Uncovering the Mysteries of the Brain

How does the brain respond to elevated ammonia? Are the effects of UCD on the brain preventable or reversible? New UCD research using specialized neuroimaging techniques may provide the answers and lead the way to developing new interventions to protect the brain.

Up to now, how hyperammonemia disrupts brain function has not been well understood. What exactly causes the brain to be injured? How much injury occurs and precisely what areas of the brain are involved? Why is there often variation in the recovery of patients after a hyperammonemic event?

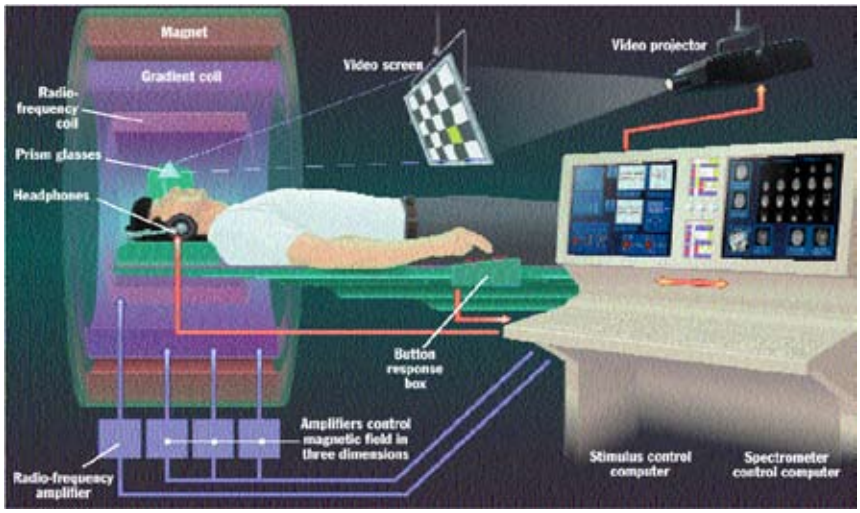
Dr. Andrea Gropman is a rare breed. Dr. Gropman is a neurologist *and* a geneticist (how smart can one person be?). She is leading critical UCD brain research that uses specialized brain imaging techniques to study how UCDs affect the brain. This special neuroimaging can be used to obtain information about the timing, extent, and reversibility of these effects, as well as the mechanism of brain injury.

Finding brain biomarkers for UCD

Can we then use these technologies to track or prevent injury? Gaining an understanding of how and why the brain is being affected in UCD adults and children is critical to improving outcomes. A crucial step is the identification of "biomarkers" in the brain. Biomarkers are biochemical features or characteristics that can be used to measure the progress of disease or the effects of treatment. Brain biomarkers for UCD could help predict the severity of a hyperammonemic event, and be useful for clinical monitoring (effects and timing of treatment) and interventional studies. These biomarkers are critical to advancing the development of new interventions and treatments to protect the brain in UCD.

Is the brain compensating?

Neuropsychological testing is also being used to measure the secondary effects of UCD on the brain. Dr. Gropman's cutting-edge research combines special neuroimaging techniques that characterize alterations in the brain chemistry and neural structure, with special neuropsychological tests. For example, while the patient is in the scanner, they perform tasks, like pressing a button when they see certain letters on a video screen. This allows Dr. Gropman to simultaneously "see" and monitor changes as the brain activates in reaction to performing tasks. The more complex the task, the more the brain activates; Dr. Gropman can then identify abnormalities or deficits in the activation patterns. She is finding that in OTC patients, the brain may be compensating for damage in one area by activating other parts of the brain. Their brains are actually working harder compared to an unaffected person to accomplish the same tasks. *(continued next page)*



Brain - *cont'd*

Previous neuropsychological studies in OTC carriers reported by Gyato, et al, indicated that despite average IQ scores, OTC carriers displayed specific neurocognitive deficits in nonverbal intelligence, fine motor/dexterity/speed, visual memory, attention and executive function skills, and math. These findings are typically associated with white matter or subcortical dysfunction. By using special imaging techniques (1H MRS, DTI and fMRI) Dr. Gropman has been able to confirm white matter injury in OTC patients and carriers affecting the frontal lobe that involves working memory and executive function.

Glutamine - a biomarker?

Over the last few years, Dr. Gropman's work has revealed that even in the absence of hyperammonemia, there are subtle or even significant alterations in the biochemistry of patients with OTC deficiency and OTC carriers . This raises an important question about the role of glutamine in OTC and CPS1 deficiencies. In animal and human studies, accumulations of ammonia, glutamine and glutamate have been shown to exert toxic effects on the brain. Clinical signs of hyperammonemia can begin at 60 micromol/L, including anorexia, irritability, lethargy, disorientation, vomiting and somnolence, eventually progressing to brain swelling and coma. A rise in glutamine levels in the blood has long been theorized to be a predictor of impending hyperammonemia. For the first time, Dr. Gropman's studies using 1H MRS revealed elevated brain glutamine in OTC patients with hyperammonemic encephalopathy (HE - an alteration of brain function or structure caused by high levels of ammonia). The results provide evidence that HE is related to elevated concentration of glutamine in the brain and a disruption of cerebral metabolism.

Dr. Gropman used the same 1H MRS technique to investigate cerebral metabolism in stable patients with partial OTC deficiency. The results showed that both symptomatic and asymptomatic patients had significant increases in glutamine and decreased concentrations of myoinositol compared to normal controls. This observation in women with OTC who were asymptomatic suggests the possibility of unrecognized biochemical disturbances and may explain some of the neurocognitive deficits observed in these patients.

It's all about the brain

The studies provide details about the pattern and type of injury in UCD and characterize several important brain biomarkers. Biomarkers in OTC deficiency include increased brain glutamine levels and possibly depletion of myoinositol – indicators of disturbed osmatic balance in brain chemistry. Markers of white matter injury reveal alterations that may impair learning and memory.

These studies need to be expanded to better understand when these alterations may be occurring, their relationship to age, early metabolic changes and progression. Most importantly, can there be recovery? The studies will help address whether even "asymptomatic" OTC patients or carriers should receive treatment to avoid long term effects on cognition.

New studies have been proposed using these techniques to identify brain biomarkers in citrullinemia and ASA – which may be different than those found in OTC deficiency. These biomarkers can then be used to access and monitor effectiveness of treatment and help evaluate current and novel therapies to improve neurological outcome. ■

How You Can Participate

Neuroimaging Studies for UCD

Eligibility:

- OTC females, carriers and late onset males, confirmed biochemically or by genetic mutation
- Ages 7-60 years of age, with stable health
- Able to comply with testing, not claustrophobic

Washington, DC Study:

- Travel to Washington, D.C. for 2 days (travel expenses paid)
- Provide a 3-day diet history
- Have blood and urine drawn for ammonia, glutamine, orotic acid, liver functions and chemistries
- Undergo 1 ½-2 hours of cognitive testing
- Undergo 4 hours of scanning, split over 2-3 sessions

Or for All OTC patients

Release the films from any previous MRIs performed before or after diagnosis (at any age)

- Simply sign a consent to have raw data from the scan released to Dr. Gropman for reinterpretation by new software and comparison

Contact Study Coordinator: Ileana Pacheco-Colon, ip126@georgetown.edu
Phone 202-657-4671