# The Value of Magnetic Resonance Imaging in the diagnosis of Heidenhain Variant of Creutzfeldt-Jakob disease CJD

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## Case 1

An 87 year old right handed woman presented with progressive loss of vision over the course of two months. She had been fully independent, despite having a mild degree of macular degeneration for years prior to the presenting illness. She was evaluated by ophthalmology and her visual loss was blamed on her macular degeneration. Six weeks after the onset of visual symptoms she started to decline cognitively, with impaired attention, orientation, memory, and word finding. She was admitted to the hospital twice over the course of two weeks because of confusion and functional deterioration. Workup included laboratory tests for metabolic encephalopathy and brain magnetic resonance imaging (MRI). She was found to have a urinary tract infection and was treated with antibiotics. When no improvement was noted, an electroencephalogram (EEG) was obtained, which showed marked slowing and bitemporal sharp waves. She was transferred to our facility for further evaluation. On examination, she was afebrile, sleepy, disoriented, inattentive, inconsistently followed simple commands, disinhibited, and irritable. Her visual acuity was difficult to assess, but it seemed she could still perceive light. Pupils were reactive and there was no ophthalmoplegia. Her motor examination was normal. There were no adventitious movements. The deep tendon reflexes were normal and the plantar response was flexor. A snout reflex was elicited. No limb ataxia was noted. Repeat brain MRI was done and was read as negative (figure 1). Repeat EEG showed multifocal delta-theta background activity with bursts of periodic diffuse spike-wave discharges. Cerebrospinal fluid (CSF) analysis showed no evidence of infection or inflammation. Neuron specific enolase (NSE) was 28 ng/mL (normal<15; indeterminate 15-30; high>30). At this point the diagnosis of probable CJD - Heidenhain type was made. Retrospective review of brain MRI showed diffusion restriction in the parieto-occipital cortex (cortical ribbon sign). There were no corresponding apparent diffusion coefficient or T2 weighted imaging (T2WI) changes. (Figure 1)

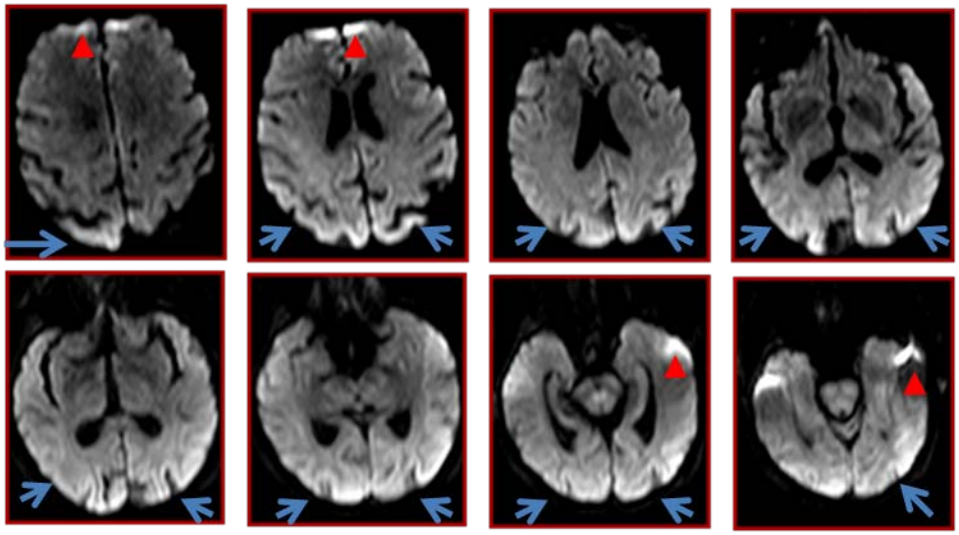


Figure 1: DWI obtained 6 weeks after symptom onset, showing restricted diffusion in the parietal and occipital cortex, the cortical ribbon sign (blue arrows.) Corresponding FLAIR and T2 images did not show changes. The hyperintense changes in the frontal pole and anterior temporal lobes are artifacts (red arrow heads.)

Over the following 10 days, she gradually became more obtunded, developed global aphasic, paratonia, brisk reflexes (including brisk jaw reflex), decorticate posturing, and myoclonus. She was eventually discharged to a hospice facility where she died one month later. The family refused an autopsy.

**Case 2**

A 67 year old right handed salesman was referred by ophthalmology for further evaluation of rapidly progressive loss of vision of four weeks duration. The patient reported loss of peripheral vision, decreasing visual acuity, optical hallucinations (intermittent grey translucent spots), and metamorphopsia (straight lines seen as broken). Two weeks after symptom onset, he was evaluated by a neurologist who performed a battery of investigations consisting of basic labs, erythrocyte sedementation rat, CSF analysis (NSE was not included), and visual evoked potential (VEP). All tests were unremarkable except for a mild symmetric increase in P100 on VEP. Subsequently, MRI of the brain and the entire spinal cord was obtained and was reported as showing only age appropriate changes. One week later, the patient developed gait unsteadiness and cognitive decline. He became

inattentive, had word finding difficulties, and developed apraxia. His primary care provider attributed some of his symptoms to anxiety and prescribed an anxiolytic. When he presented to our facility, he was fully awake and alert but significantly inattentive. Recent recall and executive functions were impaired. He had mild expressive aphasia. He was able to see and track, but had difficulty reading from a Snellen chart, and visual acuity could not be quantified. There was no ophthalmoplegia, and the pupils were reactive. There were no changes in muscle tone or power. Bilateral mirror movements were observed in both upper and lower extremities and were more pronounced on the left side. The left upper extremity also exhibited alien limb like features, which the patient was able to suppress. His deep tendon reflexes were normal. A snout reflex was present. Superficial and deep sensations were intact. There were signs of cortical sensory impairment, particularly, graphesthesia. He had bilateral upper and lower limb ataxia, as well as truncal and gait ataxia. EEG showed diffuse background slowing. CSF analysis showed no evidence of infection or inflammation. NSE was elevated at 44 ng/mL. Retrospective review of the brain MRI showed the same diffusion restriction pattern as described in Case 1 (figure 2).

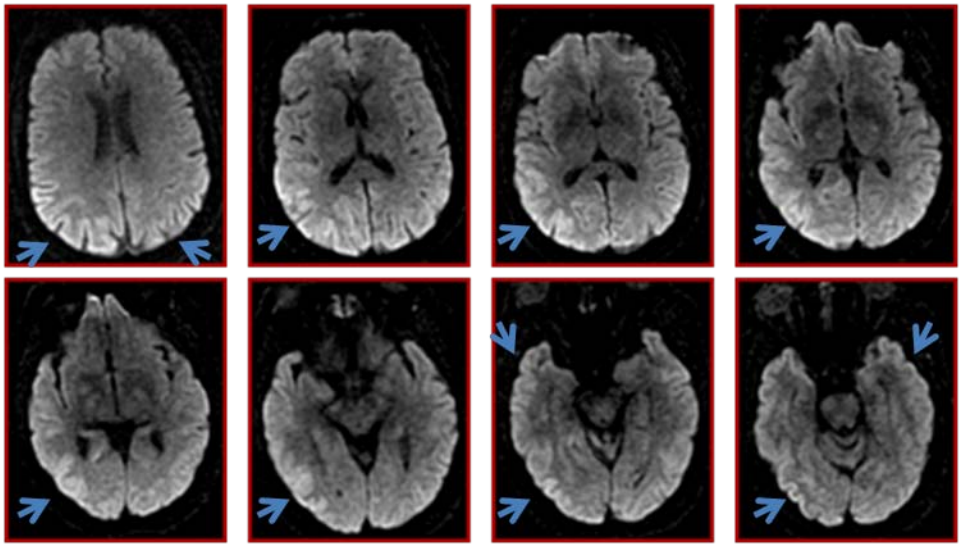


Figure 2: DWI obtained 3 weeks after symptom onset, showing restricted diffusion in the parietal and occipital cortex, the cortical ribbon sign (blue arrows). Corresponding FLAIR and T2 images did not show changes.

His condition rapidly declined. Within 10 days he developed rapid loss of short and long term memory, disorientation, incontinence, brisk reflexes, grasp reflex, myoclonus, akinetic mutism, complete cortical blindness and seizures. The patient died 6 weeks from symptom onset. Autopsy was performed and confirmed the diagnosis of CJD.

## Discussion

CJD is a rapidly progressive, invariably fatal, dementing illness that is caused by a conversion of a normally existing cellular prion protein to an abnormal isoform which ultimately triggers neuronal death. The abnormal prion can be transmitted from one neuron to another. The neuronal loss leads to vacuolation, which gives the affected brain the characteristic 'spongiform' appearance. The first cases were described by Hans Gerhard Creutzfeldt and Alfons Jakob in the early 1920's. Based on the mechanism of transmission, CJD can be divided into four subtypes: sporadic (83%), familial (14%), iatrogenic (< 1%) and variant CJD (< 1%). [1] Six phenotypes have been identified based on the initial presentation: cognitive, visual (Heidenhain's variant), affective, classic, ataxic (Oppenheimer-Brownell variant) and indeterminate. [2] The World Health Organization (WHO) diagnostic criteria are the most commonly used for diagnosis (Table 1). [3] Early pre-mortem diagnosis is important to avoid iatrogenic transmission and to identify patients for early intervention when therapies become available.

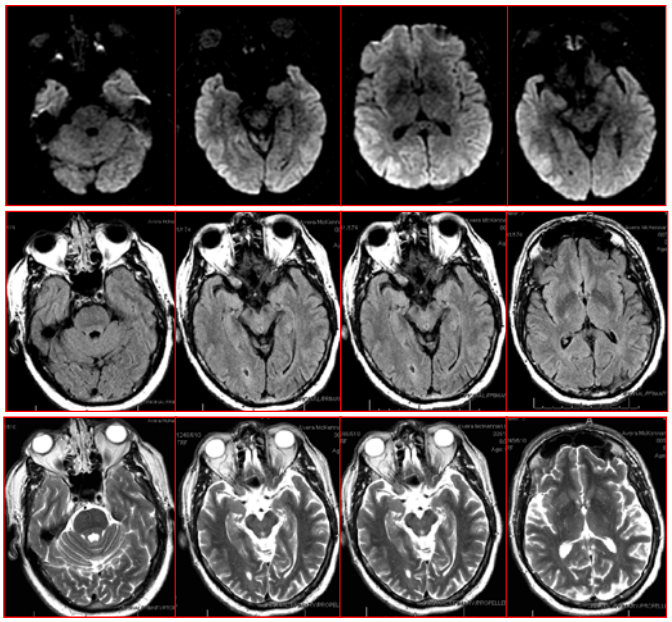
In the late 1920's, Heidenhain described a similar syndrome to what Creutzfeldt and Jakob described with the leading symptom being visual disturbance and with the spongiform changes observed mainly in the parietal and occipital cortex. [4] In 1954, Meyer et al. coined the term 'Heidenhain's variant of CJD.' [5] This variant is thought to represent 4-20% of sporadic CJD, depending on the criteria used for diagnosis. [2, 6, 7] Visual disturbances in the initial phase include decreased visual acuity, peripheral visual field defect, tunnel vision, hemianopsia, metamorphopsia, achromatopsia, palinopsia, optical hallucinations, cortical blindness, and Anton syndrome. [2] Heidenhain's variant is even more challenging to diagnose during the initial phase during which there are only visual symptoms. These patients are commonly seen by ophthalmologists first, and visual loss is sometimes attributed to a preexisting ocular condition, such as cataract or a somatoform disorder, such as conversion disorder[8]. In one study, 17/22 (77%) were initially referred to ophthalmology and two underwent cataract extraction. [7]

This is particularly important since prion protein can be transmitted through ocular tissue. [9] After the initial phase (two to four weeks), the rest of the syndrome emerges and rapidly progresses inevitably to death in less than six months. [2, 7]

EEG and CSF markers (14-3-3 protein and NSE) are the most commonly used ancillary tests to aid in the diagnosis of sporadic CJD. However, they both have important limitations. The typical EEG pattern (0.5-2 Hz periodic sharp and slow wave complexes) has low sensitivity (58%) especially early in the course of the disease, and in some genotypic and phenotypic subtypes (as low as 21%). CSF markers may be more sensitive (88%), but they are not specific. [10] The sensitivity of these tests in the Heidenhain's variant does not seem to be different from sporadic CJD with reported sensitivity of EEG ranging from 31 to79% for typical EEG findings, and from 50% to 100% for CSF markers. [2, 6, 7]

MRI is the most commonly used radiologic tool in diagnosing CJD. MRI changes correlate with spongiform changes seen at autopsy. [11] Initial reports described a characteristic pattern of T2 weight imaging (T2WI) hyperintensity in the basal ganglia. [12] These changes are seen late in the course of the disease and have overall low sensitivity, documented to be 39% in a cohort of 1036 patients with sporadic CJD. In the same cohort, the sensitivity of EEG and CSF markers was 58% and 88% respectively. [10] With the advent of new MRI sequences; fluid attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI), the sensitivity has significantly increased. In a large multicenter international study, MRI scans of 211 pathologically confirmed sCJD patients; characteristic high signal in basal ganglia was found in 63% of FLAIR and 71% of DWI imaging. [13] In another study that included 193 consecutive patients with suspected CJD (definite n=60, probable n=84, possible n=11, not CJD n=38), the differential MRI sequence sensitivity was as follows: 16% for T2WI, 47% for FLAIR, and 77% for DWI. In the same cohort, the CSF marker 14-3-3 had a sensitivity of 91% and specificity of 44%, while the sensitivity of EEG was 32%, and its specificity was 94%. [14]

Panel A



Panel B

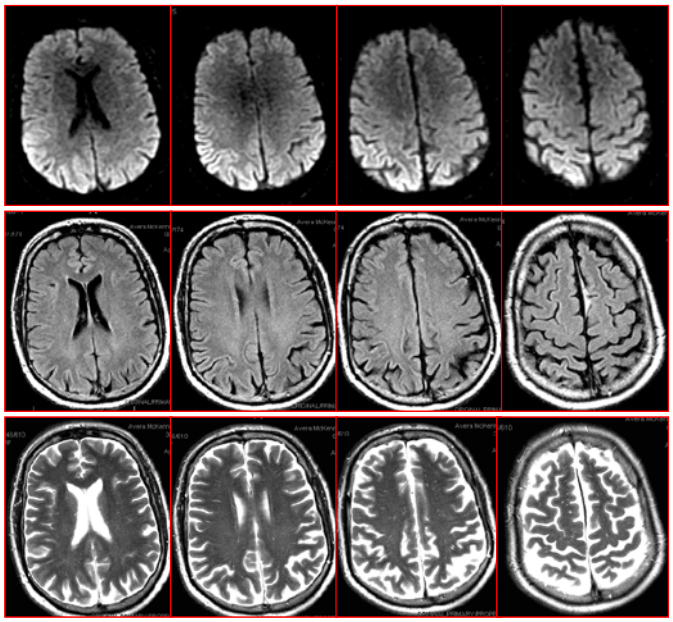


Figure 3: MRI from case 2, obtained 3 weeks after symptom onset. The DWI (upper row in panels A and B) is superior in showing early changes in the cerebral cortex compared to FLAIR (middle row), and T2WI (lower row) sequences.

After the introduction of FLAIR and DWI sequences, cortical signal change has become an important radiologic feature for sCJD. It is seen in up to 95% of patients. [15] Two patterns of cortical involvement have been described; isolated (one third of patients in one study) and in conjunction with basal ganglia lesion (two thirds of patients). [16] DWI is more sensitive to early changes than FLAIR. [17] Figure 3 from our second case is a good example of the superiority of DWI.

Based on the recent data indicating high sensitivity and specificity of DWI and FLAIR in early disease, it has been suggested that the diagnostic criteria for CJD should be modified to include MRI findings. Based on their data that showed low sensitivity and specificity of CSF markers, one group suggested replacing this test with MRI. [18] A recent multicenter study that retrospectively reviewed MRI scans of 436 sCJD patients and 141 controls estimated that adding MRI (which was positive in 83% of sCJD cases) would increase the sensitivity of the WHO diagnostic criteria from 91% to 98%.

The interobserver agreement was reported to be suboptimal in some studies. One such study reported interobserver agreement was 68% for T2WI, 80% for FLAIR imaging, and 100% for DWI. This study had a small sample size. The hard copies of images were retrospectively reviewed by two independent reviewers who were blinded to the clinical data but were aware of the study purpose. [17] In another larger study, the interobserver agreement was assessed through the agreement of three reviewers retrospectively reviewing 442 MRI scans. Again, reviewers were aware that CJD was considered but were blinded to the clinical data. In 71 of 193 cases all observers considered the MRIs to be ‘typical for sCJD’. In 52 cases, all observers classified the MRIs to be ‘not typical’. The overall agreement was 63.7%. The overall kappa (which incorporates the amount of agreement that is only achieved by chance) was 0.53. The percentage of patients with definite or probable sCJD who were considered to have “typical MRI changes” varied between the three observers from 58% to 71%. [14]

In a more recent study, DWI and FLAIR images from 40 patients with probable or definite CJD and 53 controls were reviewed by two neuroradiologists. Between the two readers, five cases of CJD were misdiagnosed as not CJD. Both readers misinterpreted two of these cases, producing seven false-negative diagnoses. Consensus review showed subtle findings in four of the five cases, particularly on DWI. The authors identified several factors that led to these errors: very subtle changes, severe magnetic susceptibility, patient motion artifacts, or poor selection of display window during filming. [19]

Both our cases were diagnosed with probable CJD, Heidenhain's variant pre-mortem. They both had isolated visual symptoms and were evaluated by ophthalmologists first. The diagnosis was histopathologically confirmed in one of them. EEG was not consistent with CJD in one case and in the second one, became suggestive of the diagnosis late in the course of the disease. NSE was indeterminant in one case and elevated in the other. MRI did show isolated restricted diffusion of the occipital and parietal cortex (cortical ribbon sign) in both patients, but these changes were missed initially which raises the question about the reliability of these MRI findings in everyday clinical practice. The reading radiologists were not aware that CJD was being considered in both cases. Could better communication between clinicians and radiologists enhance the ability of the radiologists to detect MRI abnormalities? Will the suggested amendment to the diagnostic criteria to include MRI really impact the criteria's sensitivity if these "typical MRI findings" are frequently missed outside the academic setting? These are all questions for future studies to answer.

**Teaching points:**

- The Heidenhain variant of CJD [4, 5] is one of six phenotypes described based on initial presentation: cognitive, visual (Heidenhain's variant), affective, classic, ataxic (Oppenheimer-Brownell variant) and indeterminate. [2]

- Early in the course of the Heidenhain variant-CJD, the visual symptoms are isolated and can be falsely attributed to preexisting intrinsic eye disease. [8] In one study, 17/22 (77%) were initially referred to ophthalmology and two underwent cataract extraction. [7] This is particularly important since prion protein can be transmitted through ocular tissue. [9]

- EEG and CSF markers (14-3-3 protein and NSE) have important limitations. The typical EEG pattern (0.5-2 Hz periodic sharp and slow wave complexes) has low sensitivity (58%). CSF markers may be more sensitive (88%), but they are not specific. [10]

- New MRI sequences such as fluid attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI) have high sensitivity and can be detected early in the course of the disease. [13]

- Increased cortical signal (c*ortical ribbon sign*) has become an important characteristic radiologic feature for sCJD after the introduction of FLAIR and DWI. It is seen in up to 95% of patients. [15] DWI is more sensitive to early changes than FLAIR. [17]

- Isolated DWI findings may be subtle and can be missed. [19]

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