Imaging of Genetically Defined Incipient Creutzfeldt-Jakob Disease

I. Prohovnik[1,2], J. Chapman[3], X. Guo[1], P. B. Kingsley[4], R. K. Fulbright[2], C. Hoffmann[3], E. Kahana[3], A. Gigi[3], Z. Nitzan[3], J. Schmeidler[1]

[1]Dept. Psychiatry, Mount Sinai School of Medicine, Bronx, NY, United States, [2]Dept. Diagnostic Radiology, Yale University, New Haven, CT, United States, [3]Dept. Neurology, Sheba Medical Center, Tel Aviv, Israel, [4]Dept. Radiology, North Shore University Hospital, Manhasset, NY, United States

Introduction: Transmissible Spongiform Encephalopathy (TSE) exists in, and is transmitted across, several species, by an unusual infectious molecule that does not depend on conventional genetic mechanisms. This group of diseases is scientifically intriguing, and its public health implications are not yet known[1,2]. Creutzfeldt-Jakob Disease (CJD), the most notable of the human prion diseases, is invariably fatal. The rarity of CJD, difficulty of early diagnosis, virulent course, and variable modes of transmission, have made clinical studies exceedingly difficult[3]. Previous studies have mostly consisted of small, heterogeneous samples and case reports. To overcome the difficulties of clinical research in this area, we have started a study of a singular cluster of high incidence occurring among Libyan Jews living in Israel, caused by familial transmission of a mutated prion protein (PrP) gene[4-6]. The design allows us to elucidate very early, and even premorbid, cerebral abnormalities in these patients. Here we present the general logic and structure of the study, as well as results from the first seven subjects (4 patients and 3 relatives).

Methods: All incident CJD cases in Israel that carry this mutation (E200K) are recruited and followed for the duration of the disease. Healthy mutation-carrying relatives are also identified and will be studied before, as well as after, symptomatic expression[7]. Family members lacking the mutation serve as controls. All subjects have extensive neurological and neuropsychological examinations, as well as MRI. Subjects are scanned on a 1.5T GE Signa scanner to obtain detailed anatomy (3D-SPGR), as well as T2W and FLAIR for clinical reading. In addition, we obtain DWI (with ADC measurement) and Chemical Shift Imaging (CSI). Imaging data (SPGR, ADC) are quantitatively analyzed with SPM99. All other data are analyzed by appropriate ANCOVA and regression models.

Results: On blind clinical reading of the MRIs, all controls were judged normal, and all patients were considered abnormal. The most common findings were FLAIR and DWI hyperintensity in caudate (4/4), putamen (3/4), and cortical white matter (3/4). Thus, our genetically defined patients are radiologically identical to sCJD and consistent with previous reports. Quantitative analyses[8] showed significant loss of grey matter (CSF fraction .085 Vs. .121, t_5=3.56, p<.02) and higher ADC values in cortex. Focal decreases of ADC were found in the putamen by ROI analysis (548±83 Vs 709±9 $\mu m^2/s$, $F_{1,5}$=10.54, p=.02). Three of the four patients had substantially reduced putaminal ADC values (range 450-550 $\mu m^2/s$). One patient was only reduced on the left side. The correlation of left putaminal ADC with neurological severity was -0.81. Spectroscopic data were analyzed in anterior Cingulate gyrus, caudate nucleus, lentiform nucleus, thalamus and corpus callosum. NAA was generally reduced in the patients, with the NAA/Cho ratio lowest in Cingulate gyrus, where it was also correlated with a neurological severity score. Repeated-measures ANOVA yielded a marginal Dx effect ($F_{1,20}$=6.08, p=.07), regional effect ($F_{5,20}$=3.12, p<.05) and interaction ($F_{5,20}$=2.60, p=.06). Duration of disease was correlated with this ratio in the caudate and putamen.

Discussion: This project will be the largest neuroimaging study ever conducted in this disease, and the first to observe a genetically homogenous sample. Further, it will provide data on the earliest stages of the disease, including healthy mutation carriers before frank onset of symptomatology. The large sample sizes, availability of healthy mutation carriers, the noncarriers of similar environmental and cultural background, and rapid access to symptomatic patients, are all unprecedented features that should yield definitive data on the early stages of this devastating disease.

Supported by NIH grant NS 043488.

References:

1. Armstrong et al., neurosci Letters 2003;348:37-40.
2. Asante et al., EMBO 2002;21:6358-6366.
3. Collins et al., J Clin Neurosci 2000;7:195-202.
4. Kahana et al., Science 1974;183:90-91.
5. Goldfarb et al., Lancet 1990;336:637-638.
6. Hsiao et al., NEJM 1991;324:1091-7.
7. Chapman et al., Neurology 1994;44:1683-1686.
8. Ashburner & Friston, NeuroImage 2000; 11:805–821.