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CASE SERIES

CREUTZFELDT-JAKOB DISEASE – A SERIES OF FOUR CLINICAL CASES

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Abstract. *Creutzfeldt-Jakob Disease (CJD) is a rare, progressive, and fatal degenerative brain disorder caused by prion proteins. The diagnosis of the disease is based on established criteria and biomarkers – cerebrospinal fluid analysis, real-time quaking induced conversion (RT-QuIC), magnetic resonance imaging, electroencephalographic findings and brain biopsy. We present a series of four patients with confirmed CJD, followed in our clinical center. We discuss the current diagnostic approach in these patients.*

Key words: *Creutzfeldt-Jakob disease, dementia, myoclonus, EEG, MRI, case series*

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INTRODUCTION

Transmissible spongiform encephalopathies (TSEs) or prion diseases represent a group of fatal neurodegenerative disorders, including Kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), fatal and sporadic familial insomnia and the novel prion disease variable protease-sensitive prionopathy (PSPr) in humans [1].

CJD is rapidly progressive and always fatal. It is believed to be caused by prions, leading to folding of normal proteins in the body. The infection usually leads to death within one year of symptom onset. CJD occurs worldwide and the estimated annual incidence in many countries, including the United States, has been reported to be about one to two cases per million population [5]. Normal cellular prion protein (PrPc) transforms into the disease-causing form PrP scrapie (PrPSc) either spontaneously, or as a result of PrPSc infection. PrPSc self-propagates and accumulates throughout the brain. The highly chemically stable β-pleated aggregates cause derangements in intracellular protein folding, ubiquitination, and trafficking in affected neurons. Additionally, astrocytes may swell and degrade in reaction to prion-induced injury. Neurodegeneration results from these changes [2].

During the past two years we observed four patients with CJD, diagnosed during evaluation for dementia and extrapyramidal symptoms.

CLINICAL CASE 1

A 53-year-old female presented to the clinic at the end of October 2023 with dementia, dysarthria, aphasia, and an asymmetric extrapyramidal bradykinetic syndrome more pronounced on the right side of the body with rigidity, resting tremor and Parkinsonian gait. The symptoms manifested three months earlier, when she started experiencing difficulties with performing daily activities. Shortly after that, her relatives noticed that the patient had troubles recalling their names and orienting herself in habitual surroundings. A magnetic resonance imaging (MRI) scan of the brain was performed one month after the clinical onset and it revealed no pathological changes in the brain parenchyma. Whilst experiencing further cognitive and motor decline a follow-up MRI was performed two months after symptom onset. The scan revealed symmetrical hyperintensities of the basal ganglia on DWI, T2 and FLAIR sequences (Figures 1 and 2). The caudate heads, thalami and putamina were symmetrically affected. On post-contrast scans, there was no increase of the intensity. The differential diagnosis was made and it was between metabolic disorders, intoxication and prion diseases.

Upon admission, the patient was bedridden and non-ambulant, experiencing startle myoclonia. The speech was dysarthric and slurred, and moderate cognitive impairment was established by MMSE (score 20). Her past medical history was unremarkable.

During the physical exam, the patient was disoriented for self-person, time, and space, afebrile, with a heart rate of 78, arterial blood pressure of 128/78 mm Hg with no other pathological findings. The neurological examination revealed vertical gaze palsy, asymmetric extrapyramidal bradykinetic syndrome with rigid muscle tone, cogwheel phenomenon, resting tremor (3-6 Hz on electromyography) more pronounced on the right side, with reduced range of motion in the upper and lower extremities, bradykinesia, spontaneous and startle myoclonia. Few days later her MMSE score dropped to 15 and her extrapyramidal symptoms worsened.

Clinical-laboratory investigations revealed an increased platelet count (355 G/l), an elevated erythrocyte sedimentation rate (ESR) of 45 mm/h (case series up to under 30 mm/h), elevated liver function tests (ALAT 36 U/l, reference up to under 33 U/l; ASAT 52 U/l, reference up to under 32 U/l).

The patient underwent a cerebro-spinal fluid examination (CSF) by lumbar puncture, showing normal protein and cell count; negative testing for antibodies against intracellular and surface neuronal antigens (Anti-Yo, Anti-Hu, Anti-Tr, Anti-amphiphysin, Anti-Ri, Anti-NMDAR, Anti-VGKC, Anti-LGI1, Anti-CASPR2 and Anti-AMPA). 14-3-3 protein (Western immunoblot). The presence of 14-3-3 protein was analysed by Western immunoblot and the positive result confirmed the suspected diagnosis of CJD. The patient passed away in less than a month after the diagnosis.

CLINICAL CASE 2

A 63-year-old female presented to the clinic in March 2023 with acute cognitive changes. A brain MRI was

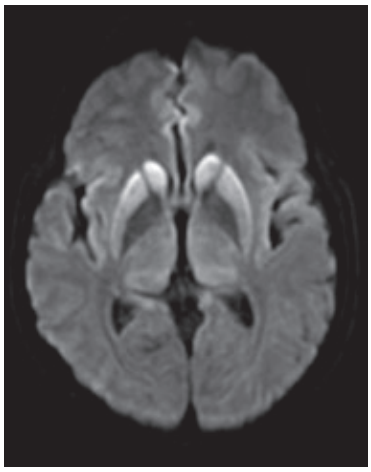

Fig. 1. MRI imaging of patient 1 – notable involvement of both caudate nuclei, putamens and thalamic areas

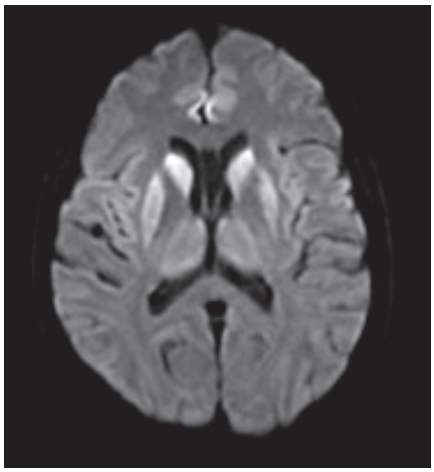

Fig. 2. MRI imaging of patient 1 – involvement of both caudate nuclei, putamens and thalamic areas, edematous basal ganglia with symmetrical hyperintense changes

conducted five days prior, revealing restricted diffusion on DWI in the left frontal, parietal and mesial cortex without contrast enhancement.

Her physical examination was normal, the neurologic examination unveiled marked deficits in constructive praxis, gnosis, and temporo-spatial orientation with left-to-right disorientation, acalculia, and finger agnosia.

The electroencephalography (EEG) in awake state recorded slow background and continuous activity of periodic sharp-waves (PSW) with triphasic appearance at a frequency of 1.5-2 Hz (Figure 3).

The rapid cognitive decline, the DWI-MRI changes and the EEG abnormalities strongly suggested CJD. CSF examination had normal results, including autoantibodies against intracellular and surface neuronal antigens (as listed above). A 14-3-3 protein was detected by Western immunoblot, thus confirming the putative diagnosis of CJD. The patient passed away in the following weeks.

CLINICAL CASE 3

A 54-year-old female with diabetes type 2 since 2011 presented to the clinic with dysarthria, loss of short-term memory, and ataxia. The symptoms began in September 2023 with rapid worsening of the memory deficit and gait and balance issues, which in turn restricted her normal daily activities, prompting hospital admission. The brain MRI revealed diffuse atrophy and T2/FLAIR-hyperintensity of the thalami.

The general exam was unremarkable. The neurological examination unveiled a severe locomotor and static ataxia, along with a mild cognitive impairment (MMSE of 21 points). Laboratory tests indicated an elevated CRP of 10.2 (reference range up to 5), thrombocytosis (400 G/l), and poorly controlled diabetes with glucose levels between 9-12 mmol/l and an HbA1C of 9.5%. CSF examination had normal results; autoantibodies testing against intracellular and surface neuronal antigens (as listed above, case #1) was negative. The EEG showed background slowing, irregularity and poor reactivity, with intermittent anterior slow waves or slow quasiperiodic sharp-waves more prominent on the right (Figure 4, marked with red arrows).

The patient was discharged with normal lab results without changes to her neurological status.

The CSF test for 14-3-3 protein came back positive.

Unfortunately, in the following month we observed a rapid decline in the patient's cognitive and goal oriented movement capabilities – akinetic mutism. She was bedridden, her MMSE dropped to 9 points. Shortly after the patient passed away.

CLINICAL CASE 4

A 54-year-old male presented to our clinic in March, 2023, with a history of rapidly worsening gait, scanning speech, dysphagia and hand clumsiness. The symptoms appeared twenty days prior hospitalization, marked by the inability to walk freely without help, along with sialorrhea, insomnia, dysphagia and an inability to perform daily tasks. Four months earlier the patient was suspected of having had a Covid-19 infection, which was not tested.

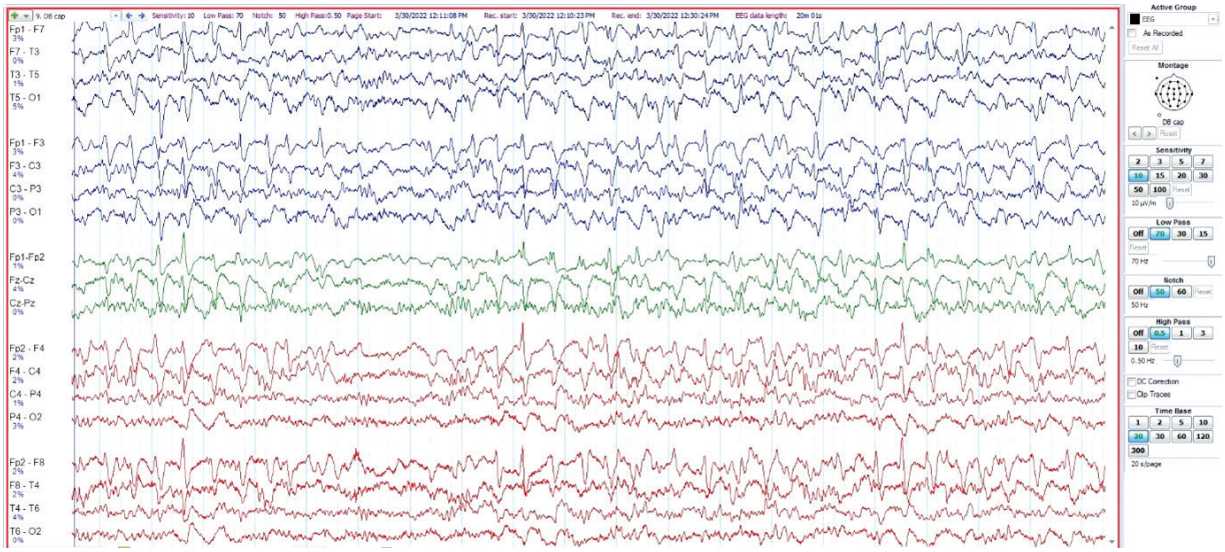

Fig. 3. EEG of patient 2 – EEG in awake state recorded an abnormal paroxysmal activity alongside triphasic periodic sharp wave complexes (PSWCs) with a frequency of 1-2 Hz

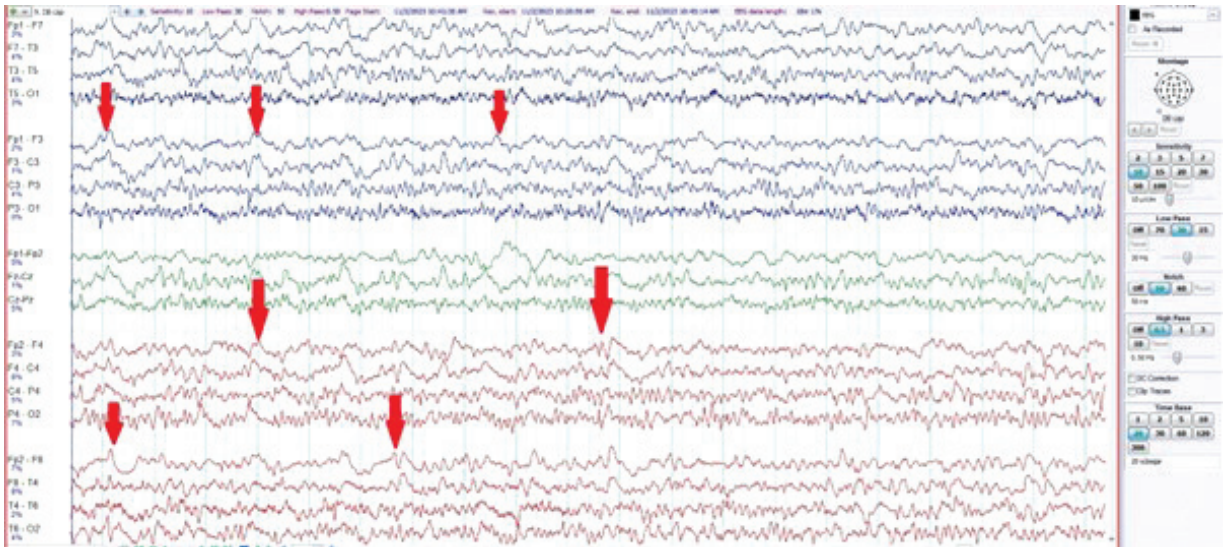

Fig. 4. EEG of patient 3 – background slowing, irregularity and poor reactivity, with intermittent anterior slow waves or slow quasiperiodic sharp-waves more prominent on the right

His somatic status was unremarkable. The neurologic examination revealed a quadripyramidal syndrome, pseudobulbar palsy, ataxia and a pancerebellar syndrome. The MRI revealed diffuse hyperintensities in the left hemisphere with fronto-mesial and posterior enhancement more pronounced on the left, alongside mild cortical atrophy and slightly enlarged ventricles (Figure 5).

CNS infection was suspected, but cell count and protein content in CSF were normal, and anti-Borrelia IgM and IgG, HIV, syphilis, anti-NMDA antibodies were also negative.

The patient's condition continued to rapidly worsen and he had a few generalized tonic-clonic seizures and subsequent, almost continuous, myoclonic seizures. In addition, the brain stem involvement signs increased with severe dysphagia and dyspnea; therefore, the patient was transferred to the ICU and required constant medication with Midazolam and intubation for artificial ventilation. An EEG done in that period showed the specific continuous activity of periodic sharp-waves with triphasic appearance at a frequency of 1-2 Hz (Figure 6), with left hemispheric predominance (correlating to the MRI lateralization of restricted diffusion). The EEG suggested CJD and prompted CSF testing for 14-3-3 protein, which came positive some weeks later. During this period, patient's general condition deteriorated with impossibility to regain independent breathing and consciousness, and by request of his relatives, he was transferred to a hospital abroad and was lost for follow-up.

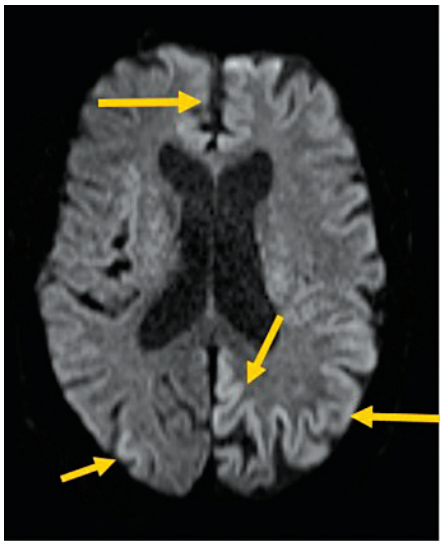

Fig. 5. MRI of patient 4 – DWI-MRI – hyperintensities more pronounced on the left, fronto-mesially (yellow arrows), with mild diffuse atrophy, with slightly enlarged ventricles

DISCUSSION

Creutzfeldt-Jakob Disease (CJD) is a rapidly progressive fatal illness induced by misfolded protein particles (prions). The diagnosis of CJD can be challenging despite the well-established diagnostic criteria of prion diseases that include the CSF biomarker 14-3-3, typical EEG with periodic sharp-wave complexes, characteristic MRI features such as restricted diffusion on DWI in neocortical areas and in the region of the basal ganglia, and the clinical symptoms myoclonus, visual and cerebellar disturbances, pyramidal or

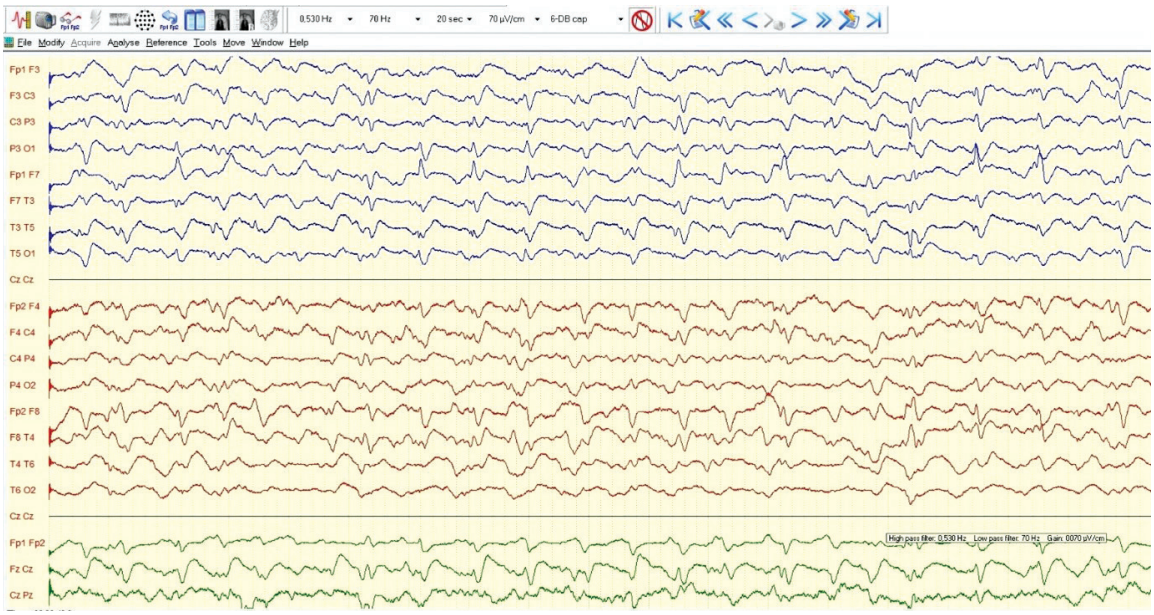

Fig. 6. EEG investigation of patient 4 – characteristic pattern of Creutzfeldt-Jakob Disease (CJD) – low-frequency triphasic periodic sharp wave complexes (PSWCs)

extrapyramidal signs, akinetic mutism, and progressive cognitive impairment. In our series, the disease was sporadic, as no familial inheritance was present. In the presented cases the disease manifested with the main neurological symptoms, including myoclonus, cerebellar ataxia, extrapyramidal and/or pyramidal signs, oculomotor signs (one case), generalized tonic-clonic seizures (one case) and rapidly progressive dementia that led to akinetic mutism. EEG in three of the four cases revealed the typical and very specific slow PSW in two of the cases, and in one (case 3), despite the developed clinical picture, only subtle changes, yet with similar periodicity/morphology were found. Likewise, in spite of severe clinical manifestation in all, the brain MRI showed just subtle changes on DWI in cases 1 and 4. Therefore, careful imaging inspection on all MRI sequences is needed and must be based on detailed clinical information with emphasis on the suspected CJD diagnosis.

The clinical diagnosis of the disease is supported/confirmed by the following [3-10]:

1. Cerebrospinal fluid – CSF analysis – detection of 14-3-3 protein, S100, neuron specific enolase (NSE), Tau protein.
2. RT-QuIC (real-time quaking induced conversion). This is the most recent advance in the application of new biomarkers' technologies confirming the clinical diagnosis by use of disease-specific protein aggregation and amplification assays. It constitutes a major breakthrough for the confident pre-mortem diagnosis of sporadic CJD. This multi-well plate-based PrPsc amplification technology uses quaking to "energise" the misfolding of prion protein monitored in real time using fluorescent dyes. The current sensitivity of CSF RT-QuIC is 92%, and the specificity is 100%.
3. MRI – T2 and FLAIR hyperintensity in the basal ganglia and/or diffusion restriction on DWI in cortical and subcortical areas (rarely insular or frontal cortices).
4. EEG is an integral part of the diagnostic process in patients with CJD. EEG usually reveals triphasic periodic sharp wave complexes with a frequency of 1-2 Hz.
5. Brain biopsy is the gold standard to confirm the presence of Creutzfeldt-Jakob disease. Biopsy sampling may be helpful in the diagnostic approach to rare cases of dementia for which a reliable diagnosis cannot be established on the basis of clinical symptoms, CSF parameters, electroencephalography, and MR imaging results.

In the described cases, the disease manifested with neurological symptoms, including startle myoclonus, rapidly progressing dementia that led to the development of personality changes and, subsequently, akinetic mutism. The diagnosis was confirmed in accordance with the widely accepted diagnostic approach, including imaging, CSF testing and EEG methods.

CONCLUSION

Creutzfeldt-Jakob Disease is a lethal, progressive ailment that should be suspected in individuals exhibiting rapidly progressing dementia coupled with extrapyramidal symptoms. The four recently diagnosed cases in Bulgaria confirm that the majority of patients succumb within a few weeks or months after clinical disease onset. Well-established and updated criteria for the diagnosis of CJD should include RT-QuIC in order to improve the early clinical diagnostic certainty and amelioration of the quality of the limited life of these patients and potential development of future therapeutic strategies.

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Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki.*

Consent for publication: *Consent form for publication was signed by the patients/relatives and collected.*

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