Creutzfeldt-Jakob Disease Presenting with Visual Blurring, Diplopia and Visual Loss: Heidenhain's Variant

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Abstract

Focal electroencephalographic abnormalities as described in Heidenhain's variant of Creutzfeldt-Jakob disease are uncommon. We report a 73-year-old male presenting with visual symptoms, right hemianopia and rapidly progressive dementia. Myoclonus was synchronous with generalised periodic epileptiform discharges on electroencephalography (EEG). In addition, there were periodic focal sharp waves at the left occipital region. Diffusion-weighted magnetic resonance brain images showed slightly increased signal intensity in the occipital parasagittal area, left more than right. 14-3-3 protein was detected in the cerebrospinal fluid. The patient died within 5 months of presentation.

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Key words: 14-3-3 protein, Dementia, Focal periodic sharp waves, Hemianopia, Myoclonus

Introduction

The electroencephalographic pattern is distinctive in many but not in all patients with Creutzfeldt-Jakob disease (CJD).[1] Often, it is one of diffuse and non-specific slowing in the background with stereotypical generalised periodic high-voltage slow and sharp wave complexes.

We report a patient with Heidenhain's variant of CJD in whom electroencephalography (EEG) demonstrated focal periodic sharp waves over the left occipital region.

Case Report

A 73-year-old man complained of visual blurring, monocular diplopia and sudden visual loss in July 1997. A thorough ophthalmological assessment revealed no visual defect. Nine days later, he was reviewed at a psychiatric clinic for anxiety, and was noticed to have slurred speech and poor co-ordination of his right hand. Initial investigations, including computed tomographic (CT) scan and magnetic resonance imaging (MRI) of the brain, were normal. However, his mental state deteriorated rapidly as he became increasingly agitated, incoherent and paranoid over the two weeks that followed. He was then discovered to have a right hemianopia. Attempts to control his psychiatric symptoms with benzodiazepines, anti-psychotic and anti-depressive agents were unsuccessful.

On admission to the hospital, examination revealed a profoundly demented patient. He was febrile, restless, and unresponsive to questions. There was severe rigidity, and myoclonic jerks were seen in the limbs, more on the left than right. His vital signs were stable. In view of the fever, rigidity, drowsiness and the recent use of anti-psychotic agents, he was diagnosed to have neuroleptic malignant syndrome and treated with bromocriptine and dantrolene.

The cerebrospinal fluid (CSF) examination was normal. Toxicology screen was unremarkable. There was leukocytosis with total white cell count at 14,700 per cubic mm. Creatine kinase was elevated at 407 U/L; it rose to 1184 U/L on Day 2 of admission before declining to 92 U/L on Day 7. A repeat CT scan of the brain was normal. MRI of the brain with diffusion studies (Fig. 1) revealed slightly increased signal intensity in the occipital parasagittal area, left more than right.

His fever settled rapidly within 48 hours. However, he remained drowsy with no verbal output. There was less rigidity, but myoclonic jerks persisted. The initial EEG, obtained seven weeks after presentation, revealed the following findings:

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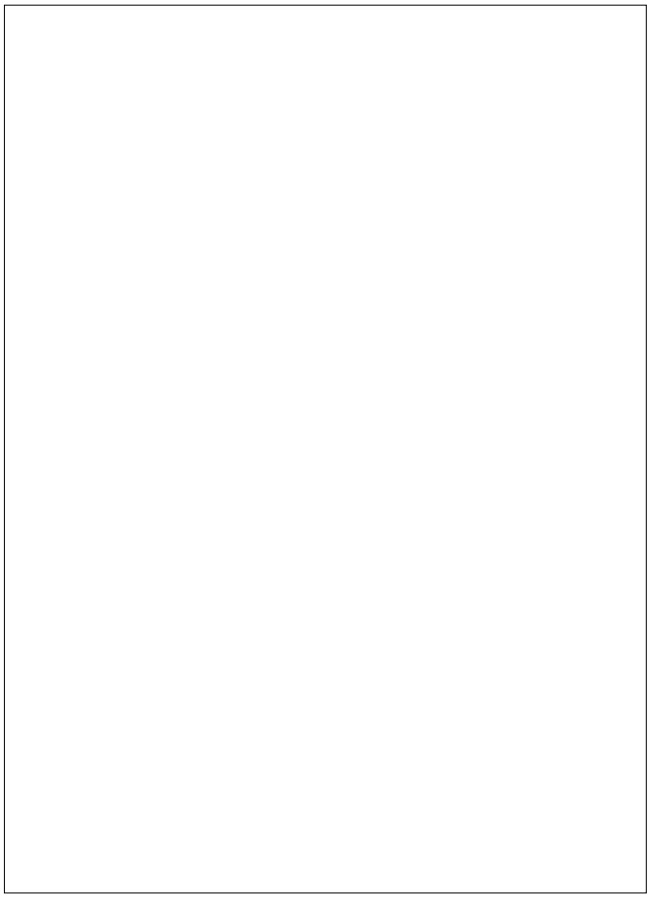

Fig. 1. Diffusion-weighted magnetic resonance brain imaging showing slightly increased signal intensity in the occipital parasagittal area, left more than right.

1) background slow activity of 6 Hz,
2) continuous diffuse slow activity of 1 to 2 Hz, and
3) generalised periodic (one per second) epileptiform discharges which were synchronous with the myoclonus.

In addition, focal periodic (one per second) sharp waves were also recorded over the left occipital region (Fig. 2). This correlated with the area of increased signal intensity on MRI.

During the next one week, when the patient was on phenytoin and phenobarbitone, the EEG showed suppression of background activity and attenuation of the focal sharp waves, although the generalised periodic epileptiform discharges persisted.

He remained unresponsive and the myoclonic jerks continued until he died 5 months after initial presentation. The CSF for 14-3-3 protein was positive. The patient's family refused consent for either brain biopsy or post-mortem.

Discussion

Creutzfeldt-Jakob disease is a rare, rapidly progressive and fatal disease of the central nervous system caused by a transmissible agent designated as

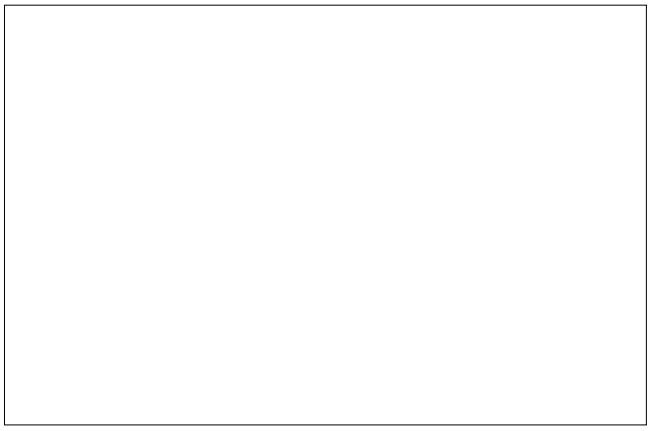

Fig. 2. Electroencephalogram showing focal periodic sharp waves over the left occipital region.

proteinaceous infectious agent (prion).[2] A great variety of clinical manifestations has been described although it is a condition characterised by myoclonus and rapidly progressive dementia. According to a clinical analysis by Brown et al in 1986,[3] 36% of 230 patients presented with exclusively neurological symptoms which were predominantly cerebellar or visual, although as high as one third of the patients had non-specific prodromal symptoms. Therefore, this may pose many a diagnostic dilemma, as is illustrated in our patient.

His initial visual symptoms and subsequent right hemianopia could mimic either a space occupying lesion in the occipital lobe or a cerebrovascular event in the similar territory. The psychiatric symptoms including agitation, anxiety, depression and paranoia could be part of paranoid psychosis, a condition not uncommonly encountered in the elderly, although the rapid deterioration was alarming. The presence of jerking movements in a confused and drowsy patient could also suggest status epileptitus.

The EEG abnormalities associated with CJD are characteristic and consist of diffuse slowing of background rhythm with periodic sharp waves occurring at 0.5 to 2.0 per second as were seen in our patient. The presence of focal periodic sharp waves over the left occipital region in our patient was uncommon, though not unusual. In fact, Furlan et al[4] described serial EEGs obtained during a six-week period from a patient with Heidenhain's variant of CJD with focal periodic complexes that at no time became generalised. This variant was reported by Heidenhain,[5] and subsequently by others,[6] who in 1929 first described three patients with the onset of dementia at an early age, two of whom also had cortical blindness.

Over the years, various diagnostic tests have been developed including examination of the CSF for 14-3-3 protein,[7] Tau-protein,[8] S-100 protein[9] and Neuron Specific Enolase.[10] Zerr et al[11] reported high levels of sensitivity and specificity with the detection of 14-3-3 protein in the cerebrospinal fluid for the diagnosis of CJD. The

14-3-3 proteins are a group of highly conserved proteins involved in the regulation of protein phosphorylation and the mitogen-activated protein kinase pathway. The positive predictive value is reportedly 94.7% and the negative predictive value 92.4%. False positive results in CSF analysis were seen in patients with herpes simplex encephalitis, hypoxic brain damage, atypical encephalitis, intracerebral metatases of a bronchial carcinoma and metabolic encephalopathy—all of which were excluded in this patient.

Bahn et al[12] first reported in 1997 the presence of markedly increased signal intensity in the caudate nuclei, putamina, thalami, cingulate gyri and right inferior frontal cortex on diffusion-weighted magnetic resonance brain images. In our patient, the MRI with and without contrast was normal. Diffusion-weighted images, however, demonstrated slightly increased signal intensity in the occipital parasagittal area, left more than right. This corresponded with the visual symptoms, right hemianopia, as well as focal periodic sharp waves over the left occipital region on the EEG.

Hence, in the setting of a patient with rapidly progressive dementia, the presence of visual symptoms and myoclonus, together with focal periodic discharges on EEG, the diagnosis of CJD (Heidenhain's variant) must be considered. The detection of 14-3-3 protein in the CSF would further add weight to the diagnosis, although neuropathological verification remains the gold standard for diagnosis.

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