Sporadic Creutzfeldt-Jacob Disease: An 8-Year Experience from a Single Center in Turkey

Sporadik Creutzfeldt-Jacob Hastalığı: Türkiye'den Bir Merkezin Sekiz Yıllık Tecrübesi

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ABSTRACT

Introduction: Our aim was to conduct a retrospective review to demonstrate the clinical, radiological, and electrophysiological features of patients with sporadic Creutzfeldt-Jacob disease (sCJD).

Method: A total of 10 patients (5 female and 5 male, with a mean age of 45 years from a range of 40 to 67 years) out of 8.259 adult patients hospitalized from January 2000 to December 2008 were diagnosed with sCJD.

Results: Eight of the patients were diagnosed on the basis of clinical, radiological, electroencephalography (EEG), and cerebrospinal fluid (CSF) findings. Two other patients also had a pathological diagnosis. The most common signs and symptoms were behavioral disturbances, movement disorders, cognitive decline, myoclonus, psychosis, focal neurological deficit, and aphasia. Nine of the patients had periodic sharp wave discharges on EEG. Seven patients were positive for the 14.3.3 protein in the CSF. Five patients had pulvinar signs-a bilateral increased signal in the pulvinar thalami on cranial magnetic resonance imaging. Eight patients were diagnosed with probable sCJD; two were diagnosed with definite sCJD. All of the patients died as a result of the disease within 24 months after the onset of symptoms.

Discussion: sCJD should be considered in the diagnosis of patients who present with rapidly progressive dementia. Clinical and radiological data appear to be sufficient for the diagnosis. However, detailed molecular examinations of the subtypes of the disease may be required for early diagnosis of cases given the wide spectra of CJD. (*Archives of Neuropsychiatry* 2013; 50: 306-311)

Key words: Sporadic Creutzfeldt-Jacob disease, cerebrospinal fluid, periodic sharp wave complexes, magnetic resonance imaging

Conflict of interest: The authors reported no conflict of interest related to this article.

ÖZET

Giriş: Sporadik Creutzfeldt-Jacob Hastalığı (sCJH) tanısı almış hastaların klinik, radyolojik ve elektrofizyolojik özelliklerinin retrospektif olarak değerlendirilmesini amaçladık.

Yöntem: Ocak 2000- Aralık 2008 yılları arasında hastaneye yatırılan 8259 yetişkin hasta arasından 10 hasta (5 kadın, 5 erkek; ortalama yaş 45; yaş aralığı 40- 67 yıl) sCJH tanısı almıştı.

Bulgular: Sekiz hastanın tanısı klinik belirti ve bulgular, radyolojik, elektroensefalografi (EEG) ve beyin omurilik sıvısı (BOS) tetkiklerinin sonuçları ile kondu. Diğer iki hastanın ek olarak patolojik tanıları da vardı. En sık belirti ve bulgular davranış problemleri, hareket bozuklukları, kognitif yıkım, miyoklonus, psikoz, focal nörolojik defisit ve afazi idi. Dokuz hastanın EEG'sinde periyodik keskin dalga deşarjları vardı. Yedi hastanın BOS incelemesinde 14.3.3 proteini saptandı. Beş hastanın kranyal magnetik rezonans görüntülemesinde her iki pulvinar çekirdeklerde sinyal artışı (pulvinar belirti) izlendi. Sekiz hastaya olası, iki hastaya kesin sCJH tanısı kondu. Tüm hastalar hastalık belirti ve bulgularının başlangıcından sonraki 24 ay içinde öldü.

Sonuç: Hızlı ilerleyici demansiyel bulgularla başvuran hastalarda ihtimali tanılar arasında sCJH düşünülmelidir. Klinik ve radyolojik tetkik sonuçları tanı için yeterli olsa da CJH'nın geniş yelpazesi düşünüldüğünde olguların erken tanınması aşamasında hastalığın alt tiplerinin detaylı moleküler inceleme ile tanınması gerekli olabilir. (*Nöropsikiyatri Arşivi* 2013; 50: 306-311)

Anahtar kelimeler: Sporadik Creutzfeldt-Jacob Hastalığı, beyin omurilik sıvısı, periyodik keskin dalga kompleksleri, magnetik rezonans görüntüleme

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

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Introduction

Creutzfeldt-Jacob disease (CJD) is a neurodegenerative disease with sporadic (sCJD) (85%), familial (10%-15%), iatrogenic (1%), and new variant forms. The incidence of sCJD is estimated to be 0.5 to 1.5 cases per million people per year (1).

According to the accepted case definition criteria for sCJD, three subgroups are defined: possible, probable, and definite (2). Classic CJD, Heidenhain, Oppenheimer-Brownell, cognitive, and affective phenotypes have all been described as variants of sCJD (3), and there is still the possibility of encountering additional phenotypes of sCJD. The wide spectra of the disease's signs and symptoms make its diagnosis challenging.

This is the first case series of sCJD reported in Turkey. We report the clinical, electrophysiological, and imaging analyses of 10 patients diagnosed with sCJD during the last 8 years and draw conclusions about the applicability of the various tools in establishing an accurate diagnosis of sCJD.

Method

We screened all patients older than 18 years of age consecutively admitted to the Neurology Department of our university hospital between January 2000 and December 2008. A total of 10 patients (5 female and 5 male) of 8.259 hospitalized patients were diagnosed with sCJD. On the basis of the clinical information, the neurological examination, electroencephalography (EEG), radiological findings, and the presence of protein 14.3.3 in the cerebrospinal fluid (CSF), the patients were classified as clinically probable, possible, or "not" CJD based on the accepted case definition criteria for sCJD (2).

The classic CJD included patients with cognitive symptoms and ataxia but without visual impairments and affective symptoms during the first week of illness. Cases presenting with dementia, memory impairment, executive dysfunction, language impairment, and/or confusion in the absence of visual, cerebellar, and mood symptoms within the first week of illness were classified as the cognitive variant. Cases were classified as the Heidenhain variant if visual disturbances such as cortical blindness, oculomotor impairment, and/or visual hallucinations were documented within the first week of illness. The Oppenheimer-Brownell variant included cases that had ataxia within the first week of illness in the absence of cognitive and visual impairments. Patients who were reported as having symptoms of depression, mood lability, mania, hypomania, and/or anxiety within the first week of illness were classified as having the affective variant if they did not meet inclusion criteria for the Heidenhain group. Cases that could not be classified into one of the aforementioned groups were designated as indeterminate (3).

Standardized magnetic resonance imaging (MRI), which included T2-weighted axial, T1-weighted sagittal, T1-weighted sagittal with gadolinium, and proton density axial images, was performed for all patients.

Results

Eight patients had clinically probable CJD, and two showed the characteristic spongy changes in the brain associated with definite CJD (4). According to different sCJD phenotypes determined by Appleby et al. (3), four cases of classic CJD (cases 5, 6, 7, and 10) and four cases of the affective variant (cases 1, 3, 8, and 9) were diagnosed. One (case 4) was classified as the cognitive variant, and one (case 2) was in the indeterminate group. None of the patients were placed in the Oppenheimer-Brownell or the Heidenhain phenotype group.

The clinical, radiological, EEG, and CSF characteristics are presented in Table 1. The most common signs and symptoms were behavioral disturbances (n=4), cognitive decline (n=4), myoclonus (n=4), movement disorders (n=3), psychosis (n=3), aphasia (n=3), and focal neurological deficits (n=1). The number of female patients was equal to males.

The mean age at disease onset was 55 years. Four patients were hospitalized within 1 month, and three patients were hospitalized 1 to 3 months after the onset of complaints. The remaining three patients were hospitalized 3 months after the onset of complaints. Three patients died within 3 months of diagnosis, six died after 4 to 10 months, and one patient died 24 months after being diagnosed.

The investigative methods (EEG, CSF analysis, and cranial MRI) were carried out as soon as the patients were hospitalized (four patients within 1 month, three patients within 1 to 3 months, and three patients at 3 to 6 months of the disease). Nine patients (90%) had periodic sharp wave complexes (PSWCs) on their EEGs.

The pulvinar sign was present on the T2-weighted images in 5 of the 10 cases. Diffusion-weighted (DW) imaging, which was performed in two cases, also showed hyperintensities in the supratentorial gray matter (Figures 1,2).

With the exception of the two patients with increased CSF protein (20%), cytological and biochemical analysis of the CSF revealed no abnormalities. Seven patients, who underwent CSF analysis, tested positive for the protein 14.3.3.

The relatives of all the patients were offered brain biopsies. Only two patients' (Case 1 and 5) relatives accepted the biopsy procedure. The pathological specimens were evaluated both at the pathology department of our hospital and at the Institute of Neurology at the Medical University of Vienna, Austria.

Discussion

The presenting features of our patients were behavioral disturbances, cognitive decline, myoclonus, movement disorders, psychosis, aphasia, and focal neurological deficits. They were all similar to features of CJD reported in the literature (5).

CJD has been found to affect males and females equally, with a mean age at onset of 65 years (1). The mean age at disease onset in our patients was 55 years. Cases before 40 or after 80 years have been rarely reported (6,7). Age at symptom onset

Table 1. Characteristics and clinical and laboratory findings of the patients

Patient	Age (Year)	Signs & Symptoms at Onset	Duration of Symptoms (Months) and Outcome	Presentation and Neurological Findings	Cranial MRI	EEG	CSF	Functional Imaging (PET or SPECT)
Case 1 (MT)	57	Cognitive decline, behavioral disturbances, psychosis	7	No cooperation, agitated, Myoclonus (+)	Pulvinar sign	PSWCs	Normal microscopic and biochemical findings, 14.3.3 not performed	Not performed
Case 2 (KC)	44	Headache, dizziness, left hemiparesis, disturbed consciousness	8	Cooperation possible; right hemiparesis, Babinski sign, and myoclonus(+)	Diffuse cortical atrophy	PSWCs	Normal microscopic and biochemical findings, 14.3.3 (+)	Not performed
Case 3 (SC)	57	Cognitive decline, behavioral disturbances	24	Noncooperated, agitated	Hyperintensity in the right limbic system predominant in the parietal and temporal regions	PSWCs	Normal microscopy, slightly increased protein level, 14.3.3 (+)	Not performed
Case 4 (AY)	40	Behavioral disturbances, aphasia	6	Noncooperated, spasticity in all the extremities (+), increased DTRs with bilateral Babinski sign (+)	Gyral hyperintensity extending to both cerebral hemispheres	PSWCs	Normal microscopic and biochemical findings, 14.3.3 (+)	Not performed
Case 5 (GS)	57	Not conscious of surroundings, aphasia, movement disorders	1	No cooperation, myoclonus (+)	Pulvinar sign	Suppression burst activity, PSWCs	Normal microscopic and biochemical findings, 14.3.3 (+)	Not performed
Case 6 (HB)	67	Not conscious of surroundings, agitation	2	No cooperation	Cortical atrophy	PSWCs	Normal microscopic and biochemical findings, 14.3.3 (+)	PET: Global hypometabolism in cerebrum and cerebellum
Case 7 (MT)	46	Movement disorders, gait problems, psychosis	4	Cooperation possible, increased tonus in all extremities, bilateral Babinski sign (+)	Pulvinar sign	PSWCs	Increased protein and LDH, 14.3.3 not performed	SPECT: Decreased Tc-99 uptake in the right frontal interhemispheric region
Case 8 (FC)	56	Cognitive decline incoherent speech, movement disorders, psychosis	7	No cooperation, no motor lateralization. Bilateral Babinski (+)	Pulvinar sign, cortical atrophy, and hyperintensity	PSWCs	Normal microscopic and biochemical findings, 14.3.3 not performed	Not performed
Case 9 (MHS)	63	Echolalia, increased reaction time	10	Disorientation, echolalia (+), increased DTRs with bilateral Babinski sign (+)	Hyperintensity in the caudate nucleus bilaterally	PSWCs	Normal microscopic and biochemical findings, 14.3.3 (+)	Not performed
Case 10 (SO)	62	Aphasia, gait problems, psychosis	3	Disorientation, no cooperation, increased DTRs with bilateral Babinski sign (+)	Pulvinar sign in the basal ganglia bilaterally	Slow wave discharges consistent with severe encephalopathy	Normal microscopic and biochemical findings, 14.3.3 (+)	Not performed

Table legend: MRI: Magnetic resonance imaging, EEG: Electroencephalography, CSF: Cerebrospinal fluid, PET: Positron emission tomography, SPECT: Single photon emission computed tomography, PSWCs: Periodic sharp wave complexes

differed significantly between sCJD phenotypes (3). Among our cases, the ages at symptom onset for case 2 (the indeterminate group), case 4 (the cognitive variant), and case 7 (classic variant) were 44, 40, and 46 years, respectively.

Classic CJD cases were admitted to the hospital shortly after symptom onset (3). They also had the shortest median survival time. Cases 5, 6, 7, and 10 were admitted to the hospital 1 to 6 weeks after symptom onset, and they died within 1 to 4 months after symptom onset.

Figure 1. T₂-weighted (A, B) and fluid-attenuated inversion recovery (C, D) images show minimal intensity increases in the putamen and caudate nuclei; increased intensities are prominent in the caudate (arrowheads), putamen nuclei (small arrows), bilateral Sylvian regions and insula (big arrows) on T₂ (E, F) and fluid-attenuated inversion recovery (G, H) images acquired 3 months after.

Figure 2. T₂-weighted (A) image shows increased intensities in the putamen, caudate nuclei, and bilateral Sylvian regions. There are intensity increases in the bilateral caudate and putamen nuclei (small arrowhead) and cortex of the left cerebral hemisphere (long arrows) in the diffusion-weighted images (B,C). ADC (D) image shows hypointensity consistent with the diffusion restriction.

EEGs were performed in all the patients, and 90% had PSWCs on their first EEG; this has been accepted as one of the World Health Organization's (WHO's) diagnostic criteria of CJD. PSWCs may be generalized, lateralized, or focal. Nine of our patients had PSWCs on their EEGs. Patients with cortical hyperintensities in diffusion MRI also had PSWCs on their EEGs. In patients with striatal involvement, PSWCs may not be seen on EEG (8). The cranial MRI in case 10 revealed hyperintensity in the basal ganglia bilaterally. The EEG in this case showed generalized slow wave discharges without PSWC. Lateralized periodical epileptic discharges (PLEDs) have been reported at the end stages of the disease (6). However, none of our patients showed PLEDs on their EEGs. The reason for this may be the early recording time of the EEGs during the disease progression.

Routine analysis of CSF is normal and shows no evidence of inflammation. Slight elevation of protein is common, but this is usually below 100mg/dl (9,10). Two patients (cases 3 and 7; 20%) had increased CSF protein.

The protein 14.3.3 test provided a useful adjunct to the clinical and EEG data. The sensitivity and specificity of this protein, which is a reliable marker of rapid neuronal destruction, are about 93% and 84%, respectively (11). Some work has suggested that the specificity of the marker increases to 99% in definitively diagnosed cases (12). CSF 14.3.3 analyses of seven of our patients were positive.

Cranial MRI increases the sensitivity of the antemortem diagnosis of CJD. In most sCJD cases, MRI shows hyperintense signal changes in the caudate nucleus, putamen, globus pallidus, thalamus, and cerebral cortex on T₂-weighted, fluid-attenuated inversion recovery, proton density, and DW images. The pulvinar sign has diagnostic value for vCJD, but studies have also reported it in sCJD cases where it was accompanied by signal changes in other regions of the brain (13,14). A true pulvinar sign (consistent with variants of CJD) must be considered only if the high signal in the pulvinar is greater than the hyperintensity in the caudate and putamen nucleus.

Studies have also suggested that DW MRIs are more sensitive to changes specific to CJD, such as ribbon-like hyperintensities in the cerebral cortex (15,16,17,18). Hyperintense signals in the basal ganglia and the cortex observed bilaterally on cranial MRIs are the result of spongiosis and degeneration. We detected these hyperintensities in 2 of the 10 patients who had undergone DW imaging (cases 3 and 4). These changes showed up as abnormal metabolism and perfusion in positron emission tomography (PET) and single photon emission computed tomography (SPECT), respectively (19,20). In case 6, global hypometabolism was performed in PET, and in case 7, decreased Tc-99 uptake in the right frontal interhemispheric region was performed in SPECT. Only two of our patients (cases 2 and 6) had cortical atrophy on their MRI without accompanying hyperintensities in the basal ganglia and the cortex. These patients had PSWCs on their EEGs, and their CSF analyses were positive for the protein 14.3.3 test.

Prions, before neuroinvasion, are assumed to replicate in the lymphoreticular tissue. Positive staining of abnormal prion

protein in the tonsillar biopsy has been reported only in variants of CJD. However, our patients were diagnosed as having sCJD, thus, we did not perform a tonsillar biopsy, the use of which for antemortem diagnosis is still questionable. Tonsillar biopsy is not recommended routinely in cases with EEG appearances typical of sCJD, but it is useful in suspected cases whose clinical features are compatible with vCJD and when MRI does not show a bilateral pulvinar high signal (9,21).

A definitive diagnosis requires microscopic examination of the brain tissue (cerebral cortex, putamen, caudate nuclei, thalami, and molecular layer of the cerebellum) to detect the characteristic spongy changes associated with the disease (4). Two patients' relatives accepted the brain biopsy, and their brain specimens were compatible with a CJD diagnosis.

According to the WHO, clinical criteria for CJD depend on the number of symptoms a patient has. Clinical diagnosis may be probable or possible. Based on these clinical and microscopic criteria, eight of our patients had clinically probable CJD, and two had definite CJD. These two patients also met clinically probable CJD criteria. Considering the lack of history of traveling to age at the onset of symptoms, the rapid progression of the disease, results of investigations, and the short survival times, all of the patients were classified as having the sporadic form of CJD.

According to the different CJD phenotypes determined by Appleby et al. (3), case 2 might be classified as a cognitive variant of sCJD or as indeterminate. Admission to the hospital 3 months after symptom onset, a prolonged interval between illness onset and diagnostic testing, and more than 4 months of survival time were compatible with cognitive variants. However, a focal neurological deficit (left hemiparesis) is not a common feature of CJD, therefore, we classified this patient as indeterminate.

Case 10 had no PSWC on the EEG. This meant that Oppenheim-Brownel diagnosis was possible, but the presence of hyperintensity in the basal ganglia excluded this diagnosis. Absence of visual symptoms at onset made the Heidenhain variant diagnosis also impossible. The absence of PSWC on the EEG could be explained by the cranial lesion being localized only to the striatum (22).

The diagnosis of this rapidly progressing mortal disease is challenging. Based on our experience with ten patients with sCJD, we wish to emphasize the importance of clinical and laboratory investigations in the diagnosis of sCJD and of focusing on the different phenotypes of sCJD in light of the recent literature.

CJD should be considered in the differential diagnosis of patients with rapidly progressive dementia and neuropsychiatric symptoms. It is important to note the stage of the disease the when patient's symptoms begin. EEG and cranial MRIs are easily accessible methods in the hospitals in Turkey. However, CSF analyses of the 14.3.3 protein, the molecular analysis, and brain biopsies may need to be performed at specific centers. Considering all these factors will help in diagnosing a patient in the context of the wide spectra of CJD.

All patients suspected of having CJD in Turkey are reported to the Ministry of Health. However, there are no data regarding the analysis of these patients. Instead, knowledge of CJD is dependent on case reports (8,23,24,25). Our study is the first to review and report on the diagnosis and analysis of patients with sCJD in Turkey. This study may serve as the first step toward a nationwide review of the data of all patients referred to the Ministry of Health and the establishment of an investigative protocol for suspected CJD cases in Turkey.

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References

1. Johnson RT. Prion diseases. *Lancet Neurol* 2005; 4:635-642.
2. World Health Organisation. Consensus on criteria for diagnosis of sporadic CJD. *Wkly Epidemiol Rec* 1998; 73:361-365.
3. Appleby BS, Appleby KK, Crain BJ, Onyike CU, Wallin MT, Rabins PV. Characteristics of established and proposed sporadic Creutzfeldt-Jakob disease variants. *Arch Neurol* 2009; 66:208-215.
4. WHO. Creutzfeldt-Jacob Disease, WHO Recommended Surveillance Standards. Geneva 1999; 35-38.
5. Bergui M, Bradac GB, Rossi G, Orsi L. Extensive cortical damage in a case of Creutzfeldt-Jacob disease: clinico-radiological correlations. *Neuroradiology* 2003; 45:304-347.
6. Brown P, Gibbs CJ Jr, Rodgers-Johnson P, Asher DM, Sulima MP, Bacote A, Goldfarb LG, Gajdusek DC. Human spongiform encephalopathy: the National Institutes of Health Series of 300 cases of experimentally transmitted disease. *Ann Neurol* 1994; 35:513-529.
7. Will RG, Matthews WB. A retrospective study of Creutzfeldt-Jacob disease in England and Wales 1970-79, I: clinical features, *J Neurol Neurosurg Psychiatry* 1984; 47:134-140.
8. Akcali A, Saygili O, Karaoglan I, Neyal M. EEG in diagnosing Heidenhain variant of probable sporadic Creutzfeldt-Jakob disease. *Archives of Neuropsychiatry* 2011; 48:71-74.
9. Prabhakar S, Bhatia R. Diagnosis of Creutzfeldt - Jakob disease. *Neurol India* 2001; 49:325-328.
10. Olsson JE. Brain and CSF proteins in Creutzfeldt-Jakob disease. *Eur Neurol* 1980; 19:85-90.
11. Zerr I, Pocchiari M, Collins S, Brandel JP, de Pedro Cuesta J, Knight RS, Bernheimer H, Cardone F, Delasnerie-Lauprêtre N, Cuadrado Corrales N, Ladogana A, Bodemer M, Fletcher A, Awan T, Ruiz Bremón A, Budka H, Laplanche JL, Will RG, Poser S. Analysis of EEG and CSF 14.3.3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. *Neurology* 2000; 55:811-815.
12. Hsich G, Kenney K, Gibbs CJ, Lee KH, Harrington MG. The 14-3-3 brain protein in cerebrospinal fluid as a marker for transmissible spongiform encephalopathies. *N Engl J Med* 1996; 335:924-930.
13. Kallenberg K, Schulz-Schaeffer WJ, Jastrow U, Poser S, Meissner B, Tschampa HJ, Zerr I, Knauth M. Creutzfeldt-Jakob disease: Comparative Analysis of MR Imaging Sequences. *ANJR Am J Neuroradiol* 2006; 27:1459-1462.
14. 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.
15. Demaerel P, Heiner L, Robberecht W, Sciort R, Wilms G. Diffusion-weighted MRI in sporadic Creutzfeldt-Jakob disease. *Neurology* 1999; 52:205-208.

16. Ukisu R, Kushihashi T, Tanaka E, Baba M, Usui N, Fujisawa H, Takenaka H. Diffusion-weighted MR imaging of early-stage Creutzfeldt-Jakob disease: typical and atypical manifestations. *Radiographics* 2006; 26:191-204.
17. Ukisu R, Kushihashi T, Kitanosono T, Fujisawa H, Takenaka H, Ohgiya Y, Gokan T, Munechika H. Serial diffusion-weighted MRI of Creutzfeldt-Jakob disease. *AJR Am J Roentgenol* 2005; 184:560-566
18. Yi SH, Park KC, Yoon SS, Kim EJ, Shin WC. Relationship between clinical course and Diffusion-weighted MRI findings in sporadic Creutzfeldt-Jakob Disease. *Neurol Sci* 2008; 29:251-255.
19. Sunada I, Ishida T, Sakamoto S, Tsuyuguchi N. A discrepancy between Tc-99m HMPAO SPECT and Tc-99m ECD SPECT in Creutzfeldt-Jacob disease. *J Clin Neurosci* 2004; 11:648-695.
20. Matsuda M, Tabata K, Hattori T, Miki J, Ikeda S. Brain SPECT with 123I-IMP for the early diagnosis of Creutzfeldt-Jakob disease. *J Neurol Sci* 2001; 183:5-12.
21. World Health Organization. Global surveillance, diagnosis and therapy of human transmissible spongiform encephalopathies: report of a WHO consultation. Geneva, Switzerland.1998.
22. Kher M, Rao MY, Acharya PT, Mahadevan A, Shankar SK. Heidenhain variant of Creutzfeldt-Jakob disease: An autopsy study from India. *Ann Indian Acad Neurol* 2009; 12:48-51.
23. Guven H, Comoglu S, Yaman S. Probable Creutzfeldt-Jakob Disease. *Turkish Journal of Geriatrics* 2006; 9:182-187.
24. Sen A, Gunaydin S, Ulker M, Arpacı B. Creutzfeldt-Jakob Disease: Two Cases. *Turkish Journal of Neurology* 2006; 12:50-58.
25. Oz B, Ersoy G, Demirkesen C. Creutzfeldt-Jakob Disease: Autopsy Presentation and Review of Literature. *Cerrahpaşa J Med* 2000; 31:42-48.