DIFFUSION-WEIGHTED SEQUENCE ON MRI FOR THE DIAGNOSIS OF CREUTZFELDT-JAKOB DISEASE

Edgard Pereira¹

ABSTRACT – Creutzfeldt-Jakob disease (CJD) is a progressive and fatal dementing illness caused by a virus like agent called prion. Currently, the definitive diagnosis can only be made through brain biopsy. Given its potential transmissibility, it is paramount to have noninvasive and reliable means to detect the disease. The present case reports on a 63 year-old man with biopsy proven CJD, and evaluates the dependability of diffusion-weighted MRI in this condition, stressing the importance of this particular sequence to its diagnosis.

KEY WORDS: prion disease, dementia, magnetic resonance imaging, diffusion-weighted sequence.

CASE

A 63 year-old man, a former US navy diver, was referred to the neurology clinic with an 8-month history of progressive memory loss and word finding difficulty. The patient started with slowing impairment of his working capacity followed by memory deterioration. He progressed to a manic state with decreased need for sleep, hostility, irritability and poor personal hygiene. His past medical history was remarkable for hypercholesterolemia. He also had a history of extensive traveling to Asia, but denied any blood transfusion or surgical procedures. His neurological examination revealed an awake individual, disoriented to place and unable to name presidents. He showed hesitancy and word finding difficulty. The content of his speech was poor and tangential. His repetition was intact. He had profound impairment of his immediate and recent memories, and was unable to perform serial 7’s. There was no right-left confusion or agnosia. Cranial nerves were intact. Motor examination was remarkable for decreased deep tendon reflexes diffusely with normal plantar responses. No abnormal movements were present. There was a stocking distribution loss of pinprick, light touch and temperature, and vibration was mildly reduced distally in both legs. Cortical sensations were normal bilaterally as well as cerebellar functions. Romberg was negative. He was treated with haldol and diazepam to control his mood and behavior.
ESR was 4, ANA and hepatitis titers were negative. RPR was non reactive. B12 and thyroid function tests were normal. CSF demonstrated a normal cell count, protein and glucose, and the 14-3-3 \( \beta \) isoform was not detected. Viral cultures of CSF were negative. EEG, as well as CT of the brain, was normal. MRI of the brain was performed using a 1.5-T scanner. The fluid attenuated inversion recovery (FLAIR) images showed areas of mild increased signal in the frontal, temporoparietal and occipital cortex bilaterally (Fig 1). The diffusion-weighted imaging (DWI) demonstrated more accurately large areas of increased signal in the frontal, temporoparietal and occipital lobes (Fig 2). The centrum semiovale, basal ganglia, and brainstem were spared. The cortical sulci, fissures and cisterns were normal. MRI repeated two weeks later did not show interval changes. The adjacent white matter was spared. Microscopic examination of the cortex specimen obtained through open brain biopsy demonstrated neuronal loss and astrocytic gliosis with extensive spongiform changes compatible with prion disease. Immunohistochemical stain for proteinase resistant prion protein was negative. The patient died 2 months after the diagnosis.

**DISCUSSION**

CJD is the most common transmissible spongiform encephalopathy in humans, with a worldwide incidence of 0.5 to 1.0 cases per million per year\(^1\). From 1979 to 1998, 4751 cases of CJD were reported in the United States, with an annual age-adjusted death rate ranging from 0.78 in 1980 to 1.13 in 1997\(^6\). The transmissible agent, a proteinase-resistant protein (PrP or prion), exists in two isoforms. One (\( \alpha \)) is a normal constituent of the human cell membrane, encoded by a gene in the chromosome 20. The other (\( \beta \)) is found in scrapie and in CJD. The human disease can be sporadic (80-90% of CJD cases), infectious, or genetic\(^7\). Familial cases occur as a consequence of mutation in the PrP gene, which therefore are both heritable and transmissible. Iatrogenic disease results from use of contaminated stereotatic brain electrodes, transplanting comeas or dura mater from affected individuals or administration of infected growth hormone extract. Although measures to reduce the iatrogenic form have been implemented, the occurrence of a new variant (nvCJD) acquired from exposure to bovine spongiform encephalopathy, may spawn donor groups whose tissue and blood could be used in complete ignorance of their potential infectivity\(^8\).

The clinical diagnosis of CJD may be suggested in a middle age patient with progressive dementia, myoclonus, and cerebellar signs. However, this triad overlaps other demential disorders\(^9\), or it may not be manifested as in the present case. The clinical
diagnosis, therefore, relies on few unpredictable tests. The classical EEG findings of periodic complexes of spikes or slow activity at intervals of 0.5 to 2.0 seconds may or not be seen in the late stage of the disease, and its occurrence is not patognomonic for CJD, being associated with other entities easily mistaken for this disorder. Moreover, EEG changes are not characteristic of the nvCJD. Detection of 14-3-3 proteins in the CSF, considered to be the most reliable diagnostic tool, with a sensitivity of 94% and specificity of 84%, was thought to be false positive only for diseases easily distinguished from CJD such as subarachnoid hemorrhage or inflammatory CNS disorders. It is now known to have misleading results, either being falsely positive in patients with disorders resembling CJD, such as frontotemporal demential and Alzheimer disease, or falsely negative in some typical autopsy proven sporadic CJD, in a large number of genetic CJD, and in many patients with nvCJD. CT is of no help in the diagnosis, showing no abnormalities (80%) or nonspecific atrophy. Extensive literature now exists describing MRI findings in patients with CJD. These nonspecific abnormalities include symmetric bilateral increased signal intensity in the basal ganglia and thalami on T2- and proton density weighted images, with normal signal on T1-weighted images. However, conventional sequences seem not to be very sensitive for CJD, since no major changes could be identified in 21% of patients in a study of 29 patients with iatrogenic CJD. In addition, adjacent CSF signal may obscure cortical abnormalities on conventional MRI sequences, making this diagnostic tool almost useless in the so-called occipital (Haidenhain) variant. The use of FLAIR images may circumvent somewhat this problem in detecting cortical abnormalities, and the k-space reordered by inversion time at each slice position sequence may even improve the conventional FLAIR in this particular. On the other hand, DWI has been shown to increase the MRI resolution and yields better demonstration of the abnormal findings in patients with CJD. Such abnormalities were also found to correlate with those areas of disturbed metabolism by PET and SPECT scans. The physicochemical basis for diffusion abnormalities in this disease is unclear, but perhaps the compartmentalization of water within the vacuoles may restrict the diffusion of its molecules and be responsible for the high signal observed on DWI.

Although previous reports have demonstrated the greater sensitivity of DWI as compared to routine MRI sequences, all histologically confirmed CJD have also shown typical changes in the EEG and/or a positive 14-3-3 protein immunoassay in the CSF. The majority of them were also remarkable for high signal in the basal ganglia bilaterally on DWI. The present case, however, was unique in that both EEG and CSF analysis have shown normal results, and DWI abnormalities were restricted to the cerebral cortex.

In conclusion, findings on DWI increase the diagnostic accuracy in CJD and may be the most conspicuous abnormalities seen in this disease. DWI also might guide the stereotactic biopsy to an area of increased pathological activity to maximize its efficacy and safeness. Moreover, its short scanning time ensures few artifacts, especially in patients with myoclonus. Thus, this report substantiates the DWI features in CJD and adds further support to its role as the sequence of choice for the diagnosis of this condition, particularly when other auxiliary tests are negative.

REFERENCES