



# Creutzfeldt-Jacob Disease, As a Rare Cause of Dementia Should Not be Forgotten: Single-Center Experience

Tek Merkez Deneyimi: Unutulmaması Gereken Nadir Bir Demans Nedeni Olarak Creutzfeldt-Jacob Hastalığı

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## ABSTRACT

**Introduction:** Dementia, which is an important public health problem, is divided into two groups as primary and secondary dementia. Creutzfeldt-Jacob disease (CJD), which is rarely seen, is a secondary cause of dementia with a rapidly progressive course. It is a fatal neurodegenerative disorder of infectious spongiform encephalopathy that can affect humans and animals. Sporadic CJD is the most common type that can present in four forms and has typical clinical presentations of progressive cognitive impairment, myoclonus, and ataxia. We aimed to discuss the demographic, clinical, and laboratory findings of CJD cases diagnosed in the neurointensive care unit. **Methods:** Sixteen patients were included in this retrospective study. Age, sex, complaints on admission, duration from symptom onset to mortality, neurologic examination, brain magnetic resonance imaging (MRI), electroencephalography (EEG), and the protein 14.3.3 status of the cerebrospinal fluid (CSF) were recorded. **Results:** The mean age was  $61.18 \pm 9.1$  years (range, 37–73 years), and the most common complaints on admission were cognitive impairment, disturbance in consciousness, ataxia, and gait disturbance. CSF protein 14-3-3 was positive in 100% of patients. The most common findings were periodic sharp and wave complexes on EEG, cortical or putamen and caudate nucleus hyperintensity, cortical and cerebellar atrophy on MRI. One of the patients was diagnosed as variant CJD, and the others were diagnosed as the sporadic form. **Conclusions:** CJD should be kept in mind in patients with myoclonus or ataxia accompanied by progressive cognitive impairment. Neuroimaging, serial EEG recordings, CSF analysis, and histopathologic examination should be performed for diagnosis.

**Keywords:** Prion diseases, Creutzfeldt-Jacob disease, Cognitive impairment, Myoclonus, Electroencephalography

## ÖZET

**Giriş:** Önemli bir halk sağlığı sorunu olan demans primer ve sekonder demans olmak üzere iki gruba ayrılmaktadır. Çok nadir olarak görülen Creutzfeldt-Jacob hastalığı (CJH), hızlı progresif seyir gösteren bir sekonder demans nedenidir. CJH insanları ve hayvanları etkileyebilen enfeksiyöz spongiform ensefalopatilerden, ölümcül bir nörodejeneratif hastalıktır. Dört formu olan hastalığın en sık görülen formu olan sporadik CJH olgularında progresif kognitif bozukluk, miyoklonus ve ataksi tipik klinik tablodur. Bu çalışmada Nörolojik yoğun bakım ünitesinde tanı alan CJH olgularının demografik, klinik ve laboratuvar bulgularını tartışmayı amaçladık. **Yöntem:** Retrospektif olarak planlanan bu çalışmaya 16 hasta dahil edildi. Hastaların yaş, cinsiyet, başvuru şikayetleri, semptom başlangıcından mortaliteye kadar geçen süre, nörolojik muayene, beyin manyetik rezonans görüntüleme (MRG), elektroensefalografi (EEG) ve beyin omurilik sıvısında (BOS) protein 14.3.3 durumu kaydedildi. **Bulgular:** Ortalama yaş  $61.18 \pm 9.1$  (37-73) olan hastaların başvuruda en sık karşılaşılan şikayetleri sırayla bilişsel bozukluk, bilinç bozukluğu, ataksi ve yürüme bozukluğu idi. BOS'ta protein 14.3.3 hastaların % 100'ünde pozitif idi. En sık saptanan EEG bulgusu periyodik keskin dalga kompleksleri, en sık saptanan beyin MRG'de kortikal veya putamen ve kaudat nükleus hiperintensitesi ve kortikal ve serebellar atrofi idi. Bir hasta varyant CJH, diğer hastalar ise sporadik form olarak değerlendirildi. **Sonuç:** Progresif kognitif bozukluk ve eşlik eden miyoklonus veya ataksi varlığında CJH tanısı mutlaka akılda tutulmalıdır. Tanı için beyin görüntüleme, seri EEG kayıtlamaları, BOS analizi ve yapılabilirse histopatolojik inceleme yapılmalıdır.

**Anahtar Kelimeler:** Creutzfeldt-Jacob hastalığı, elektroensefalografi, kognitif bozukluk, miyoklonus, prion hastalıkları

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## INTRODUCTION

Dementia, which is an important public health problem, is very common in the society especially in the older age group and it is divided into two groups as primary and secondary dementia. While the most common cause of primary dementia is Alzheimer's Disease, the most common cause of secondary dementia is vascular dementia. One of the causes of secondary dementia is Creutzfeldt–Jakob disease (CJD) and it is the prototype of progressive dementia.

CJD is a very rare cause of dementia and fatal neurodegenerative disorder of infectious spongiform encephalopathy that can affect humans and animals.<sup>1</sup> It is characterized by the accumulation of pathologic prion protein in the central nervous system.<sup>2</sup> The incidence of the disease varies between 0.5 and 1.5 per million and is similar in both sexes. Although the age of onset of the disease is often over 65 years, cases that encompass all ages between 14 and 92 years have been reported to date.<sup>3</sup>

The most common form of the disease is sporadic CJD (sCJD) of unknown etiology, with 85% frequency, followed by the familial (fCJD), variant (vCJD), and iatrogenic (iCJD) forms.<sup>4</sup> The most typical clinical presentation of sCJD includes ataxia, progressive cognitive impairment, and myoclonus. In addition, psychiatric, visual, cerebellar, pyramidal, and extrapyramidal findings are common in the course of the disease.<sup>5</sup> Although the disease does not have precisely known risk factors, some forms have been thought to be associated with various factors. Usually, the age of onset is 60 years of age for sCJD, at an earlier age for fCJD, and on the third to the fourth decade for vCJD. fCJD cases have been thought to have an autosomal dominant inheritance. iCJD has been known to have the risk of contamination of brain tissue. There was evidence that vCJD may develop by consuming contaminated animal meat.

Currently, no cure is available for CJD. Although the mean interval from diagnosis to death in sCJD cases has been reported to be 4–6 months,

there have been reported cases of surveillance from weeks to several years.<sup>6</sup> Female sex and younger age at onset were associated with longer survival.<sup>7</sup>

Early diagnosis of the disease is important in terms of reducing the relatives of patients seeking medical treatment and prevention of iatrogenic transmission. CJD is one of the preliminary diagnoses that should be evaluated in patients with middle-advanced age presenting with progressive cognitive complaints, myoclonia, and movement disorders, balance disorder, or psychiatric complaints in primary care.

In this article, we aimed to discuss the demographic, clinical, and laboratory findings of CJD cases diagnosed at our neurology intensive care unit (NICU).

## METHODS

This single-center retrospective study was carried out in our tertiary healthcare center in Adana, Turkey after obtaining the approval of the local ethics committee (Cukurova University, Faculty of Medicine, Ethics Committee for Non-invasive Clinical Research -Decision No: 2019-10-92). In this study, the archived files of 3,841 patients who stayed at our tertiary hospital NICU between 2000 and 2019 were reviewed; 17 patients who were diagnosed as CJD were included. Patients who had no available medical documentation were excluded. Age, sex, symptoms on the onset, the interval between symptom onset and mortality, neurologic examination findings, cerebral magnetic resonance imagination (MRI), electroencephalography (EEG), and protein 14.3.3 status of the cerebrospinal fluid (CSF) were recorded. The diagnosis of CJD was made based on the diagnostic criteria for sCJD surveillance (Table 1).<sup>8</sup>

The IBM Statistical Package for the Social Sciences Version 20 was used to analyze the data obtained from the assessments. The descriptive statistics of the quantitative data were presented as a minimum, maximum, mean  $\pm$  standard deviation (SD), or median, whereas qualitative data were presented as number (n) and frequency (%).

**Table 1. Diagnostic criteria for the surveillance of sporadic Creutzfeldt–Jakob disease from January 1, 2017<sup>a</sup>**

<b>1.1 DEFINITE</b>
Progressive neurologic syndrome AND Neuropathologically, immunohistochemically, or biochemically confirmed
<b>1.2 PROBABLE</b>
1.2.1 I + two of II and typical electroencephalogram <sup>a</sup> OR 1.2.2 I + two of II and typical brain magnetic resonance imaging findings <sup>b</sup> OR 1.2.3 I + two of II and positive cerebrospinal fluid (CSF) protein 14-3-3 OR 1.2.4 progressive neurologic syndrome and positive real-time quacking-induced conversion in CSF or other tissues
<b>1.3 POSSIBLE</b>
I + two of II + duration of <2 years
I Rapidly progressive cognitive impairment
II A Myoclonus
B Visual or cerebellar problems
C Pyramidal or extrapyramidal features
D Akinetic mutism

<sup>a</sup> Generalized periodic complexes

<sup>b</sup> High signal in the caudate/ putamen or at least two cortical regions (temporal, parietal, occipital) on brain magnetic resonance imaging, either diffusion-weighted imaging, or fluid-attenuated inversion recovery

## RESULTS

Sixteen patients were included in the study [10 men, mean age  $61.18 \pm 9.1$  years (range, 37–73 years)]. The most common symptom on onset was cognitive impairment, followed by gait disturbances. The most frequently observed neurologic examination finding was cognitive

decline. The protein 14.3.3 level in the CSF could not be measured in 1 patient, but it was positive in 15 patients. The mean duration of follow-up was five months, and one newly diagnosed patient remains alive and is still being followed-up (Table 2).

**Table 2. Demographic and clinical features**

	Female n (%)	Male n (%)	Total n (%)
Patient number	6 (37.5)	10 (62.5)	16 (100)
Age (mean $\pm$ SD)	$62.33 \pm 6.47$ (54–72)	$60.5 \pm 10.64$ (37–73)	$61.18 \pm 9.1$ (37–73)
Symptom on onset			
Psychiatric	2 (33.3)	3 (30)	5 (31.25)
Cognitive/ consciousness disturbance	6 (100)	9 (90)	15 (93.75)
Speech disorder	0 (0)	1 (10)	1 (6.25)
Ataxia/ gait disturbance	1 (16.6)	8 (80)	9 (56.25)
Seizure	1 (16.6)	0 (0)	1 (6.25)
Myoclonus	1 (16.6)	3 (30)	4 (25)
Anorexia	1 (16.6)	0 (0)	1 (6.25)
Sleep disorder	1 (16.6)	0 (0)	1 (6.25)
Initial neurologic examination findings			
Cognitive impairment	4 (66.2)	8 (80)	12 (75)
Akinetic mutism	2 (33.2)	1 (10)	3 (18.75)
Dysarthria	1 (16.6)	1 (10)	2 (12.5)
Cerebellar impairment	1 (16.6)	4 (40)	5 (31.25)
Extrapyramidal findings	4 (66.2)	3 (30)	7 (43.75)
Myoclonus	1 (16.6)	5 (50)	6 (37.5)
Protein 14-3-3 positivity in the CSF	5 (100)	10 (100)	15 (100)
Mean survey	4.1 (2–6)	5.5 (1–12)	5 (1–12)

CSF, cerebrospinal fluid; SD, standard deviation

A 72-year-old man had epilepsy. A 37-year-old man who presented with cognitive and psychiatric symptoms was diagnosed as vCJD. Periodic sharp-wave complexes (PSWC) were the most common EEG finding, and the most common MRI findings were cortical or putamen and nucleus caudatus hyperintensity, and cortical and cerebellar atrophy

(Table 3). In the first EEG recording, only 37.5% (n = 6) of the patients had characteristic PSWC findings. Hyperintensity on MRI was seen in the deep gray matter in 37.5% (n = 6), in the cortex in 43.75% (n = 7), and in both deep gray matter and cortex in 25% (n = 4).

**Table 3. Brain MRI and EEG findings on admission and follow-up**

Patient number	Age	Sex	EEG at admission	EEG at follow-up	Brain MRI at admission	
					Deep gray matter	Cortical
1	54	F	PSWC	GPED		Bilateral severe cerebral atrophy
2	57	M	Diffuse slowing	PSWC	Bilateral putamen and caudate nucleus hyperintensity	Bilateral frontal and temporal hyperintensity
3	67	F	Diffuse slowing	PSWC	Bilateral putamen hyperintensity	Severe cerebral and cerebellar atrophy
4	58	F	PSWC	GPED	Bilateral putamen and caudate nucleus hyperintensity	Right temporal and parietal hyperintensity
5	72	M	Abnormal background activity	PSWC		Bilateral frontal hyperintensity
6	72	F	Normally	PSWC		Cerebral and cerebellar atrophy
7	60	F	Abnormal background activity	PSWC		Bilateral frontal hyperintensity
8	63	M	Abnormal background activity	PSWC		Cerebral and cerebellar atrophy
9	79	M	Abnormal background activity	PSWC		Severe cerebral and cerebellar atrophy
10	60	M	PSWC	PSWC	Bilateral putamen and caudate nucleus hyperintensity	
11	71	M	PSWC	PSWC		Cerebral and cerebellar atrophy
12	55	M	Abnormal background activity	PSWC		Severe cerebral and cerebellar atrophy
13	61	M	Abnormal background activity	PSWC		Cerebral and cerebellar atrophy
14	63	F	PSWC	PSWC	Bilateral putamen and caudate nucleus hyperintensity	Right frontal and temporal hyperintensity
15	55	M	Abnormal background activity	PSWC	Bilateral putamen and caudate nucleus hyperintensity	Cerebral and cerebellar atrophy
16	37	M	PSWC	PSWC		Right temporal and parietal hyperintensity

EEG, electroencephalography; F, female; GPED, generalized periodic epileptiform discharges; M, male; MRI, magnetic resonance imagination; PSWC, periodic sharp and wave complexes

## DISCUSSION

Prion diseases are a group of neurodegenerative diseases that have long incubation periods and progressive clinical symptoms. Behavioral problems, headache, loss of appetite, weight loss, fear, and psychotic symptoms can be seen in the prodromal phase of CJD, which accounts for more than 90% of prion diseases. Onset with psychiatric symptoms is not uncommon. For this reason, patients first consult the psychiatry outpatient clinics and may be diagnosed as psychosis and depressive disorder. In this study, the initial symptoms were psychiatric complaints in five cases, loss of appetite in one case, and sleep disturbance in one case. The most common

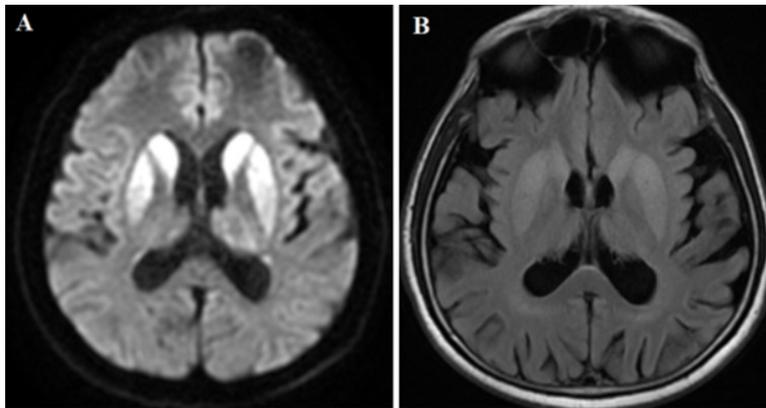
psychiatric complaints were depressive symptoms and paranoid thoughts.

Progressive cognitive impairment, myoclonus, and ataxia predominate in CJD cases that present with obvious clinical findings. Impairment of consciousness, as well as pyramidal, extrapyramidal, and cerebellar signs, may be noted on neurologic examination. Usually, most patients present with mutism in the advanced stage. The initial clinical manifestations of our 16 patients were cognitive impairment in 12 (75%), extrapyramidal signs in 7 (43.75%), cerebellar signs, and myoclonus in 5 (31.25%), and impairment of consciousness in 3 (18.75%).

Clinical exam, EEG, brain MRI, and CSF analysis are crucial for the diagnosis of the disease, and the definitive diagnosis can be made by histopathologic analyses. Unfortunately, a brain biopsy was not possible to perform in our patients. Therefore, all of our patients were diagnosed as possible CJD (15 cases of sCJD, 1 case of vCJD) based on history, clinical course, neurologic examination, serial EEG examinations, brain MRI, and CSF results of protein 14-3-3. In another series of 16 cases reported from Turkey, all cases were diagnosed as sCJD.<sup>9</sup> vCJD accounts for less than 1% of all prion diseases.<sup>10</sup> Although vCJD cases are typically seen at a younger age (mean, 26 years), they present with psychiatric symptoms, such as anxiety, agitation, depression, and psychosis. Therefore, patients are usually diagnosed as primary psychiatric disorders before the diagnosis of vCJD.<sup>11</sup> A few months after the onset of psychiatric symptoms, neurologic symptoms, such as cognitive and cerebellar dysfunction, dysesthesias, and

involuntary movements, appear.<sup>10</sup> Dementia and kinetic mutism predominate in the later stages of the disease.

In the early stage of CJD, diffusion MRI may show increased signal in the cortex or caudate and anterior putaminal localization. In this study, only 37.5% of patients had bilateral caudate and putaminal hyperintensity on brain MRI (Image 1). In the middle stage, unilateral or bilateral and symmetric or asymmetric lesions can be seen in the same localization. During this period, lesions on the FLAIR sequence may be better visualized, but diffusion may not be apparent on MRI, and generalized atrophy and ventricular dilatation can be observed in all sequences. In the advanced stage, generalized atrophy and ventricular dilatation are noteworthy. In some cases, a slight signal increase in the cortex or basal ganglia may be seen on DWI sequences.<sup>12,13</sup>



**Image 1. A. Bilateral hyperintense signals in the caudate and putamen (hockey stick sign) on diffusion-weighted (DWI) MRI. B. FLAIR sequence MRI shows (Patient 15)**

EEG is a very useful tool for the diagnosis of CJD. In 67% to 95% of patients, the characteristic EEG pattern during the disease is periodic synchronous biphasic or triphasic sharp-wave complexes, which were reported to be 67% sensitive and 86% specific for CJD.<sup>14</sup> In the early stage of the disease, EEG is normal or may show nonspecific deceleration. Occasionally, the first finding may be intermittent frontal rhythmic delta activity.<sup>15</sup> The characteristic PSWCs may appear weeks or months after the onset of the disease and typically comprise sharp waves, spikes, or triphasic waveforms with a frequency of 1–2 Hertz.<sup>16</sup> In this study, we detected PSWCs in 12 patients by serial EEG monitoring (Image 2). Moreover, PSWCs can

differentiate CJD cases from the other prion diseases; these can be seen in sCJD and fCJD cases but not in vCJD cases.<sup>17</sup> Although PSWCs may not be seen in the early stages of the disease, they may occur later in the disease course. Therefore, serial EEG recordings are very important for the diagnosis of patients with suspected CJD. In the terminal period, PSWCs are not seen because of very low voltage activity and the subsequent electro cerebral inactivity. PSWCs may be masked by benzodiazepines and barbiturates, and these activities are much less common in patients with iCJD.<sup>18</sup>



**Image 2. Periodic sharp-wave complexes in EEG of patient 4**

Previous studies suggested an association between MRI findings and EEG activities.<sup>19</sup> Several studies have reported that PSWC activities were associated not with the deep gray matter but with cortical lesions, suggesting that cortical lesions are the source of PSWC activity.<sup>20</sup> Contrary to published literature, this study showed one patient in whom there was no significant relationship between the EEG and MRI findings in the first week of clinic admission (Table 3). There had been studies on the determination of some proteins in the CSF for CJD diagnosis; of these proteins, the most commonly used for CJD diagnosis has been protein 14.3.3. The other proteins that have been investigated for CJD diagnosis were S100 protein, neuron specific enolase, thymosin  $\beta$ 4, and tau protein.<sup>21</sup> Although protein 14.3.3 positivity for the diagnosis of CJD has been reported to have varying sensitivity and specificity, it was found to be 92% sensitive and 80% specific in one study.<sup>22</sup> This meant that protein 14.3.3 negativity does not exclude the diagnosis and that protein 14.3.3 positivity does not always indicate CJD. False positivity may be present in herpes simplex encephalitis, paraneoplastic diseases, cerebral metastases, hypoxic encephalopathy, and metabolic encephalopathy.<sup>23</sup> Therefore, along with clinical findings, protein 14.3.3 positivity, as well as characteristic EEG and MRI findings, can reinforce the diagnosis of CJD. In our study, the rate of protein 14.3.3 positivity in the CSF was 100%. In recent years, the real-time quacking-induced

conversion was developed and found to be 92% sensitive and 98.5% specific for the diagnosis of CJD.<sup>24</sup>

Primary care physicians are the most important health personnel in the early diagnosis of the disease. It is the primary care physician who often encounters the patient first. They also encounter these patients in the advanced stages of the disease in CJD patients' stage care services. Important suggestions to keep in mind in the care of these patients are as follows; 1-Current evidence suggests that there is no risk of disease transmission through normal social or routine contact to healthcare workers, family members or others. 2- Families do not need to take precautions other than routine infection control practices during the care of these patients. 3- Feeding utensils, feeding tubes, suction tubes, razors or personal care items do not require special precautions. 4- Physicians following CJD patients should inform the staff responsible for the laboratory, morgue and funeral procedures at risk of contact with high or low infective materials.<sup>25</sup>

In conclusion, CJD should be kept in mind in patients with progressive cognitive impairment, when there are accompanying myoclonuses or ataxia and precedent psychiatric symptoms. Diagnostic neuroimaging, serial EEG recordings, CSF analysis, and, if possible, the histopathologic examination should be performed.

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