

Hereditary Disease Foundation & Terrance Cardinal Cook Health Care Center

Metabolic Discussion on Huntington's Disease

January 13, 2000, New York, New York

Prepared by Susan E. Browne, Ph.D.

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On January 13, 2000, the Terence Cardinal Cook Health Care Center and the Hereditary Disease Foundation, held a Metabolic discussion on Huntington's Disease.

10 a.m.

Tour of the care facilities for HD patients at the Terence Cardinal Cook Health Care Center (TCCHCC) for all participants.

11 a.m.

Discussion group commences.

Minutes

1) Dr. Tony Lechich welcomed all participants to the workshop, and gave a brief overview of the history, attributes, and goals of the Terrence Cardinal Cooke Health Care Center James White Huntington's Disease Unit. He then outlined the principal aims of this workshop meeting:

(ii) Review the current status of knowledge gained from metabolic imaging studies to date, in both HD patients and in animal models of the disease;

(iii) Discuss which future applications of imaging techniques in HD research will be the most beneficial uses of the techniques available, with respect to a) understanding the pathogenesis of disease, and b) potential therapeutic approaches;

(iv) Discuss ways in which both the research community and HD patient population in the NY area can interact to make full use of the resources available and accelerate the progress of HD research.

2) Welcome, introductions, and overview of Hereditary Disease Foundation goals and aims of this meeting by Co-Chairs Nancy Wexler and Lucy Brown.

3) Introductions and synopses of relevant research interests - all participants.

Group Discussion

4) Which *in vivo* metabolic imaging methods are currently used by HD researchers within this group?

(i) Functional imaging studies (positron emission tomography, PET; single photon emission tomography, SPET; functional magnetic resonance imaging, fMRI):

- Local rates of cerebral glucose metabolism (ICMRgl)
- Regional cerebral blood flow (rCBF)
- Cerebral neuropharmacology: Dynamic alterations in receptor populations, distributions, binding

affinity; including dopamine D1-like and D2-like receptors (reflecting GABA neurons); Opioid receptors; Benzodiazepine binding to GABA A receptor complex modulatory site.

- 1H-NMR spectroscopy: NAA (N-acetylaspartate), lactate, creatine, phosphocreatine etc. quantitation *in vivo*.

(ii) Structural imaging (Volumetric MRI)

5) Which areas of imaging research are ripe to explore, and which can be addressed by this research group / which research areas should be given the highest priority?

Flint Beal and Jullie Pan reported evidence from HD and epilepsy studies supporting the utility of NAA as an *in vivo* marker of neuronal function. Dr. Beal proposed that NAA levels, striatal volume and D2-receptor distribution are valuable existing surrogate markers of disease progression, and that lactate levels also seem predictive of disease status and indicative of metabolic status. Dr. Beal reported that 1H-NMR spectroscopy studies showed striatal lactate levels were abnormally increased in 3 of 7 pre-symptomatic individuals who had tested positive for the HD gene., while all symptomatic patients examined (31/31) showed lactate elevations which were ameliorated by chronic treatment with the metabolic enhancer coenzyme Q10.

1H spectroscopy is also being used in different mouse HD models (to date in R6/2 and Borchelt mice). With the many different mouse models to be characterized, and the opportunity to investigate the effects of age and CAG repeat number, there are currently many applications for imaging techniques. Susan Browne also reported initial quantitative glucose use studies in transgenic mouse models of HD - in particular, evidence of CAG repeat length-dependent increases in cerebral glucose use in presymptomatic Hdh mice - demonstrating the utility of this technique in mouse models.

Dr. Beal went on to suggest that another beneficial technique applicable to both HD patients and animal models, is the use of phosphorus magnetic resonance spectroscopy in muscle. This determines levels of metabolic markers, including PCr and ATP, and their functional recovery after stress or in response to therapeutic agents. He cited recent reports by Dr. Tony Schapira (UK) of below normal muscle mitochondrial ATP production in Friedrich's Ataxia patients, and a strong negative correlation between mitochondrial ATP generation and the trinucleotide repeat length in these patients.

6) Safety and Interpretation Issues

Questions were raised as to the safety of repeating imaging protocols in human subjects. Nancy Wexler pointed out that, relative to pre-1993 imaging studies, we now have the benefit of knowing whom within the population will be affected by the disease, facilitating prospective studies over a patient's life-span. Dr. Kegeles proposed that MRI studies are safer to perform repeatedly in humans, whereas for PET studies 1-2 year intervals between scans are preferable.

There was discussion about the drawbacks vs. necessity of sedation or anesthesia during imaging protocols. Jullie Pan and Hoby Hetherington reported their experiences with epilepsy patients and sedation during scanning. Craig Branch and Joseph Helpert suggested giving patients the opportunity to become familiar with the scanner and its environment prior to scanning; their use of a "simulator" scanner; and the benefits of having family members/friends present. The minimum scanning time was also discussed - depending on data required, the consensus opinion was approx. 40mins to 1 hour.

The interpretational complications arising from measuring functional parameters under the influence of anesthesia/sedation were also discussed. The conclusion was that within the HD subject population this is probably an unavoidable situation, unless studies are limited to pre-symptomatic subjects. Dr. Lechich pointed out that some complications are unavoidable since the majority of HD patients are on multiple medications.

7) There was much informal discussion over lunch, and an opportunity to meet with Mrs. James White, who provided both an insight into the effects of HD on a family, and optimistic encouragement.

8) Short slide presentations, by:

Andy Feigin and David Eidelberg: Findings from PET studies of striatal hypometabolism, co-varying with hyper-metabolism in the occipital cortex of HD patients. Striatal hypometabolism correlated with CAG repeat length. Dr. Feigin also stressed the importance of correcting for the effects of atrophy (ie. by measuring raclopride binding).

Susan Browne: Increased glucose metabolism in the brains of Hdh transgenic HD mice, prior to behavioral changes, cell loss, NII formation. Hypermetabolism seems to be CAG length dependent and dose-dependent. This is of particular interest since elevated glucose uptake may be expected to precede decline, with associated cell loss, if a metabolic defect exists. Similar glucose use increases have been reported in early stage Friedrich's Ataxia, and in HD patients (unpublished observations; MFB).

Jullie Pan: Described the method for measuring metabolic rate fluctuations and potentially determining the site of a metabolic defect by measuring the rate of flux of ^{13}C from ^{13}C -glucose to ^{13}C -glutamate - a NMR visible non-radioactive label.

Lawrence Kegeles: Described potential PET and MR methods for measuring GABA levels in the brain in vivo, including GABA shift, DA/GABA interactions, and MR spectroscopy.

Craig Branch and Joseph Helpert: Described potential applications for perfusion MR imaging in rats (still to be adapted to mice). One benefit is that this technique can be performed as often as animals can be anaesthetized - ie. every 2-3 days: useful for longitudinal studies. They also described other studies in an Alzheimer's disease mouse model (PS/APP AD transgenic mice).

Concluding Discussion

9) Questions that imaging studies can and should address are:

(i) In human patients, when and where does the pathology in HD begin? What is the earliest age that brain abnormalities can be detected? Longitudinal studies of volunteers from families would be useful. All siblings from an affected family would have to volunteer beginning as early as possible-in their teens at least-for annual MRI studies, for example. The dream of having an MRI in Venezuela was discussed informally after the meeting, and Joe Helpert said it would not hurt to ask some of the companies that make the magnets to consider a donation of an old magnet being discarded. The big question addressed here, too, is "When is the right time to institute therapy?"

(ii) In human patients and animal models, it is important to understand whether there are metabolic defects. Both PET and spectroscopic imaging studies can address basic metabolic questions, not only in brain, but perhaps also in peripheral tissue, like muscle. To study oxidative stress and to look at basic glucose extraction in HD is important and can be done with imaging studies.

(iii) Imaging studies can be used to monitor future therapeutic studies.

(iv) Some concern was expressed that the imaging studies should move quickly beyond measuring what is at hand; as soon as possible, hypothesis-driven, mechanistic studies should be designed.

(v) The group felt that another meeting would be useful, perhaps in June.

(vi) The group was very grateful to have heard about the population of HD patients at the Terrence Cardinal

Cooke Health Center, and hopes to be able to collaborate with the Center in future studies.