

Creutzfeldt-Jacob disease: conventional brain MR imaging findings

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ABSTRACT - Sporadic Creutzfeldt-Jacob disease (CJD) is a rare fatal neurodegenerative prion disease. Clinical findings of CJD consist of a rapid onset dementia, myoclonus, and neurologic disorders. Definitive diagnosis is established with histopathologic confirmation of brain parenchyma or autopsy materials. Periodic triphasic electroencephalography (EEG) changes and detection of 14-3-3 protein in cerebrospinal fluid are subsequent diagnostic criteria. A case of a 63-year-old female with painful rigidity, noncooperation, disorientation and bilateral postural tremor is reported. She had hypoactive deep tendon reflexes, moderate agitation, and drowsiness without any facial asymmetry. Her speech was extremely dysarthric and unintelligible, along with akinetic mutism. This case of sporadic CJD is presented with magnetic resonance imaging, EEG results, clinical history and laboratory findings.

Key words: electroencephalography; Creutzfeldt-Jacob disease, sporadic; magnetic resonance imaging, diffusion

INTRODUCTION

Creutzfeldt-Jacob disease (CJD) is a rare fatal neurodegenerative disease caused by deposition of infectious protein called prion in the brain (proteinaceous infectious particle lacking functional nucleic acid, pathologic isoform of prion protein PrP^{Sc}-Sc indicates scrapie) (1). It is usually characterized by rapidly progressive dementia, ataxia, myoclonus and other neurologic disorders such as visual disturbances. Electroencephalography (EEG) is characterized by periodic sharp wave complexes and intermittent rhythmical delta activity, but unfortunately we currently do not have any treatment ex-

cept for palliative symptomatic and supportive one (1,2). The incidence of CJD is 1/1 000 000/year, mean age at onset is usually around 60 years, with 6- to 24-month surveillance after clinical diagnosis (1-5). Sporadic CJD accounts for 85%-90% of all cases, while the remaining 10%-15% belong to the familial, iatrogenic and variant CJD (1,5,6).

Current diagnostic criteria for CJD require demonstration of the specific neurologic symptoms

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combined with characteristic EEG changes in addition to the presence of 14-3-3 protein in the cerebrospinal fluid (CSF). EEG and CSF 14-3-3 protein demonstration have sensitivities ranging of 53%-90% and specificities of 85%-100% (1-7). Recent studies have shown that magnetic resonance imaging (MRI) has a reasonable sensitivity of 60%-90% and high specificity of 95% in depicting CJD (5-7). MRI revealed diffuse cortical atrophy, symmetric or unilateral hyperintensities in the basal ganglia, cerebral cortex and thalamus on T2 weighted (T2W) images, and cortical ribboning (1,2,6,7). Diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) imaging may improve the sensitivity of routine MRI in the detection of neuro-parenchymal abnormalities, especially in the subcortical parts and neocortex (4,5,8).

In this article, brain MRI of a probable sporadic CJD case will be presented. The diagnosis was based on clinical history and presentation, EEG and laboratory findings, as well as MRI results, which were in concordance with the World Health Organization (WHO) clinical diagnostic criteria (1-3,6,7).

CASE REPORT

A 63-year-old female with complaints of altered balance, gait disturbances and anxiety, without any history of trauma, presented to our hospital. Her symptoms started in April 2011, and she had normal brain computed tomography (CT) scan and electromyography (EMG) at that time. She initially had psychiatric consultation and was treated with Solian (Amisulpride), without any benefit. She was referred to the Neurology Department in July 2012 and therapy with Akineton (Biperiden)-Madopar (Carbidopa) was initiated. Despite this treatment, her clinical presentation worsened, so she was admitted to the Hacettepe University Hospital in December 2012 due to increasingly akinetic state, myoclonic jerks and generalized seizure. During that time, the patient was uncooperative and disoriented, while neurologic examination revealed painful rigidity and bilateral postural tremor. She had hypoactive Babinski, deep tendon reflex. She showed moderate agitation, drowsiness without any facial asymmetry, and her extraocular movements were intact.

The pupils were isochoric at midline with normal direct and indirect light reflexes, her speech was extremely dysarthric and unintelligible, without

any visual hallucination and insomnia; meanwhile, she showed positive response to auditory and tactile stimuli. From day 4 of her hospital stay, the patient developed akinetic mutism, EEG revealed generalized slow waves, 5-6 Hz tetra frequency waves in background activity without any short interval triphasic periodic wave discharge and epileptic discharges. Control EEG taken one week later predicted the same slow waves with vigilance,

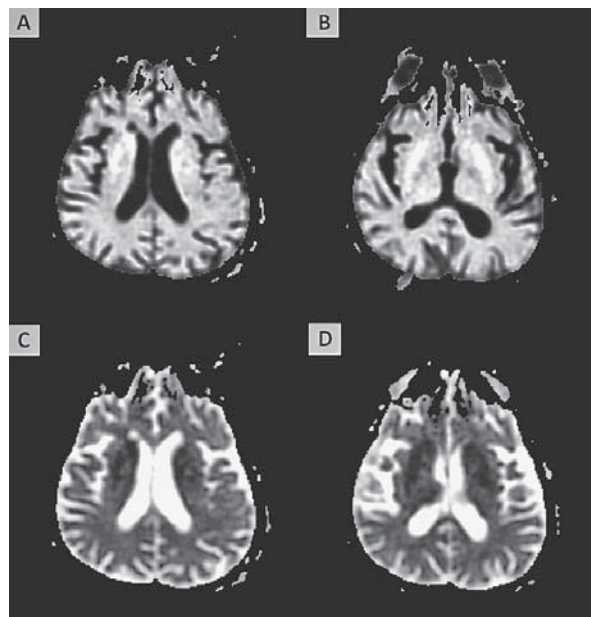


Fig. 1a-b. Brain MRI taken on January 7, 2013: restricted diffusion demonstrated in basal ganglia and periventricular white matter on DWI and ADC images.



Fig. 2. In sagittal FLAIR sequence, symmetric basal ganglia and white matter hyperintensities were also evident.

most prominent in frontal hemisphere. She had no abnormality on EMG. MRI of the brain taken 15 days after admission to the hospital revealed diffusion restriction on bilateral caudate, putamen and cingulate gyri, on FLAIR images; symmetric confluent basal ganglia hyperintensities were observed (Fig. 1a-b, Fig. 2). CSF analysis showed elevated protein (62 mg/dL; normal range 0-10 mg/dL), normal glucose and no pleocytosis, with positive 14-3-3 protein on Western blot CSF. No abnormality could be detected in laboratory tests and general physical examination.

In differential diagnosis, infectious or limbic encephalitis, paraneoplastic syndrome, epilepsy or Alzheimer-like dementia were considered, nevertheless, she had negative NMDA paraneoplastic receptor antibodies (NMDAR Ab) with normal glucose and electrolytes, without any leukocytes or lymphocytes in CSF and no viral panels microbiologically. The possibility of sporadic CJD was accepted, as she had no family history, no family CJD gene and long-lasting clinical presentations. She was discharged from the hospital with brain MRI follow-up due to her refusing longer hospitalization, with partial recovery of her general condition and complaints. She was prescribed Beparine (bemiparin sodium) and Protonix (pantoprazole sodium) on routine follow-up for symptomatic relief and supportive treatment.

Follow-up MRI taken one month later showed further diffusion restriction of the cingulate gyri, putamen and caudate nucleus symmetrically, with acute increasing thalamic diffusion restriction (Fig. 3). These long-lasting diffusion restrictions of basal ganglia and thalamus were also important markers of CJD in this patient. There was no cortical rib-

boning, no neocortical and limbic involvement, while precentral gyrus-precuneus-angular and parahippocampal areas-mesial cortex were relatively spared on MRI.

DISCUSSION

CJD is a fatal progressive prion disease characterized by atypical triad of rapidly progressive dementia, myoclonus manifesting as a response to auditory and tactile stimuli, and typical EEG findings (periodical sharp and slow wave complexes) (1,2,7,9).

Recently, MRI and 14-3-3 protein immunoassay in CSF have been established as valuable progressing tools in the diagnosis of suspected CJD cases. MRI generally reveals bilateral hyperintense areas predominantly in the basal ganglia, mild cerebral atrophy, increased signal in the cerebral cortex (cortical ribboning) with 67%-93% sensitivity and specificity (5,7,10). Zerr *et al.* (11) showed sensitivity of 94% and specificity of 84% of protein 14-3-3, however, this protein can also be detected in viral encephalitis, Hashimoto encephalitis, amyotrophic lateral sclerosis, and other types of dementias (2,5,7,12-14). Besides 14-3-3 protein, markers such as neuron-specific enolase, amyloid beta, tau protein, astrocytic protein S 100 and neopterin have also been investigated (2,6,9,12,15). Steinhoff *et al.* (13) report on the sensitivity of 64% and specificity of 91% for EEG examinations in the diagnosis of CJD, while Zerr *et al.* (11) found a sensitivity of 66% and specificity of 74% of EEG in terminal stages, where myoclonus is absent.

In previous reports, DWI and FLAIR images have also been suggested for the suspected diagnosis of CJD, mostly restricted diffusion in the cerebral cortex and subcortical structures in DWI and extensive abnormal hyperintensity in cortical gray matter, accompanying lenticulo-striatal abnormality with or without thalamic abnormality in FLAIR imaging, strongly predicted the diagnosis of CJD (4,5,9,12-15). Mostly, the neocortex-corpora striatum-limbic cortex and thalamus were abnormally involved: frontal lobes were most often affected, followed by parietal and temporal lobes (5,13,16). Symmetric bilateral involvement, predominantly on the anterior striatum while sparing globus pallidus was a frequent sign, and pulvinar sign in case of bilateral posterior thalamic involvement might help in diagnosing variant CJD with high signal at pulvinar and thalamus on FLAIR images (4,5,13,17-19). Primary motor and sensory cortices on either

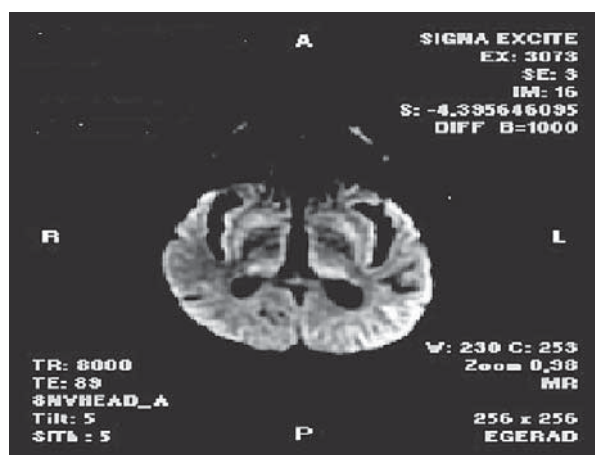


Fig. 3. Control brain MRI taken on February 6, 2013: restricted diffusion in bilateral thalamus was clearly depicted on DWI images.

side of the central rolandic cortex were never identified as abnormal in previous reports of CJD, while primary sensorimotor and visual cortices were always notable exceptions (2,5,15,17,18). Globus pallidus and precentral gyrus hyperintensities were less frequently encountered on FLAIR/DWI, named 'precentral sparing' with diffuse cortical involvement (2,5,7,9,17).

DWI demonstrated markedly more sensitive results than routine MRI and FLAIR imaging. DWI could detect pathology even in the very early stages of the disease, within 3 weeks of the onset of symptoms and before arising of abnormal EEG waves, thus being assumed as an important tool in the early diagnosis of CJD (4,5,8,9,12,13,15). Matoba *et al.* (20) showed that hyperintensities of basal ganglia and neocortex during the early stages were more extensive than in the later stages of the disease in which there was disappearance of abnormal signals in the cortex. Conventional MRI might only reveal discrete abnormalities of the basal ganglia, whereas DWI can demonstrate multifocal regions of hyperintensities in the cerebral cortex in addition to basal ganglia and thalamus, which appeared to be specific for CJD (2,5,6,13,15,17,19).

Shiga *et al.* (12) report on the sensitivity and specificity of 93% for DWI in the diagnosis of CJD, and Young *et al.* (16) on 91% sensitivity and 95% specificity for DWI and FLAIR imaging in the diagnosis of CJD, respectively. Vitali *et al.* (5) state that deep white matter hyperintensities, which were more apparent on DWI than FLAIR images, were diagnostic for CJD, whereas reduction of apparent diffusion coefficient (ADC) in the subcortical regions might also support the diagnosis of CJD. The cause for restricted diffusion on DWI could be attributed to the accumulation of abnormal vacuoles in the cytoplasm and microvacuolation neuritic process with accompanying spongiform degeneration of neural parenchyma histopathologically, while deposition of prion protein might restrict free diffusion of water in the cerebrum (3,13,15-19).

A combination of FLAIR and DWI techniques had more than 90% sensitivity, specificity and accuracy in the differentiation of CJD from other dementias. However, confirmation of the CJD diagnosis is definitely based on neuropathologic examination of the brain tissue obtained either by brain biopsy or postmortem sampling (2,5,9,13,16,17).

The present report on our CJD patient contributes to the relevant literature on sporadic CJD, with myoclonic jerks, akinetic mutism, inappropriate

behavior, typical synchronous periodic slow EEG waves, presence of 14-3-3 protein in CSF, and typical diffusion restriction in basal ganglia-cingulate gyri and thalamus on DWI, lacking cerebellar and extrapyramidal signs with the presence of dementia. In this case, brain MRI including DWI was performed as a diagnostic tool and in patient follow-up.

CONCLUSION

According to the WHO diagnostic criteria for probable diagnosis of CJD, the presence of specific EEG findings and 14-3-3 protein positivity in CSF samples or presence of at least 2 criteria, including myoclonus, visual disturbances, cerebellar-pyramidal or extrapyramidal findings and akinetic mutism with progressing dementia are needed (2,4,5,13,17). MRI, mainly DWI, a noninvasive screening tool without administration of IV contrast agent, might improve the *in vivo* diagnosis of CJD and could reduce the need of brain biopsy for accurate diagnosis. DWI findings, which were restricted diffusion at basal ganglia, neocortex, subcortical area and thalami, should probably lead to mandatory diagnosis of CJD even at the very beginning of symptoms.

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Konvencionalni MRI nalazi u Creutzfeldt-Jakobovoj bolesti

SAŽETAK - Sporadična Creutzfeldt-Jakobova bolest (CJB) je rijetka, fatalna, neurodegenerativna bolest uzrokovana prionom. Klinički nalazi CJB očituju se naglim početkom demencije, mioklonusom, neurološkim poremećajima. Definitivnu se dijagnozu postavlja histopatološkom potvrdom materijala mozga ili materijalom dobivenim autopsijom. Daljnji drugi dijagnostički kriteriji su periodičke trofazne EEG promjene i nalaz proteina 14-3-3 u cerebrospinalnom likvoru. Prikazana je 63-godišnja pacijentica s bolnom ukočenošću, nemogućnošću kooperacije, dezorijentacijom i bilateralnim posturalnim tremorom. Imala je smanjene duboke tetivne reflekse, umjerenu agitaciju, pospanost bez ikakve facijalne asimetrije. Govorila je izrazito dizartrično i nerazgovjetno uz akinetički mutizam. Ovaj slučaj bolesnice sa sporadičnim CJB prikazan je slikovnim prikazom magnetskom rezonancijom, rezultatima EEG-a, poviješću bolesti i laboratorijskim nalazima.

Ključne riječi: EEG, sporadična Creutzfeldt-Jakobova bolest, difuzija, MRI