Three Cases of Creutzfeldt-Jakob Disease with Visual Disturbances as Initial Manifestation

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Abstract
We report our findings in 3 cases of Creutzfeldt-Jakob disease (CJD) with visual disturbances as the initial manifestations. These cases were found to have the Heidenhain variant of CJD. Two cases initially presented with progressively blurred vision and homonymous hemianopia. The other case initially presented with blurred vision and a decrease in the central sensitivity in both eyes. These 3 cases developed neurological symptoms about 4 weeks after the onset of visual symptoms. All were diagnosed with the Heidenhain variant of CJD based on the clinical course and confirmed by positive assays of the cerebrospinal fluid for the 14-3-3 protein and tau protein. In addition, the diagnosis was confirmed by the findings of diffusion-weighted magnetic resonance imaging and electroencephalography. Patients can present with isolated visual symptoms which precede a decline in cognition by weeks due to the predominant-ly occipital lobe disease. The 3 patients were referred to the neurology department within 1 month of onset. The early diagnosis was necessary to avoid spread of the infection. In cases of suspected CJD, it is important to consult a neurologist quickly to make a definitive diagnosis.
of CJD. Ophthalmologists should be aware that visual impairments may be the first indication of CJD.

Introduction

Creutzfeldt-Jakob disease (CJD) is a rapidly progressive neurodegenerative disease characterized by dementia, myoclonus, and other neurological signs [1, 2]. CJD is a transmissible spongiform encephalopathy caused by prions which are proteinaceous infectious particles [3]. Although CJD may be transmitted iatrogenically or genetically, 80–90% of cases are sporadic CJD for which the cause is not determined. Visual symptoms are reported to be present in at least 20% of patients with CJD [4, 5], and the typical neurological signs are not always present at the early stage of CJD. A subclass of patients with CJD present with isolated visual symptoms which persist even without any cognitive decline for a few weeks. These cases are known as the Heidenhain variant of CJD [1, 3, 6].

We reviewed the medical records of 12 patients with CJD who were diagnosed at Urayasu Hospital, Juntendo University, Chiba between January 2007 and December 2018. There were 3 cases of CJD with visual disturbances as the initial manifestation among the 12 patients with CJD. We report our findings in these 3 cases with the Heidenhain variant of CJD.

Case Reports

Case 1

A 61-year-old man visited our clinic and reported progressive blurring of his vision with visual field defects of 3 weeks’ duration. At his initial examination he had no systemic problems and no history of major surgery or blood transfusions. There was no history of hypertension, diabetes mellitus, or any other major medical or surgical illnesses. His visual acuity was 20/40 OD and 20/25 OS, but he had left homonymous hemianopia (Fig. 1a). The results of ocular examination were normal except for a slight cortical cataract in both eyes. Optical coherence tomography of both eyes was normal. Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain were normal. The second medical examination 2 weeks later showed that his visual acuity had decreased and the visual field defects had worsened (Fig. 1b). These ocular changes were accompanied by a progression of dysarthria and gait disorder. His visual acuity had decreased to 20/400 OD and 20/200 OS and the left homonymous hemianopia had worsened. The amplitude of the b-wave of electroretinogram (ERG) was reduced (Fig. 1c). He was admitted to our neurology department for more detailed examinations.

Biochemical blood investigations including hemogrophy, random blood sugar, renal and liver function tests, thyroid profile, and serum vitamin B12 levels were normal. Electroencephalography (EEG) revealed periodic sharp wave complexes, and cerebrospinal fluid (CSF) analyses were positive for surrogate markers of neurodegeneration, i.e., 14-3-3 protein >2,440 pg/mL and total tau protein 5,775.6 pg/mL with a normal range of 80–350 pg/mL. Prion seeding activity was determined by RT-QuIC. Diffusion-weighted MRI (DWI) of the brain
showed high signal intensity in the cortex and occipital lobes on the right side (Fig. 1d), and the EEGs showed periodic synchronous discharges (PSDs) with myoclonic jerks suggestive of CJD.

In view of the rapidly progressive dementia associated with myoclonus, a tentative diagnosis of CJD was made. The visual symptoms preceded the dementia, and hence a Heidenhain variant of CJD was strongly suspected. Nine days after his hospitalization, the patient progressed to severe dementia, urinary disturbances, and an eating disorder.

Case 2

A 65-year-old man presented with deteriorating vision, and he reported that his vision was "fogging up." He was examined at another ophthalmological clinic but no abnormality was identified. He continued complaining of blurred vision for about 1 month and the blurred vision was accompanied by progression of his dementia. The signs were left unilateral spatial neglect, myoclonus, gait disorder, and drowsiness. At his initial examination, his visual acuity was 20/40 in both eyes, and the central sensitivity of his visual fields was decreased in both eyes (Fig. 2).

The results of our ocular examination were normal except for slight cortical cataracts in both eyes. He was admitted to our neurology department for more detailed examinations. DWI of the brain showed high signal intensity in the right temporal and parietal lobe, and EEG showed PSDs with myoclonic jerks suggestive of CJD. CSF analysis was positive for surrogate markers of neurodegeneration, i.e., 14-3-3 protein >3,833 pg/mL and total tau protein 3,620 pg/mL.

The patient progressed to drowsiness and severe dementia. He was not cooperative enough for his visual acuity to be measured. He developed pyramidal signs, myoclonus, as well as akinetic mutism and became bedbound for the last month. These clinical findings were consistent with the Heidenhain variant of CJD.

Case 3

A 77-year-old man visited our clinic because of progressive blurring of his vision of 1 month's duration. He and his family hoped for him to have cataract surgery. At the time of his initial examination, he had no systemic problems although his visual acuity was 20/600 OD and 20/400 OS, and he had right homonymous hemianopia (Fig. 3). The results of ocular examination were normal except for cortical cataracts in both eyes. One week later, he developed myoclonus, confusion, and short-term memory difficulty. During the course of his illness, he developed monotonic speech which gradually progressed to akinetic mutism and severe bradykinesia. He was admitted to our neurology department for more detailed examinations. DWI of the brain showed high signal intensity in the cortex and occipital lobes bilaterally, and EEG showed PSDs with myoclonic jerks suggestive of CJD. CSF analysis was positive for surrogate markers of neurodegeneration, i.e., 14-3-3 protein >3,220 pg/mL and total tau protein 2,200 pg/mL.

Fourteen days after his hospitalization, the patient progressed to severe dementia, urinary disturbance, and eating disorder. He became bedbound for the last month. The clinical findings were consistent with the Heidenhain variant of CJD.
Discussion

The findings of these 3 cases are summarized in Table 1. Our patients initially presented with visual symptoms, although the most common clinical manifestations of CJD are progressive cognitive decrease, dementia, myoclonus, and ataxia. The results of the ocular examination in the 3 patients were normal except for a slight cortical cataract in both eyes. It was thought that their degree of cataract alone could not entirely account for their visual loss. Cases 1 and 3 initially presented with progressively blurred vision and homonymous hemianopia. Case 2 initially presented with blurred vision and decreased central sensitivity in both eyes. This is consistent with the Heidenhain variation of CJD. The Heidenhain variant of CJD persists even without any cognitive decline for a few weeks [1]. All 3 cases had also developed neurological symptoms after about 4 weeks from the onset of the visual symptoms. The presenting clinical features in patients with the Heidenhain variant of CJD consisted of visual field defects, abnormal color vision, abnormal visuospatial perception, visual hallucinations, visual neglect, cortical blindness, visual agnosia, and rarely isolated eye movement abnormalities [1, 2, 6]. Patients may initially complain of vague visual disturbances and may subsequently give up reading, watching television, and such activities [3]. The patients then develop rapidly progressing dementia and death usually occurs within 12 months [1, 2, 7].

Our 3 patients were referred to the neurology department within 1 month of onset. DWI is a more sensitive method for detecting brain abnormalities in the early stage of CJD than traditional neuroimaging, including CT and routine MRI (T1, T2, and FLAIR). This is probably due to cellular lysis and membrane disruption [3]. CT scans and routine MRI of the brain were normal in the early stage of case 1, as it is in about 21% of cases [5, 8]. Therefore, when routine primary tests are negative, DWI is the neuroimaging choice for the diagnosis of CJD. MRI in our cases showed high intensities in the occipital cortex on DWI.

The CSF assay for the 14-3-3 protein and the tau protein NSE is useful for the diagnosis of CSF [9, 10]. However, it may be negative in some patients with pathologically confirmed CJD. The 14-3-3 assay is also not specific for CJD, and it may be positive in patients with stroke, hypoxic ischemic injury, and herpes encephalitis in cases with neuronal death [3]. The specificity of this finding may be as high as 95%, but the sensitivity varies from 45 to 85% [4]. All of our cases were positive for the 14-3-3 protein and the tau-protein. CSF assays for the 14-3-3 protein and the tau protein, if positive, may also aid in the diagnosis of patients in whom suspicion for CJD is high.

The characteristic triad of dementia, myoclonus, and abnormal EEGs may not be present in as many as 25% of patients with the Heidenhain variant of CJD [5]. The characteristic changes in the EEG of patients with CJD are periodic sharp wave complexes which are present in 70% of the patients. Our cases showed such periodic triphasic complexes in the EEGs. A total of 15.1% of patients show only a diffuse slowing of the EEGs [10].

Some studies reported that the ERG may be a useful adjunctive test in cases of suspected CJD [11, 12]. Patients with CJD have been found to have a reduction in the b-wave amplitude of the ERGs. This abnormality is most likely related to the degenerative changes in the outer plexiform layer and Müller cells [11]. Although a decrease in the b-wave amplitude is not specific for CJD, the magnitude of this finding may be correlated with the progressive reduction in the b-wave amplitude during the course of the disease. ERG abnormalities may appear
before the emergence of characteristic EEG findings in CJD, particularly among patients with visual symptoms [3].

CJD affects vision in various ways. The selective reduction of the b-wave of the ERGs indicates a retinal involvement, but the visual disturbances may occur without any retinal alterations. Optical coherence tomography and fundus examinations of the retina in our cases showed no abnormalities. The variations in the clinical manifestations were probably caused by the different locations of the accumulations of pathogenic prion protein in the nervous system [12]. It has been reported that 19% of cases of classic CJD show visual signs and symptoms at the onset of the disease, 32% show signs and symptoms at the patients’ first visit to an ophthalmology department, and 42% show signs and symptoms at some point during the course of the disease [11, 12]. In addition, 3.7% of CJD patients had isolated visual symptoms at onset, and 77% of these patients initially visited an ophthalmologist [6]. In these patients, CJD was diagnosed by the ophthalmologist.

Patients with the Heidenhain variant of CJD present with isolated homonymous hemianopsia or other visual disturbances, often in the absence of specific MRI, EEG, and laboratory abnormalities. About 25% of patients with the Heidenhain variant of CJD may lack the characteristic triad of dementia, myoclonus, and abnormal EEGs [5]. This rare group can cause diagnostic difficulties.

In a United Kingdom study, patients with the Heidenhain variant constituted 40% of all sporadic CJD patients who had undergone ophthalmic surgery [13, 14]. Early visual impairments due to prion diseases would prompt ophthalmologists to perform surgery. Hamaguchi et al. [14] reported that in 1.8% of patients with prion disease, eye tissues were operated on within 1 month before the onset of the prion disease or after the onset. There were no patients with sporadic CJD who underwent eye surgery in our hospital. Ophthalmologists should use disposable instruments whenever possible to avoid cross-contamination.

The Heidenhain variant of CJD must be considered a differential diagnosis in all patients who present with isolated visual complaints and either normal conventional brain neuroimaging or findings that do not completely correlate with the signs and symptoms. In such patients, DWI and FLAIR MRI may reveal early cortical changes. CSF assays for the 14-3-3 protein and tau protein, if positive, may also aid in the diagnosis for patients in whom the degree of suspicion for CJD is high.

An early diagnosis is desirable for avoiding the fear of infection in CJD. In suspected CJD patients, it is important to consult the neurology department quickly for an exact diagnosis of CJD. Ophthalmologists should be aware that visual impairments may be the first indication of CJD.

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Statement of Ethics

This case report was conducted according to good clinical practice. The authors state that they have full control over all primary data and have no ethical conflicts to disclose.

Disclosure Statement

The authors indicate no financial support or financial conflict of interest.

Author Contributions

Involved in design and conduct of the study: T. Sakuma and A. Mizota; collection, management, analysis, and interpretation of the data: T. Sakuma, S. Watanabe, A. Ouchi, and Y. Sakanishi; preparation, review, or approval of the manuscript: T. Sakuma, S. Watanabe, A. Ouchi, Y. Sakanishi, A. Mizota, and N. Ebihara.

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Fig. 1. a–d Goldmann visual field tests. Dark-adapted bright flash ERGs and DWI in case 1. a The visual field at the first examination was left homonymous hemianopia. b The visual acuity and visual field defect has worsened on the next medical examination after 2 weeks. c The b-wave amplitude of ERG was reduced. d The DWI showed high signal intensity in the cortex and occipital lobes on the right side (arrows). DWI, diffusion-weighted magnetic resonance imaging; ERG, electroretinogram.

Fig. 2. Goldmann visual field test in case 2. The central sensitivity of visual fields was slightly depressed in both eyes.
Fig. 3. Humphrey visual field test in case 3. The visual field testing showed right homonymous hemianopia, and the right eye was especially poor.

Table 1. Summarized data of the Heidenhain variant of 3 CJD cases

| Case | Sex and age | Initial visual symptom | Initial visual acuity | Time of referring to neurology from onset of visual symptoms | DWI findings | Time to onset of neurological symptoms from onset | CSF (14-3-3/tau) | EEG | ERG |
|------|-------------|------------------------|-----------------------|-------------------------------------------------------------|--------------|-----------------------------------------------|-----------------|-----|-----|
| Case 1 | male, 61 years | progressively blurred vision and visual field defect (left homonymous hemianopia) | 20/40 OD | 5 weeks | high signal intensity in the cortex and occipital lobes on the right side | 5 weeks | +/- |
| Case 2 | male, 65 years | blurred vision and visual field defect (central sensitivity down in both eyes) | 20/25 OS | 4 weeks | high signal intensity in the right temporal lobes and the parietal lobe | 5 weeks | +/- |
| Case 3 | male, 77 years | progressively blurred vision and visual field defect (right homonymous hemianopia) | 20/40 OD | 5 weeks | high signal intensity in the cortex and occipital lobes bilaterally | 5 weeks | +/- |

CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; DWI, diffusion-weighted magnetic resonance imaging; EEG, electroencephalography; ERG, electroretinogram; PSD, periodic synchronous discharge.