



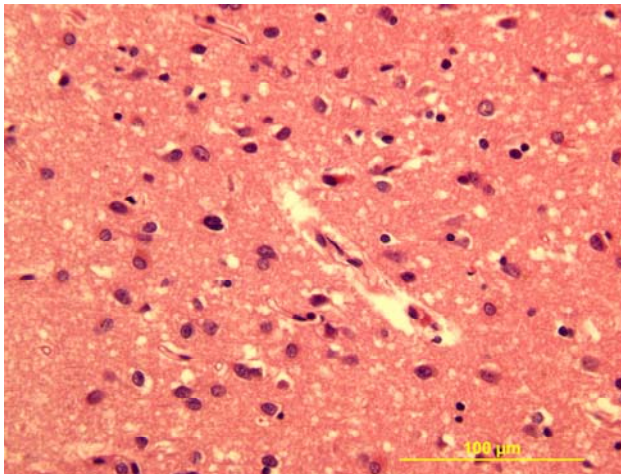
HOLY C.O.W.!

IT'S...

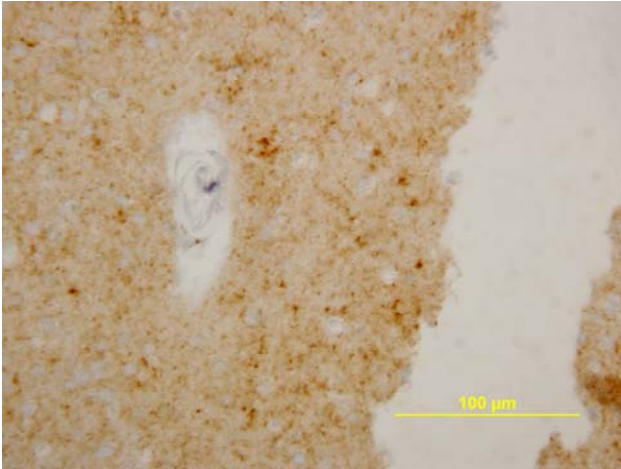
Clinical Question of the Week #2
July 7th, 2008 through July 14th, 2008

Please e-mail your answers to Kuo, Tim, Wendy, or Kevin (klian@mednet.ucla.edu; tprovias@mednet.ucla.edu; wsimon@mednet.ucla.edu; kbreger@mednet.ucla.edu) by 0800 on Monday, July 14th, 2008. The resident or intern with the most correct answers at the end of each month will receive a prize!

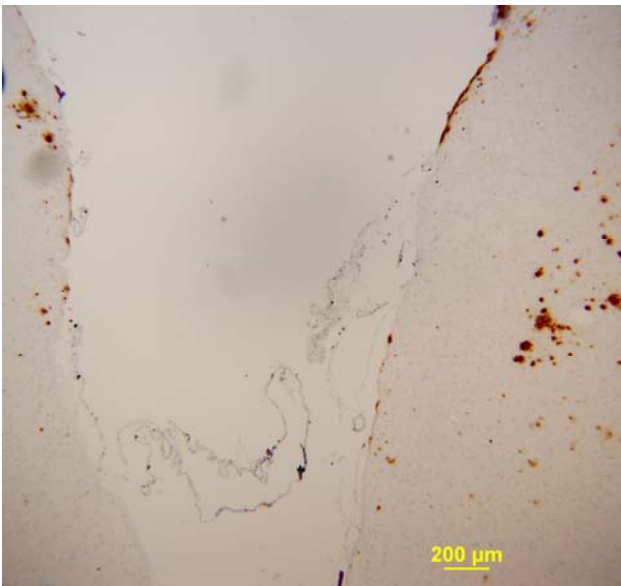
Case: A 78-year-old woman was brought in by her family for increasing confusion over the past few weeks. The family reports that she was in her usual state of health until two weeks ago, when she became disoriented. This was followed by memory loss, altered gait, and ultimately aphasia. On evaluation, she could not cooperate enough to follow commands, did not communicate, had unstable gait, but no sensory abnormality. She had not had any recent travel, sick contacts, fevers or chills. Initial laboratory evaluation and imaging were unrevealing. Despite all supportive measures, the patient's condition continued to deteriorate. Brain biopsy specimens are shown below.



Standard H&E staining of frontal lobe.



Immunohistochemistry stain #1 to frontal lobe.



Immunohistochemistry stain #2 to hippocampus.

Questions:

1. What is the diagnosis?

Creutzfeldt-Jakob disease, the most frequent of human prion diseases, occurs with a frequency of 1:1,000,000 worldwide, although clusters appear in Africa, Israel, Italy, and Slovakia likely due to familial CJD. Forms include sporadic (sCJD), familial (fCJD), iatrogenic (iCJD), and variant (vCJD). Mean age of onset is approximately 60 years of age.

Clinical features include progressive neurologic decline and myoclonus, including startle myoclonus. MR imaging in early disease reveals DWI abnormality, while later disease is notable for generalized atrophy and ventricular enlargement. EEG may reveal periodic synchronous bi- and tri-phasic sharp wave complexes (PSWCs) with high specificity, however with lower sensitivity. While a “probable CJD” diagnosis may be obtained with clinical criteria, definitive diagnosis requires neuropathologic diagnosis with one or more of the following: spongiform degeneration, PrPSc plaques, or demonstration of PRNP gene mutations. Currently there is no treatment, and the disease is uniformly fatal. (0.5)

2. What laboratory finding is found in association with this condition?

The 14-3-3 protein (found in CSF) has a moderate positive predictive value for CJD. However, the assay may be “falsely positive” in the setting of HSV encephalitis, metabolic encephalopathy, paraneoplastic disease, cerebral metastases, and hypoxic encephalopathy. Additionally, the lack of a positive test does not rule out CJD, particularly in cases of familial CJD and nonclassical sCJD. Thus, it should only be used as an adjunctive test. (0.5)

3. What is the protein that the immunohistochemistry stains are binding?

The immunohistochemistry stains bind to the PrP (protease-resistant) prion protein. Specifically, there are two isoforms of the prion protein, the normal PrP^C (for common) protein found on the membranes of cells, and the abnormally conformed PrP^{Sc} (for scrapie, the mammalian analogue to CJD) which is capable of changing the conformation of the common PrP into the abnormal form and results in accumulation as this form is resistant to proteases. Other neuropathologic techniques for PrP involve protease digestion of PrP^C followed by staining for the PrP^{Sc} specific protein. (1)

4. Who is attributed with discovery of this disease, and which institution is he from?

Stanley Prusiner at UCSF isolated the prion protein in 1982, and he coined the term prion from **proteinaceous** and **infectious**, with **-ion** as a reference to virion. The clinical syndrome was originally described by Hans Gerhard Creutzfeldt and Alfons Maria Jakob in 1920. (0.5 for Prusiner, 0.5 for C&J, 0.5 extra if you said UCSF is the best med school in America)