

CREUTZFELDT-JAKOB DISEASE: CASE REPORT AND REVIEW OF THE LITERATURE

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SUMMARY – Creutzfeldt-Jakob disease (CJD) is a rare, fatal neurodegenerative disease caused by an infectious protein called prion and is characterized by spongiform changes, neuronal loss, reactive astrocytic proliferation and accumulation of pathologic cellular protein, occurring in 3 general forms: sporadic or spontaneous, genetic or familial, and acquired form including a variant form of CJD. Clinical presentation of CJD is characterized by progressive dementia, neurologic symptoms and visual impairment, development of akinetic mutism, and eventually death, usually from respiratory infection. The diagnosis is based on clinical presentation, electroencephalogram, and typical cerebrospinal fluid and magnetic resonance imaging findings. A case is presented of a 56-year-old woman with progressive dementia, typical neurologic symptoms, positive cerebrospinal fluid and typical magnetic resonance imaging findings. The clinical, pathologic and imaging findings of this rare condition are also discussed.

Key words: *Creutzfeldt-Jakob syndrome – diagnosis; Creutzfeldt-Jakob syndrome – etiology; Prions; Magnetic resonance imaging; Brain pathology; Humans; Case report*

Introduction

Transmissible spongiform encephalopathies or prion diseases are rare, fatal disorders caused by infectious protein called prion, and characterized by myriads of vacuoles in the brain giving it a 'spongy' appearance under the microscope. They affect animals and humans: the most common forms of prion disease in animals are scrapie in sheep and bovine spongiform encephalopathy (BSE) in cattle. For the first time in history, scrapie was recorded in the 18th century, while the BSE or mad cow disease epidemic first became evident in 1985 in the United Kingdom (UK): cattle were infected by consumption of meat and bone meal

nutritional supplements contaminated with scrapie-infected sheep carcasses¹.

Human spongiform encephalopathy was first described in 1920 by two German neurologists, Hans Gerhard Creutzfeldt and Alfons Maria Jakob, thus called Creutzfeldt-Jakob disease (CJD). The worldwide prevalence of CJD is one person *per* 1 million, while the annual incidence is one person *per* 2 million, showing a slight female predominance². CJD is characterized by progressive dementia, neurologic symptoms and impaired vision, and eventually death in terminal stage. Clinical presentation, positive CJD biomarkers in cerebrospinal fluid (CSF), electroencephalogram (EEG) and typical magnetic resonance imaging (MRI) findings are crucial for making the diagnosis of CJD^{2,3}.

We present a case of a middle-aged woman with progressive dementia, typical neurologic symptoms, positive CSF and typical MRI findings. We also discuss clinical, pathologic and imaging findings in this rare condition.

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Case Report

In May 2009, a 56-year-old woman was admitted to University Department of Neurology, Dubrava University Hospital, due to progressive decline of cognitive functions during 6 months prior to hospitalization. This condition began with hand and head tremor, hypersensitivity to sound, disorientation in time and space, and inability to perform routine duties. Except for controlled hypertension, she was previously healthy, non-smoker and non-alcoholic.

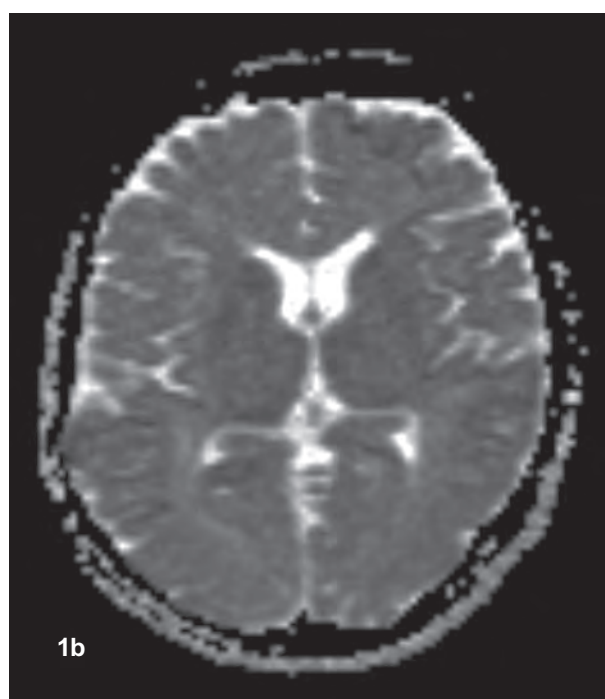
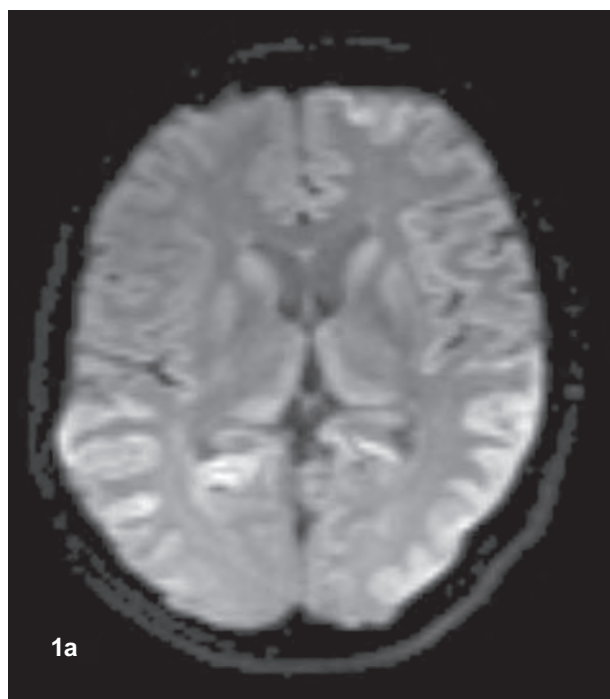
On admission, she was disoriented in time, partially disoriented in space, had voice tremor, head tremor, hand and leg tremor, and muscle hypertonia. Routine urine analysis, blood count and serum chemistry, immunologic blood tests and thyroid hormone levels were normal. She was negative for hepatitis virus A and B, and for human immunodeficiency virus type 1 and type 2.

Initial CSF study showed normal protein, sugar and electrolyte content, normal blood brain barrier function, and was negative for neurotropic viruses and *Borrelia burgdorferi*. EEG was diffusely slow and arrhythmic.

Psychological testing confirmed specific clinical presentation of rapidly progressive dementia.

MRI of the brain (1.5 T MR imaging system, Avanto Siemens, Erlangen, Germany) revealed bilateral and symmetrical hyperintense signal on diffusion-weighted images, localized in the frontal, parietal and partially temporal cerebral cortex, caput nuclei caudati and putamen (striatum), and medial and dorsal thalamic nuclei, followed by hypointense signal on apparent diffusion coefficient map (ADC) (Fig. 1 a, b, c, d). Fluid attenuated inversion recovery (FLAIR) sequence revealed asymmetric and discretely hyperintense signal localized in the parietal and posterior temporal cerebral cortex, and symmetric hyperintensities of caput nuclei caudati and putamen (striatum), and medial and dorsal thalamic nuclei (Fig. 2). Cortical and striatal hyperintensities were more pronounced as compared to thalamic hyperintensity. T1-weighted (T1WI) and T2-weighted (T2WI) images did not show signal intensity changes, and there was no contrast enhancement. Magnetic resonance spectroscopy (MRS) revealed decreased N-acetyl-aspartate (NAA) level, increased choline (Cho) level and reduced NAA/Cho ratio.

MRI findings were strongly suggestive of CJD, therefore repeat CSF analysis was performed only for CJD biomarkers, which were positive: 14-3-3 protein was positive, while S-100 protein (10.2 µg/L), neuron-



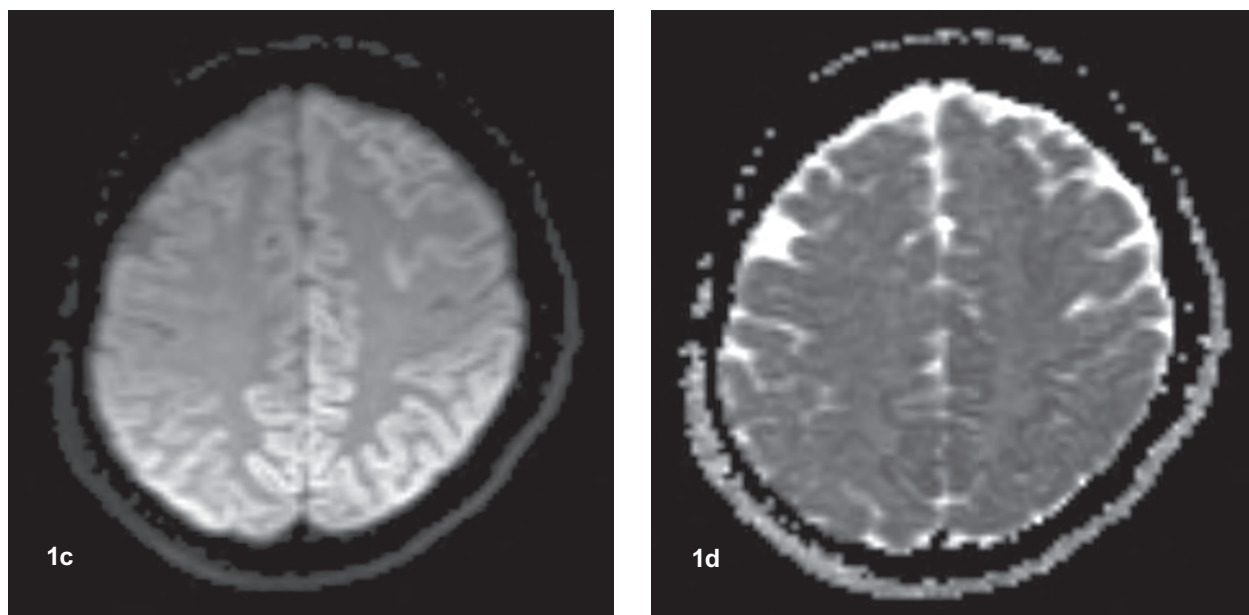


Fig. 1. MRI: DWI (a, c) reveals bilateral hyperintense signal within the frontal, parietal and posterior part of temporal cerebral cortex (cortical ribbon), caput nuclei caudati and putamen (striatum), and medial and dorsal thalamic nuclei (double hockey stick sign), followed by hypointense signal on ADC (b, d).

specific enolase (NSE) (33.7 $\mu\text{g/L}$), and total-tau (τ -tau) protein (1190.0 pg/mL) levels were elevated.

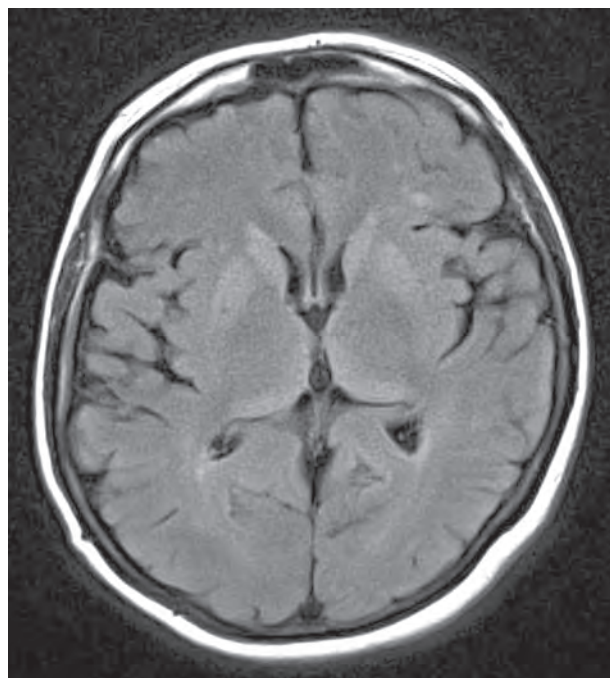


Fig. 2. MRI: FLAIR revealed discretely hyperintense signal localized in the left temporal cerebral cortex, and symmetric hyperintensities of the striatum and a double hockey stick sign.

Clinical presentation, MRI and CSF findings, together with atypical EEG indicated CJD, therefore, after four-week hospital stay at our Department the patient was transferred to Fran Mihaljević University Hospital for Infectious Diseases, where she was hospitalized until death due to respiratory tract infection at the end of December 2009. During the last 6 months, the disease progressed with progression of neurologic symptoms and dementia, and development of akinetic mutism, so the patient was only administered symptomatic therapy. Postmortem examination was not performed because the patient's husband refused the procedure.

Methods of Literature Search

Review of the literature was done by MEDLINE search of the published literature using the following keywords: human spongiform encephalopathies, Creutzfeldt-Jakob disease, dementia, prion, magnetic resonance imaging, diffusion-weighted images, and diagnostic criteria. Some of the data used in this article are common knowledge, but most of the data used were abstracted from the literature listed as references.

Discussion

Creutzfeldt-Jakob disease (CJD) is a rare, fatal neurodegenerative disease caused by a proteinaceous infectious particle that lacks nucleic acid called prion^{3,4}. Prion proteins occur in both a normal form, which is harmless protein found in the neurons as normal cellular prion protein (PrPc), and in an infectious or pathologic form, called scrapie prion protein (PrPSc), which causes the disease⁴. The normal and pathologic forms of the prion protein have the same sequence of 253 amino acids, but the pathologic form of the protein takes a different folded shape than the normal protein. With time, the disease-causing PrPSc can accumulate and aggregate to the levels that result in brain tissue damage, neuronal death and development of CJD⁵.

Prion diseases in humans occur in three general forms: sporadic or spontaneous, genetic or familial, and acquired form. Sporadic CJD (sCJD) is the most common of the human prion diseases, accounting for approximately 85% of cases: the etiology is unknown, predominantly affects individuals aged 55-75, lasts from several weeks to up to two years, and the clinical onset is characterized by mental-cerebellar-visual symptoms, comprising a broad spectrum of clinical-pathologic variants³. The main causes of the phenotypic heterogeneity are believed to be prion strains (isolates that show distinct disease phenotypes upon transmission to syngeneic animals, persisting on serial transmission), and the host genotype variability in the gene encoding PrPc (PRNP) located at chromosome 20⁴. In 1999, Parchi *et al.* established the molecular basis of pathologically distinct phenotypes of sCJD and proposed a classification of sCJD according to homozygosity or heterozygosity for methionine (M) or valine (V) at the polymorphic codon 129 of the PRNP and electrophoretic mobility of the protease-resistant fragment of the PrPSc (types 1 and 2): six subtypes with distinctive phenotypic features were defined⁶. In 2009, Parchi *et al.* updated the classification including a third parameter referring to distinctive histopathologic features (kuru type amyloid plaques, predominant cortical pathology with confluent vacuoles and perivacuolar PrPs staining, prominent thalamic pathology with atrophy): pure subtypes include subtypes established by previous nomenclature, with six new, so-called mixed subtypes established by the 2009 classification⁴.

Genetic and acquired prion diseases account for 10%-15% and 1% of human prion diseases, respectively. The genetic form of disease results from different mutations in the coding region of the PRNP located at the short arm of chromosome 20. All of the mutations are inherited in an autosomal dominant pattern. Depending on the mutation, the inherited forms of disease have been classified as familial CJD, Gerstmann-Sträussler-Scheinker disease (GSS), and fatal familial insomnia (FFI). The most commonly occurring mutation is located on codon 200 producing an illness that is indistinguishable from sCJD, so-called familial CJD. GSS typically begins at an earlier age than sCJD, has a prominent cerebellar component and evolves over a longer period of time (years rather than months). FFI has been named so because most patients have severe and intractable insomnia in addition to the usual features of CJD. Today, we know that all three 'diseases' are merely variations on a theme, and that all can be considered as being fundamentally the same and caused by the same disease process.

The acquired prion diseases include kuru, iatrogenic, and variant CJD (vCJD). Kuru is a prion disease first discovered in 1959 among the aboriginal Fore-people in the Eastern Highlands of Papua New Guinea: it was transmitted in connection with cannibalistic rituals of eating all body parts of the deceased, including the brain. The disease has evanesced with eradication of cannibalism.

There have been more than 400 patients that contracted CJD through the use of neurosurgical instruments, stereotactic EEG electrodes, human pituitary hormone, dura mater grafts, corneal transplant, and blood transfusion^{1,7}. In previously reported case-control studies, as well as in the study by Hamaguchi *et al.*, blood transfusion could be the route of secondary transmission, but it was never shown to be a significant risk factor for CJD⁷. The number of new patients with iatrogenic CJD has decreased, but we must remain vigilant against prion diseases to reduce the risk of iatrogenesis⁷.

Variant CJD (vCJD) first appeared in 1996 in the UK: until December 2008, 210 cases of vCJD had been reported (164 in the UK and 46 in other countries)⁸. It is causally linked with BSE and it is thought to be transmitted from cattle to humans¹. Clinically, the most striking feature of vCJD is young

age of its victims, ranging from 14 to 52 years, with an average duration of 7 to 14 months. In their study, Mead *et al.* defined the polymorphic codon 129 of PRNP as the main genetic risk factor for vCJD⁹. At the beginning of vCJD, psychiatric or sensory symptoms predominate.

The neuropathology of CJD is characterized by spongiform degeneration (vacuolation) of neurons, neuronal loss, intense reactive astrocytic proliferation, and accumulation of PrPSc, possibly forming plaques⁵. Spongiform degeneration involves cerebral cortex, striatum, thalamus and cerebellar cortex, and it is the most prominent histologic feature characterized by numerous oval and rounded vacuoles in the neuropil between the nerve cell bodies that occur both singly and in confluent groups resulting in large vacuoles that substantially distort the cytoarchitecture⁵. The spongiform change results in neuronal loss, gliosis and severe brain atrophy. A large number of amyloid plaques surrounded by a halo spongiform changes called 'florid plaques' are diagnostic for vCJD^{3,5}.

The incubation period of CJD ranges from 3 to 22 years, with subacute onset and progressive deterioration¹⁰. Clinical presentation of CJD is characterized by psychiatric and neurologic symptoms, and visual impairment that may progress to blindness. Rapidly progressive dementia is the most striking symptom. Initially, patients experience problems with muscular coordination; personality changes, including impaired memory, judgment, and thinking; and blurred vision. People with the disease may also experience insomnia, depression, or unusual sensations. As the illness progresses, the patients' mental impairment becomes severe, they develop myoclonus, pyramidal and extrapyramidal symptoms. Eventually, the state of akinetic mutism develops and the patients enter coma. Pneumonia and other, usually respiratory infections often occur in these patients and lead to death.

The diagnosis of CJD relies on a combination of clinical presentation, neurologic testing, pathologic examination, and cross-sectional imaging. Because CJD is such a rare disease, initial laboratory studies are aimed at ruling out all other potential endocrine, infectious, neoplastic, metabolic, and neurologic disorders. Other diagnostic procedures include CSF analysis, EEG, MRI and MRS, and brain biopsy, possibly tonsil biopsy³.

CSF analysis is necessary for two reasons: to rule out other etiologies such as infections or autoimmune conditions, and to detect biomarkers for CJD (neuronal proteins released into the CSF during extensive brain tissue destruction) such as the 14-3-3 protein, NSE, S-100 protein and t-tau^{3,11,12}. In two thirds of sCJD cases, EEG shows typical pattern of 'periodic slow and sharp wave' complexes, or it can show a less definite but still suggestive pattern of 'burst wave suppression'. Regarding vCJD, EEG is usually unspecific, but without complexes typical or suggestive of CJD.

Periodic slow and sharp wave complexes in EEG and elevated 14-3-3 protein in CSF are considered to be reliable criteria for the diagnosis of CJD¹³. In our case, clinical presentation and CSF findings were suggestive of CJD, while EEG was unspecific.

Neuroimaging has dramatically changed our ability to accurately diagnose dementia: currently, MRI is more useful for the diagnosis of prion disease than for any other dementia¹⁴. Computed tomography is not useful in the diagnosis of CJD because it will only reveal brain atrophy. MRI is an important diagnostic tool in CJD not only for making the diagnosis of CJD, but for ruling out the other possible etiologies and monitoring changes during the course of disease.

Characteristic MRI findings in CJD are best seen on diffusion-weighted images (DWI) and to a lesser extent on FLAIR images, and are 91% sensitive and 95% specific for the diagnosis of CJD¹⁵. These findings include hyperintense signals within the cerebral cortex called 'cortical ribbon', within caput nuclei caudate and putamen (striatum), and thalamus^{2,3}. The 'double hockey stick sign' refers to increased signal in the medial and dorsal thalamic nuclei, while the 'pulvinar sign' refers to increased signal in the dorsal thalamic nuclei, called pulvinar. Hyperintense signal on DWI is followed by hypointense signal in ADC map, and reflects restricted diffusion of water molecules at the microscopic level due to numerous, small sized vacuoles and accumulation of PrPSc, while hyperintense signal on FLAIR is due to reactive gliosis^{2,3}. These changes will not show contrast enhancement after its application.

In the early phase of CJD, signal changes are detected earliest on DWI, less frequently on FLAIR, while signal intensity is normal on T1WI and T2WI. With disease progression, there is an expansion of signal changes and progressive cerebral atrophy¹⁶. In

late stages of CJD, hyperintense signal on DWI may disappear with normalization on ADC due to reactive gliosis¹⁶. In the end stage, there is severe cerebral and cerebellar atrophy and atrophy of the brain stem with ventricular enlargement.

Cortical signal changes in CJD involve all lobes, mainly frontal (89%), limbic (79%), parietal (72%) and temporal (65%) cortex, while the precentral and central gyri are usually spared. In the majority of cases, hyperintensities in cortex and striatum are symmetric, although an unilateral predominance is possible^{3,17}.

In sCJD, hyperintense signals in cerebral cortex and striatum are the most common MRI findings. Hyperintensities in the pulvinar thalami have also been reported in sCJD, but they are usually less pronounced than in the striatum, whereas in vCJD the highest signal is always in the pulvinar¹⁷.

In comparison with literature data, in our case MRI findings strongly indicated CJD: typical cortical and striatal hyperintensities, and medial and dorsal thalamic nuclei hyperintensities were present and more pronounced on DWI as compared to FLAIR, and more pronounced in the cortex and striatum than in the thalamus^{3,16,17}.

Magnetic resonance spectroscopy (MRS) is a non-invasive technique that allows for evaluation of specific brain metabolites, including N-acetyl-aspartate (NAA) as a neuronal marker, creatine (Cr) as a marker of neuronal metabolism, and myoinositol (mI) as a glial marker. In CJD, MRS reveals reduced NAA content and/or increased mI content in the affected areas due to neuronal loss and reactive gliosis, followed by marked reduction of the NAA/Cr and NAA/mI ratios¹².

Positive pathologic findings on brain biopsy or autopsy confirm the diagnosis of CJD, including immunohistochemical detection of the pathologic protein (PrPSc)³. Autopsy of patients with CJD is always performed in autopsy examination halls specially aimed for patients with prion diseases.

Brain biopsy for CJD can be a dangerous procedure and is not performed routinely because of the previously mentioned and accepted diagnostic procedures, and possible false-negative findings³. It is only advisable when an alternative treatable disease is suspected. Due to the route of infection in vCJD, PrPSc infects peripheral lymphoid tissue like tonsils. Therefore, in vCJD it is possible to confirm the diagnosis with tonsil

biopsy⁹. Because of the possible complications for the patient and the risk of infection for the team, the procedure is only performed in clinically difficult cases³.

In our case, tonsil biopsy was not performed because of the reasons mentioned above and because we presumed an autopsy should be performed after the patient's death. Unfortunately, although autopsy was strongly advised to the family and the patient's daughter was in favor of the procedure, the patient's husband refused it for reasons that are unknown to us.

Radiological differential diagnosis includes Leigh's disease, carbon monoxide poisoning, cerebral hypoxia, cortical ischemia, postictal changes, encephalitis, and possibly tumors (lymphoma and metastases)³. Clinical picture of progressive dementia in combination with the neuroimaging findings described should lead to the diagnosis of CJD.

Treatment for all forms of CJD is largely symptomatic, as no established curative agents have been identified. A number of different experimental agents are currently under investigation including quinacrine, which prevented conversion of PrPC to PrPSc in *in vitro* studies¹⁸. Pentosan polysulfate has been shown to increase incubation time in animal studies by affecting prion production, replication and the associated cell toxicity, but data in humans are not clear¹⁹. Flupirtine²⁰ demonstrated a trend towards improving cognitive function but showed no survival improvement.

Since postmortem examination was not performed, we could not reach definitive confirmation; clinical presentation, CSF and MRI findings were typical for CJD, but distinction between the forms of the disease was missing. There are no heterohistory data suggesting the possibility that the patient had a familial form of CJD. The course of the disease, the patient's age and MRI findings suggested a sporadic form of CJD, while clinical presentation and duration of about 12 months could indicate both sporadic and variant form of the disease. In conclusion, we presume that our patient probably had a sporadic form of CJD^{3,11,16,17}.

The aim of this case report and review of the literature is to emphasize the possibility of CJD in a small population like Croatian and encourage our colleagues, neurologists and radiologists, to think of it in their practice when encountering a young or middle-aged patient with clinical presentation and imaging findings similar to those described above.

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Sažetak

CREUTZFELDT-JAKOBOVA BOLEST: PRIKAZ SLUČAJA I PREGLED LITERATURE

M. Špero i I. Lazibat

Creutzfeldt-Jakobova bolest (CJD) je rijetka i smrtonosna neurodegenerativna bolest koju uzrokuje infektivna bjelančevina nazvana prion, a obilježena je spužvastim promjenama, gubitkom neurona, reaktivnom proliferacijom astrocita i nakupljanjem patološke stanične bjelančevine. Bolest se javlja u tri glavna oblika: sporadični ili spontani, genetski ili obiteljski, te stečeni oblik uključujući varijantni oblik CJD. Klinički je CJD obilježena progresivnom demencijom, neurološkim simptomima i poremećajem vida, razvojem akinetskog mutizma, te konačno smrću, najčešće zbog dišne infekcije. Dijagnoza se temelji na kliničkim značajkama, elektroencefalogramu, te tipičnim nalazima likvora i magnetske rezonancije. Prikazuje se slučaj 56-godišnje bolesnice s progresivnom demencijom, tipičnim neurološkim simptomima, te pozitivnim nalazima likvora i magnetske rezonancije. Također se raspravlja o kliničkim i patološkim nalazima, te nalazima slikovnog prikazivanja u ovoj rijetkoj bolesti.

Ključne riječi: *Creutzfeldt-Jakobov sindrom – dijagnostika; Creutzfeldt-Jakobov sindrom – etiologija; Prioni; Magnetska rezonancija; Moždana patologija; Ljudi; Prikaz slučaja*