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Primary White Matter Involvement in Sporadic-Type Creutzfeldt-Jakob Disease? Which Came First, the Chicken or the Egg?

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Primary White Matter Involvement in Sporadic-Type Creutzfeldt-Jakob Disease? Which Came First, the Chicken or the Egg?

Prion diseases have been the subject of much attention in the scientific and lay media for several years, especially recently. No doubt, in large part this has been due to the appearance and recognition of variant Creutzfeldt-Jakob disease (vCJD) in the population. First striking Britain and Europe in the 1990s, this past year has seen the entire beef industry in Canada and the United States brought to its knees by this disease. Feeding practices have been forever changed. Major trading partners have come to restrict or place outright bans on the transborder movement of cattle and beef products to protect their populations from the ingestion of prions. Hospitals, surgeons, and pharmaceutical companies underwent a similar process several years ago concerning the use of cadaveric material (eg, dura, growth hormone) and the reuse and sterilization of instruments used in neurosurgery to avoid iatrogenic CJD (iCJD). Despite the recognition and attention that these newer subtypes of CJD have attracted (vCJD and iCJD), the most common form is still the sporadic type (sCJD), seen in about 85% of the cases (1 case per 1,000,000 population per year), whereas familial cases account for most of the balance. Characteristically it affects people older than 60 years. Rapidly progressive dementia, ataxia, and myoclonus are the usual symptoms. All cases are fatal, usually within 6–8 months.

Neuroradiology has come to play a very important role in the diagnosis of all types of CJD. No longer is our job simply to exclude structural causes of dementia or ataxia or myoclonus. We are in a position to make a specific diagnosis, and are expected to do so. With our knowledge of the imaging manifestations of CJD, when we encounter an MR finding of bilateral caudate and putaminal lesions, we include sCJD high in our differential diagnosis. Fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) have been particularly helpful in the detection of these lesions. It is also because of FLAIR and DWI that multifocal cortical lesions have come to be appreciated as quite common in sCJD. Do cases with cortical lesions define a new subtype of CJD? Probably not. It is just that we have better tools to detect previously occult lesions.

It is not surprising that, as our imaging methods get better and our case experience with sCJD increases, we will come to recognize more forms and subtypes, much the same as geneticists and molecular biologists have recognized different molecular phenotypes in this disease. In this issue of the *AJNR,* Matsusue et al describe a "panencephalitic" type of sCJD. They call it "pCJD" and indicate that it is characterized by extensive primary involvement of the cerebral white matter as well as the cerebral gray matter. Although extensive white matter involvement has been de-

scribed in several small series of sCJD before (1–3), Matsusue et al contend that previous authors have not been able to establish whether the white matter changes represented primary or secondary degeneration.

An aim of their study was to elucidate, by using serial MR imaging and histologic examinations in six autopsy cases, whether the white matter lesions in pCJD are primary lesions or are due to secondary degeneration. In their study, serial MR images of brains revealed that lesions appeared in the cerebral gray matter 2–5 months after the clinical onset of symptoms and in the cerebral white matter around the lateral ventricles approximately 5 months after the onset. The white matter lesions rapidly extended to the deep and subcortical white matter during the next several months and then to the entire cerebral white matter 10 months after clinical onset. Severe brain atrophy was profound for all cases except case 1. (The average brain weight in cases 2–6 was 730 g.) Death in case 1 occurred 8 months after clinical onset. In the others, death occurred an average of 2 years after the beginning of the illness.

We find the imaging results in this study important. If we were to analyze a single MR imaging examination in any one of these patients at just one point in time, especially if that point were later than 6 months after the onset of illness, the presence of a large number of white matter lesions might dissuade us from considering sCJD as the likely diagnosis. More likely, a demyelinating disorder or chronic microangiopathic disease would be considered as the cause of the white matter lesions, and, if the white matter lesions were the dominant findings, close scrutiny of basal ganglia and cortex might be bypassed. Serial examinations showing rapid progression might avoid such a misdiagnosis, but once a patient is improperly (or too narrowly) diagnosed, serial examinations may not be done. The authors are to be congratulated for obtaining serial MR imaging examinations in their cases. They convincingly demonstrate the progressive nature of the lesions and the profound progressive brain atrophy. They demonstrate that sCJD should be considered as a possible diagnosis when gray *and* white matter lesions are present in a patient with the proper clinical setting.

On the other hand, despite bringing our attention to this valuable diagnostic point, we do not think that Matsusue et al have proved that the white matter lesions in their six cases are primary. Why not? In our view, proof that the white matter lesions are primary could take one of two forms (preferably both).

One way would be to show a clear temporal relationship. Serial MR examinations would need to convincingly show that the white matter lesions preceded

the gray matter lesions. They have not shown this. Of their six cases, white matter lesions preceded gray matter lesions in only one case. In four cases, the gray matter lesions were clearly first, whereas, in the other one case, white and gray matter lesions were both present at the first MR imaging examination. Further weakening their argument is that the two best sequences for detecting the gray matter lesions in CJD—FLAIR and DWI—were not performed in most cases in this series. FLAIR was done in only a minority of their cases, and DWI was not done in any. Many early gray matter lesions could have escaped detection, further weakening their argument for the primacy of the white matter lesions.

The other acceptable form of proof would be if the neuropathologic features of primary versus secondary white matter lesions visualized at autopsy could be unequivocally distinguished from one another. We do not think this is possible in these cases because of the length of the illnesses and severe loss of brain parenchyma. The authors contend that the histologic features of severe loss of myelin and axons, with spongiform changes and gemistocytic astrocytosis are exceptional features of secondary degeneration. Hence, they conclude that these features indicate primary involvement of the white matter. We do not agree.

Although the profound neuronal loss and gliosis in the cortex would lead one to intuitively assume the changes in the white matter and descending tracts are secondary, this is not necessarily the case. With such severe cortical neuronal loss, it is impossible to tell histologically which occurred first, the white matter lesions or the gray matter ones. Which is the chicken and which is the egg? It cannot be determined. Histologic examination cannot be conclusive in determining whether the white matter changes are primary or secondary in "end-stage brains."

On the other hand, a different hypothesis can be considered. Perhaps the presence or absence of white matter lesions is not so much determined by whether a case is a panencepahilitic form of CJD, but rather by the duration of disease. Consider that most patients with sCJD die before 8 months of onset, yet five of six patients in this series survived 2 years or longer! Why did these patients live so much longer than those with the usual sCJD course? Parchi et al (4) analyzed 300 cases of sCJD. Twelve of them were panencephalopathic. All were of long duration, and they had different molecular phenotypes. This argues against the hypothesis that pCJD is a specific subtype of CJD rather than a consequence of a different molecular phenotype that predisposes to long disease duration. Perhaps these six patients had a different molecular phenotype, one that allowed them to survive longer? Perhaps most patients with sCJD that survive longer than a year develop profound white matter disease? We have learned much about the etiologic, genetic, pathologic, and imaging characterisitcs of CJD. There is still a long way to go.

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Memory and the Mammillothalamic Tract

Memory is the diary that we all carry about with us.
                                        Oscar Wilde (1895–1941)

Memory is a complex phenomenon. Its study has spawned a diverse terminology. Signoret (1) suggested that memory could be divided into five separate processes: a holding process for momentary retention; an acquiring process that encodes material; a storing process (consolidation) that permanently preserves the memory; a retrieval process; and a scanning process allowing for the recall of relevant material from a panoply of stored memories. In clinical practice, a specific memory disorder may arise by contributions of more than one of these processes.

The amnestic syndrome is characterized by an impairment of recent memory, preservation of the ability for immediate recall, and preservation of remote memories. It has been referred to as Korsakoff syndrome on the basis of the description of the memory disturbance accompanying alcoholic peripheral neuropathy by S. S. Korsakoff in a series of papers published between 1887 and 1891. This memory disorder results from a discrete inability to encode and store new memories. It has been reported in association with thiamine deficiency, cerebrovascular disorders, head trauma, and anoxic injury. The cognitive functions, language, and behavior of persons with an amnestic syndrome may remain perfectly normal. The anatomic basis of this disorder has been a source of controversy. Pathologic studies of alcoholic patients with Korsakoff syndrome invariably demonstrated gliotic lesions of the mammillary bodies. Many authorities attributed the memory disturbance to these lesions; however, lesions of the mammillary bodies were often present in the absence of the amnestic syndrome. Subsequent studies demonstrated that lesions of the dorsal medial nuclei of the thalami cor-

related with the amnestic syndrome in alcoholic patients (2, 3) and the role of the mammillary bodies in the memory disorder was largely, although not entirely, dispelled (4–6). The importance of the dorsal thalamus to recent memory acquisition was corroborated by other observations, such as the appearance of an amnestic syndrome following penetrating trauma to this region (7).

In this issue of the *AJNR,* Yoneoka et al report on a patient with bilateral isolated lesions of the mammillothalamic tracts (MTT) that were associated with Korsakoff syndrome. They propose that bilateral lesions of the MTT are sufficient to cause an amnestic syndrome. Discrete bilateral lesions of the MTT are rare, probably explaining why this association had not been previously reported. The finding should not, however, be surprising. The mammillary complex reciprocally innervates the hippocampus and via the MTT communicates with the anterior thalamus from which fibers pass to the hippocampal formation via the cingulate cortex. The role of the hippocampal-limbic system in the acquisition and storage of new memories is well established. Scoville and Milner (8) demonstrated that a permanent impairment in memory followed bilateral medial temporal lobe resection that extended sufficiently posteriorly to damaged portions of the anterior hippocampus and hippocampal gyri, and D'Esposito (9) demonstrated bilateral lesions of fornix may also result in an amnestic syndrome. Most evidence indicates that bilateral lesions of segments of the temporal or diencephalic or both limbic systems are necessary to impair learning. This case report adds one more site of the hippocampal-limbic system—namely, the MTT—from which bilateral lesions may result in amnesia.

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