalent asymmetric reflexes, and upper limb jerks. She underwent an extensive battery of routine laboratory analysis, screening for infections, paraneoplastic and non-paraneoplastic antibodies, lumbar puncture with CSF analysis, video-EEG polygraphy and 3 Tesla-MRI. All laboratory tests resulted normal. CSF analysis revealed normal cell count, glucose and albumin quotient, and a positivity for tau protein (tau> 1200 pg/ml) and 14-3-3 protein. At admission, despite patient's artefact due to movements, diffusion- weighted images showed hiperintensity of left caudate nucleus (Fig. 1a). Polygraphy showed generalized slow background activity clearly prevalent over the left hemisphere and frequent left fronto-temporal spikes. Surface electromyography (EMG) showed myoclonus over the deltoid bilaterally (Fig. 1b). The patient progressively and quickly declined within two weeks, showing diffuse myoclonic jerks and akinetic mutism clinically. During this dramatic worsening the repeated EEG showed the appearance of periodic sharp slow-waves bilaterally (Fig. 2b). Comparably, MRI diffusion sequences showed a hyperintensity of the caudate nucleus bilaterally together with FLAIR images (Fig. 2a).

Conclusion

Current diagnostic criteria for probable sCJD include, in addition to the typical clinical signs and the finding of 14-3-3 protein in CSF, typical MRI and EEG signs (1, 2). Considering that many patients do not have histological confirmation, brain MRI and EEG are two not invasive tools that help in many cases. The neuroimaging hallmark of sCJD is increased grey matter signal on T2-weighted, FLAIR, and DW MRI imaging. In most cases, MRI shows bilateral symmetric markedly hyperintense caudate nuclei and putamina, whereas the thalami and the cortex are usually involved to a lesser degree. However, diffusion sequences are preferred because are short and limit the risk of motion artefacts (3).
Moreover the typical pattern of FLAIR/diffusion hyperintensity and restricted diffusion can differentiate sCJD from other rapidly progressive dementia and it helps to recognize different subtypes of CJD (4, 5). The pattern of extensive increased neocortical and/or striatal FLAIR and diffusion signal abnormality has a diagnostic accuracy for CJD approaching 95% (5, 6).
In sCJD, the EEG usually exhibits characteristic abnormalities, ranging from less specific diffuse slowing and frontal rhythmic delta activity (FIRDA) in early stages, to more pathognomonic PSW complexes in middle and late stages (7). However, both brain MRI lesions and EEG abnormalities of sCJD have high sensitivity and low specificity (7, 8), and there are just few cases in literature reporting a correlation between EEG discharges and cortical lesions alone or associated with deep brain grey matter hyperintensities (4).
To our knowledge, this is the first case describing a time course parallelism between the limited involve-

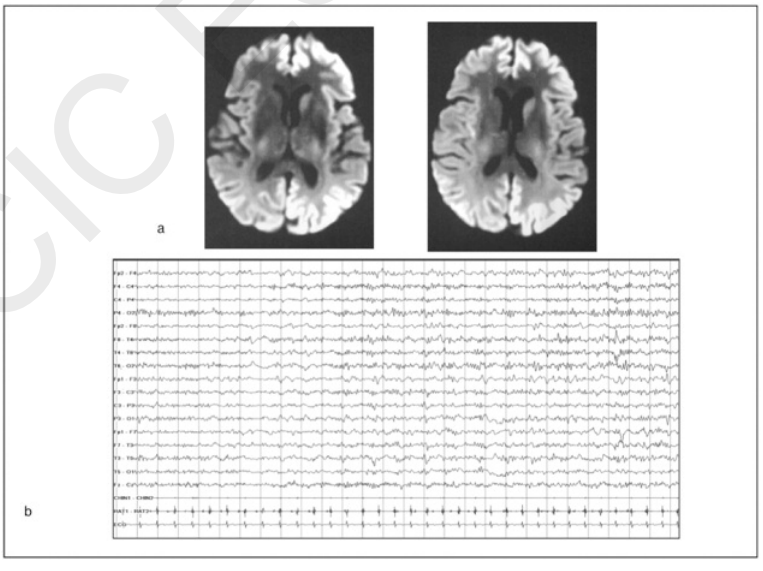

Figure 1 - a) Axial MRI diffusion sequence showing signal hyperintensity localised over the head of the left caudate nucleus; b) EEG showing generalized slow background activity and left fronto-temporal spikes while the two EMG channels (deltoids) show myoclonus bilaterally.

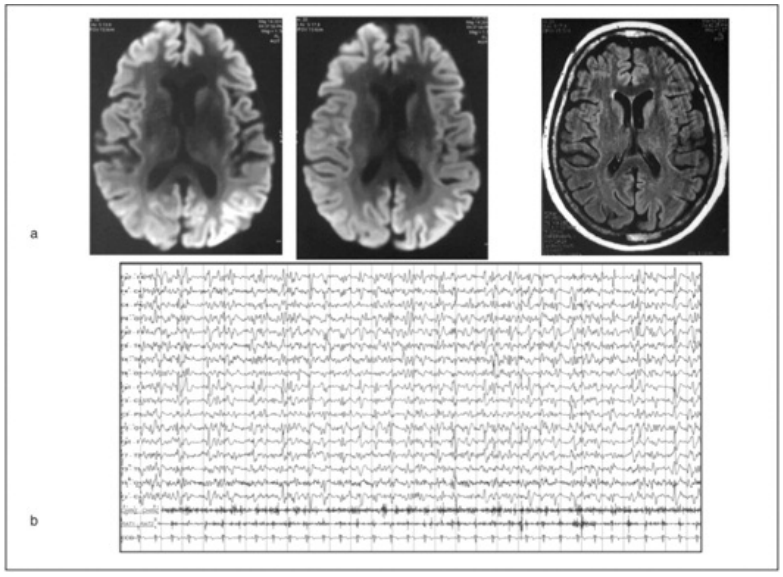

Figure 2 - a) Two weeks later, axial MRI FLAIR and diffusion sequences showing a hyperintensity of the caudate nucleus bilaterally. b) EEG showing the appearance of periodic sharp slow-waves bilaterally.

ment of caudate nucleus (visible on MRI) and EEG abnormalities driving a dramatic clinical worsening. Furthermore, in our case the cortical involvement was also present and widespread compared to the more obvious hyperintensity of the head of the caudate nucleus shifting from unilateral to bilateral following the clinical worsening. The rapid spread of the prion protein from the left to the right caudate may suggest cross-hemispheric propagation trough commissural fibers as showed in experimental mice, following intraocular inoculation of prion protein (9).

In conclusion, we can speculate that early appropriate interpretation of subcortical MRI FLAIR hyperintensity together with restricted diffusion in deep grey matter nuclei should alert the pre-autopsy diagnosis of sCJD and may suggest a rapid electro-clinical deterioration. Further cases with proven histology are mandatory to give strongest interpretation.

Consent

Written informed consent was obtained from the patient's husband for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this Journal.

List of abbreviations

sCJD: sporadic Creuzfeldt-Jacob Disease; PSW: Periodic sharp waves; EEG: Electroencephalogram; MRI: Magnetic Resonance Imaging.

Competing interests

The Authors declared no conflicts of interest with respect to the research, authorship, funding, and/or publication of this article.

Acknowledgements

GB: drafting/revising the manuscript. AL: revising/critique the manuscript, study concept or design, supervision. AG: critique the manuscript. FP, PP and MS, collection of data. All authors read and approved the final manuscript.

References

1. Zerr I, Kallenberg K, Summers DM, Romero C, Taratuto A, Heinemann U, Breithaupt M, Varges D, Meissner B, Ladogana A, Schuur M, Haik S, Collins SJ, Jansen GH, Stokin GB, Pimentel J, Hewer E, Collie D, Smith P, Roberts H, Brandel JP, van Duijn C, Pocchiari M, Begue C, Cras P, Will RG, Sanchez-Juan P. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. Brain. 2009; 132:2659-2668.
2. Vitali P, Maccagnano E, Caverzasi E, Henry RG, Haman A, Torres-Chae C, Johnson DY, Miller BL, Geschwind MD. Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. Neurology. 2011; 76:1711-1719.
3. Tschampa H J, Kallenberg K, Urbach H, Meissner B, Nicolay C, Kretzschmar HA, Knauth M, Zerr I. MRI in the diagnosis of sporadic Creutzfeldt-Jakob disease: a study on inter-observer agreement. Brain. 2005; 128:2026-2033.
4. Mizobuchi M, Tanaka C, Sako K, Nihira A, Abe T, Shirasawa A. Correlation between periodic sharp wave complexes and diffusion-weighted magnetic resonance images in early stage of Creutzfeldt-Jakob disease: a report of two cases. Seizure. 2008;17:717-722.
5. Meissner B, Kallenberg K, Sanchez-Juan P, Collie D, Summers DM, Almonti S, Collins SJ, Smith P, Cras P, Jansen GH, Brandel JP, Coulthart MB, Roberts H, Van Everbroeck B, Galanaud D, Mellina V, Will RG, Zerr I. MRI lesion profiles in sporadic Creutzfeldt-Jakob disease. Neurology. 2009;72:1994-2001.
6. Meissner B, Kallenberg K, Sanchez-Juan P, Collie D, Summers DM, Almonti S, Collins SJ, Smith P, Cras P, Jansen GH, Brandel JP, Coulthart MB, Roberts H, Van

Everbroeck B, Galanaud D, Mellina V, Will RG, Zerr I. MRI in the diagnosis of sporadic Creutzfeldt-Jakob disease: a study on inter-observer agreement. Neurology 2009; 72:1994-2001.
7. Wieser, K Schindler, D Zumsteg. EEG in Creutzfeldt-Jakob disease. Clinical Neurophysiology. 2006;117:935-951.
8. Steinhoff BJ, Zerr I, Glatting M, Schulz-Schaeffer W, Poser S, Kretzschmar HA. Diagnostic value of periodic complexes in Creutzfeldt-Jakob disease. Ann Neurol. 2004; 56:702-708.
9. Lee H, Rosenmann H, Chapman J, Kingsley PB, Hoffmann C, Cohen OS, Kahana E, Korczyn AD, Prohovnik I. Thalamo-striatal diffusion reductions precede disease onset in prion mutation carriers. Brain. 2009;132:2680-2687.